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The Second COVID-19 Wave in India: Awaiting Light at the End of the Tunnel

By Mayuri Trivedi and Vivekanand Jha

The unfolding story of COVID-19 in India has shown how a narrative can change quickly. It was only a few months ago that experts around the world were wondering what explained India's relatively cheap escape (until then) from the ravages of the COVID-19 pandemic. India is now back in the news, but this time, the reports are highlighting the utter collapse of the healthcare system, shortage of critical supplies and hospital beds, people dying on the curbsides, and striking images of over-busy cremation and burial grounds. Amid this chaos, care of patients with chronic illnesses like kidney diseases has been marginalized (1).

The causes of this second wave of the pandemic have been debated but can be largely divided into changes in the virus genome and people-related factors. With regard to the former, it has been a combination of the B.1.1.7, first identified in the United Kingdom, or the "Kent" variant, and the new B.1.617, first identified in India (2). This SARS-CoV-2 variant contains mutations in the spike proteins that portend enhanced viral infectivity with potential to escape neutralizing antibodies (however, this has not been confirmed) and has been designated by the World Health Organization (WHO) as a "variant of concern." (3)

It is convenient to blame the virus because that deflects attention from the people-related factors, such as the failing healthcare system or misguided human behavior.

As the cases declined from September 2020, and the country emerged from one of the strictest lockdowns in the world (10 weeks of complete lockdown followed by phased relaxation over 8 months), which had a major impact on the economy, India let down its guard and concluded that the pandemic was over. Serosurveys had shown that 30% to 60% of the population had been infected, leading to a belief that "herd immunity" had already been achieved or was around the corner. There was a sense of triumph and talks of Indian exceptionalism—propagated by the community and political leadership—and a premature euphoria over the protection by herd immunity. Large political rallies and religious gatherings involving tens of thousands of individuals were held, with little adherence to COVID-19-appropriate behavior. Social events that involved large gatherings like weddings, postponed during the first wave,

Continued on page 8

More Cities and Counties Declare Racism a Public Health Crisis

By Melanie Padgett Powers

The number of cities and counties that have issued declarations about racism has skyrocketed since George Floyd was killed in 2020 and Black Lives Matter protests erupted across the United States.

As of spring 2021, 109 cities, 76 counties, and 8 states have formally declared racism a public health crisis, according to Rita Soler Ossolinski, program director for the National League of Cities' program Race, Equity, and Leadership.

"I think there's real intentionality behind them," Soler Ossolinski said. "The first step is acknowledgment." These declarations can begin to "normalize" the conversation around racism. The next step is accountability, she said, by developing plans and programs to address racial inequalities. "Racism is a system; it's not necessarily a pejorative remark."

In Ohio, both the Franklin County Board of Health (1) and the City of Columbus City Council (2) declared racism a public health crisis. Columbus is the state capital and largest city in the state. The Board of Health committed to creating an equity and justice-oriented organization, identifying areas where it can embrace diversity and incorporate anti-racism

Continued on page 9

Inside

THE FIRST FDA-APPROVED TREATMENT

BENLYSTA is indicated for patients aged ≥5 with active, autoantibody-positive systemic lupus erythematosus (SLE) receiving standard therapy and patients aged ≥18 with active lupus nephritis receiving standard therapy. The subcutaneous (SC) formulation is approved for patients aged ≥18. BENLYSTA is not recommended in patients with severe active central nervous system lupus or in combination with other biologics.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATION

Previous anaphylaxis with BENLYSTA.

WARNINGS AND PRECAUTIONS

Serious Infections: Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents, including BENLYSTA. The incidence of serious infections was similar in patients receiving BENLYSTA versus placebo, whereas fatal infections occurred more frequently with BENLYSTA. The most frequent serious infections in adults treated with BENLYSTA IV included pneumonia, urinary tract infection, cellulitis, and bronchitis. Use caution in patients with severe or chronic infections, and consider interrupting therapy in patients with a new infection.

Progressive Multifocal Leukoencephalopathy (PML): Cases of JC virus-associated PML resulting in neurological deficits, including fatal cases, have been reported in patients with SLE receiving immunosuppressants, including BENLYSTA. If PML is confirmed, consider stopping immunosuppressant therapy, including BENLYSTA.

Hypersensitivity Reactions (Including Anaphylaxis): Acute hypersensitivity reactions, including anaphylaxis (eg, hypotension, angioedema, urticaria or other rash, pruritus, and dyspnea) and death, have been reported, including in patients who have previously tolerated BENLYSTA. Generally, reactions occurred within hours of the infusion but may occur later. Non-acute hypersensitivity reactions (eg, rash, nausea, fatigue, myalgia, headache, and facial edema) typically occurred up to a week after infusion. Patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk. With BENLYSTA SC, systemic hypersensitivity reactions were similar to those in IV trials. Healthcare providers (HCPs) should monitor patients during and after IV administration and be prepared to manage anaphylaxis; discontinue immediately in the event of a serious reaction. Premedication may mitigate or mask a hypersensitivity response. Advise patients about hypersensitivity symptoms and instruct them to seek immediate medical care if a reaction occurs.

Infusion Reactions: Serious infusion reactions (eg, bradycardia, myalgia, headache, rash, urticaria, and hypotension) were reported in adults. HCPs should monitor patients and manage reactions if they occur. Premedication may mitigate or mask a reaction. If an infusion reaction develops, slow or interrupt the infusion.

Depression and Suicidality: In adult trials, psychiatric events reported more frequently with BENLYSTA IV related primarily to depression-related events, insomnia, and anxiety; serious psychiatric events included serious depression and suicidality, including 2 completed suicides. No serious depression-related events or suicides were reported in the BENLYSTA SC trial. Before adding BENLYSTA, assess patients' risk of depression and suicide and monitor them during treatment. Instruct patients/caregivers to contact their HCP if they experience new/worsening depression, suicidal thoughts, or other mood changes.

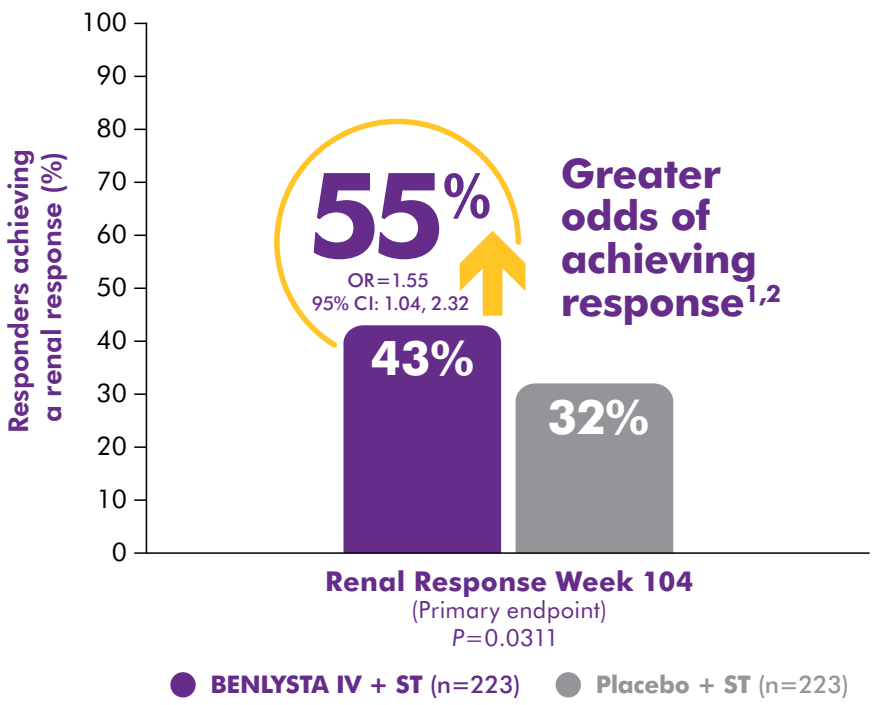
Malignancy: The impact of BENLYSTA on the development of malignancies is unknown; its mechanism of action could increase the risk for malignancies.

Immunization: Live vaccines should not be given for 30 days before or concurrently with BENLYSTA as clinical safety has not been established.

Use With Biologic Therapies: BENLYSTA has not been studied and is not recommended in combination with other biologic therapies, including B-cell targeted therapies.

FOR LUPUS NEPHRITIS

Significantly more patients on BENLYSTA achieved renal response vs standard therapy (ST) alone at Week 104*†



* In a Phase III double-blind multicenter study, 448 adult patients with active lupus nephritis were randomized to BENLYSTA + ST or placebo + ST as induction and maintenance therapy. BENLYSTA 10 mg/kg or placebo was administered by intravenous (IV) infusion over 1 hour on Days 0, 14, and 28, and at 4-week intervals thereafter through Week 104. Renal response (Primary Efficacy Renal Response) at Week 104 was defined as eGFR ≥60 mL/min/1.73m^2 or no worse than 20% below pre-flare value, uPCR ≤0.7, and not a treatment failure. Treatment failures were defined as patients who received prohibited medications. To be considered a responder, patients had to meet all 3 components.

† ST was defined as mycophenolate mofetil + high-dose steroids for induction, followed by mycophenolate mofetil + low-dose steroids for maintenance; OR cyclophosphamide + high-dose steroids for induction, followed by azathioprine + low-dose steroids for maintenance.

References: 1. Data on File, GSK. **2.** Furie R, Rovin BH, Houssiau F, *et al.* Two-year, randomized, controlled trial of belimumab in lupus nephritis. *N Engl J Med.* 2020;383:1117-1128.

See more results at DiscoverBENLYSTAHCP.com

IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS

The most common serious adverse reactions in adult SLE clinical trials were serious infections, BENLYSTA IV 6.0% (placebo 5.2%), some of which were fatal infections, BENLYSTA IV 0.3% (placebo 0.1%). Adverse reactions occurring in ≥3% of adults and ≥1% more than placebo: nausea 15% (12%); diarrhea 12% (9%); pyrexia 10% (8%); nasopharyngitis 9% (7%); bronchitis 9% (5%); insomnia 7% (5%); pain in extremity 6% (4%); depression 5% (4%); migraine 5% (4%); pharyngitis 5% (3%); cystitis 4% (3%); leukopenia 4% (2%); viral gastroenteritis 3% (1%).

In adult patients with active lupus nephritis, serious infections occurred in 14% of patients receiving BENLYSTA IV (placebo 17%), some of which were fatal infections, BENLYSTA 0.9% (placebo 0.9%). Adverse reactions occurring in ≥3% of adults and ≥1% more than placebo were consistent with the known safety profile of BENLYSTA IV in SLE patients.

Adverse reactions in pediatric patients aged ≥5 years receiving BENLYSTA IV were consistent with those observed in adults.

The safety profile observed for BENLYSTA SC in adults was consistent with the known safety profile of BENLYSTA IV with the exception of local injection site reactions.

USE IN SPECIFIC POPULATIONS

Pregnancy: There are insufficient data in pregnant women to establish whether there is drug-associated risk for major birth defects or miscarriage. After a risk/benefit assessment, if prevention is warranted, women of childbearing potential should use contraception during treatment and for ≥4 months after the final treatment.

Pregnancy Registry: HCPs are encouraged to register patients and pregnant women are encouraged to enroll themselves by calling 1-877-681-6296.

Lactation: No information is available on the presence of belimumab in human milk, the effects on the breastfed infant, or the effects on milk production. Consider developmental and health benefits of breastfeeding with the mother's clinical need for BENLYSTA and any potential adverse effects on the breastfed child or from the underlying maternal condition.

Pediatric Use: The safety and effectiveness have not been established for BENLYSTA IV in SLE patients <5 years of age, and in active LN patients <18 years of age, and for BENLYSTA SC in SLE and LN patients <18 years of age.

Please see Brief Summary of full Prescribing Information for BENLYSTA on the following pages.

Benlysta (belimumab)
Intravenous Use 120 mg/vial
Subcutaneous Use 200 mg/mL

BRIEF SUMMARY

BENLYSTA (belimumab) for injection, for intravenous use.
BENLYSTA (belimumab) injection, for subcutaneous use.

The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE

BENLYSTA (belimumab) is indicated for the treatment of:

- patients aged 5 years and older with active, autoantibody-positive systemic lupus erythematosus (SLE) who are receiving standard therapy, and
- adult patients with active lupus nephritis who are receiving standard therapy.

Limitations of Use

The efficacy of BENLYSTA has not been evaluated in patients with severe active central nervous system lupus. BENLYSTA has not been studied in combination with other biologics.

Use of BENLYSTA is not recommended in these situations.

4 CONTRAINDICATIONS

BENLYSTA is contraindicated in patients who have had anaphylaxis with belimumab.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections: Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents, including BENLYSTA. Overall, the incidence of serious infections in controlled trials was similar in patients receiving BENLYSTA compared with placebo, whereas fatal infections occurred more frequently in patients receiving BENLYSTA.

In controlled trials of BENLYSTA administered intravenously in adults with SLE, the incidence of serious infections was 6.0% in patients receiving BENLYSTA compared with 5.2% in patients receiving placebo. The most frequent serious infections included pneumonia, urinary tract infections, cellulitis, and bronchitis. Fatal infections occurred in 0.3% of patients receiving BENLYSTA and in 0.1% of patients receiving placebo *[see Adverse Reactions (6.1)]*.

In a controlled trial of active lupus nephritis, adults received BENLYSTA administered intravenously plus standard therapy or placebo plus standard therapy. Serious infections occurred in 14% of patients receiving BENLYSTA and in 17% of patients receiving placebo. Fatal infections occurred in 0.9% (2/224) of patients receiving BENLYSTA and in 0.9% (2/224) of patients receiving placebo *[see Adverse Reactions (6.1)]*.

In a postmarketing safety trial of BENLYSTA administered intravenously to adults with SLE, the incidence of serious infections was 3.7% in patients receiving BENLYSTA compared with 4.1% in patients receiving placebo. Fatal infections occurred in 0.45% of patients receiving BENLYSTA and 0.15% of patients receiving placebo *[see Adverse Reactions (6.1)]*.

In a controlled trial of BENLYSTA administered subcutaneously in adults with SLE, the incidence of serious infections was 4.1% in patients receiving BENLYSTA and 5.4% in patients receiving placebo. Fatal infections occurred in 0.5% of patients receiving BENLYSTA and in none of the patients receiving placebo *[see Adverse Reactions (6.2)]*.

Consider the risk and benefit before initiating treatment with BENLYSTA in patients with severe or chronic infections. Consider interrupting therapy with BENLYSTA in patients who develop a new infection while receiving it and monitor these patients closely.

Progressive Multifocal Leukoencephalopathy (PML): Cases of JC virus-associated PML resulting in neurological deficits, including fatal cases, have been reported in patients with SLE receiving immunosuppressants, including BENLYSTA. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. Consider the diagnosis of PML in any patient presenting with new-onset or deteriorating neurological signs and symptoms and consult with a neurologist or other appropriate specialist as clinically indicated. In patients with confirmed PML, consider stopping immunosuppressant therapy, including BENLYSTA.

5.2 Hypersensitivity Reactions, including Anaphylaxis: Acute hypersensitivity reactions, including anaphylaxis and death, have been reported in association with BENLYSTA. These events generally occurred within hours of the infusion; however, they may occur later. Non-acute hypersensitivity reactions including rash, nausea, fatigue, myalgia, headache, and facial edema, have been reported and typically occurred up to a week following the most recent infusion. Hypersensitivity, including serious reactions, has occurred in patients who have previously tolerated infusions of BENLYSTA. Limited data suggest that patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk.

In the controlled clinical trials of BENLYSTA administered intravenously in adults with SLE, hypersensitivity reactions (occurring on the same day of infusion) were reported in 13% (191/1,458) of patients receiving BENLYSTA and 11% (76/675) of patients receiving placebo. Anaphylaxis was observed in 0.6% (9/1,458) of patients receiving BENLYSTA and 0.4% (3/675) of patients receiving placebo. Manifestations included hypotension, angioedema, urticaria or other rash, pruritus, and dyspnea. Due to overlap in signs and symptoms, it was not possible to distinguish between hypersensitivity reactions and infusion reactions in all cases *[see Warnings and Precautions (5.3)]*. Some patients (13%) received premedication, which may have mitigated or masked a hypersensitivity response; however, there is insufficient evidence to determine whether premedication diminishes the frequency or severity of hypersensitivity reactions.

In a controlled trial of BENLYSTA administered subcutaneously in adults with SLE, systemic hypersensitivity reactions were similar to those observed in the intravenous clinical trials.

BENLYSTA for intravenous use should be administered by healthcare providers prepared to manage anaphylaxis. In the event of a serious reaction, discontinue BENLYSTA immediately and administer appropriate medical therapy. Monitor patients during infusion and for an appropriate period of time after intravenous administration of BENLYSTA. Consider administering premedication as prophylaxis prior to intravenous dosing *[see Dosage and Administration (2.1) of full prescribing information]*.

Inform patients receiving BENLYSTA of the signs and symptoms of hypersensitivity reactions and instruct them to seek immediate medical care should a reaction occur.

5.3 Infusion Reactions: In the controlled clinical trials of BENLYSTA administered intravenously in adults with SLE, adverse events associated with the infusion (occurring on the same day of the infusion) were reported in 17% (251/1,458) of patients receiving BENLYSTA and 15% (99/675) of patients receiving placebo. Serious infusion reactions (excluding hypersensitivity reactions) were reported in 0.5% of patients receiving BENLYSTA and 0.4% of patients receiving placebo and included bradycardia, myalgia, headache, rash, urticaria, and hypotension. The most common infusion reactions (≥3% of patients receiving BENLYSTA) were headache, nausea, and skin reactions. Due to overlap in signs and symptoms, it was not possible to distinguish between hypersensitivity reactions and infusion reactions in all cases *[see Warnings and Precautions (5.2)]*. Some patients (13%) received premedication, which may have mitigated or masked an infusion reaction; however, there is insufficient evidence to determine whether premedication diminishes the frequency or severity of infusion reactions. Consider administering premedication as prophylaxis prior to intravenous dosing *[see Dosage and Administration (2.1) of full prescribing information, Adverse Reactions (6.1)]*.

BENLYSTA for intravenous use should be administered by healthcare providers prepared to manage infusion reactions. The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. Healthcare providers should be aware of the risk of hypersensitivity reactions, which may present as infusion reactions, and monitor patients closely *[see Warnings and Precautions (5.2)]*.

5.4 Depression and Suicidality: In controlled clinical trials of BENLYSTA administered intravenously in adults with SLE, psychiatric events were reported more frequently in patients treated with BENLYSTA (16%) than with placebo (12%) and were related primarily to depression-related events, insomnia, and anxiety. Serious psychiatric events and serious depression were reported in 0.8% and 0.4% of patients receiving BENLYSTA and 0.4% and 0.1% of patients receiving placebo, respectively. Two suicides (0.1%) were reported in patients receiving BENLYSTA (one with 10 mg/kg and one with 1 mg/kg) *[see Adverse Reactions (6.1]*.

In a postmarketing trial of BENLYSTA administered intravenously in adults with SLE, serious psychiatric events and serious depression were reported in 1.0% and 0.3% of patients receiving BENLYSTA, and 0.3% and <0.1% of patients receiving placebo, respectively. The overall incidence of suicidal ideation or behavior or self-injury without suicidal intent was 0.7% of patients receiving BENLYSTA and 0.2% of patients receiving placebo. No suicide was reported in either group *[see Adverse Reactions (6.1)]*.

The intravenous trials above did not exclude patients with a history of psychiatric disorders.

In a controlled trial of BENLYSTA administered subcutaneously in adults with SLE, which excluded patients with a history of psychiatric disorders, psychiatric events were reported less frequently in patients receiving BENLYSTA (6%) compared with those receiving placebo (11%). There were no serious depression-related events or suicides reported in either group *[see Adverse Reactions (6.2)]*.

Assess the risk of depression and suicide considering the patient's medical history and current psychiatric status before treatment with BENLYSTA and continue to monitor patients during treatment. Instruct patients receiving BENLYSTA (and caregivers, if applicable) to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts or behavior, or other mood changes. Consider the risk and benefit of continued treatment with BENLYSTA for patients who develop such symptoms.

5.5 Malignancy: The impact of treatment with BENLYSTA on the development of malignancies is not known. In the controlled clinical trials of BENLYSTA administered intravenously in adults with SLE, malignancies (including non-melanoma skin cancers) were reported in 0.4% of patients receiving BENLYSTA and 0.4% of patients receiving placebo. In the intravenous controlled clinical trials, malignancies, excluding non-melanoma skin cancers, were observed in 0.2% (3/1,458) and 0.3% (2/675) of patients receiving BENLYSTA and placebo, respectively. In the controlled clinical trial of BENLYSTA administered subcutaneously in adults with SLE (N=836), the data were similar. The mechanism of action of BENLYSTA could increase the risk for the development of malignancies.

5.6 Immunization: Live vaccines should not be given for 30 days before or concurrently with BENLYSTA as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving BENLYSTA or the effect of BENLYSTA on new immunizations. Because of its mechanism of action, BENLYSTA may interfere with the response to immunizations.

5.7 Concomitant Use with Other Biologic Therapies: BENLYSTA has not been studied in combination with other biologic therapies, including B-cell targeted therapies. Therefore, use of BENLYSTA is not recommended in combination with biologic therapies.

6 ADVERSE REACTIONS

The following have been observed with BENLYSTA and are discussed in detail in the Warnings and Precautions section:

- **Serious Infections** *[see Warnings and Precautions (5.1)]*
- **Hypersensitivity Reactions, including Anaphylaxis** *[see Warnings and Precautions (5.2)]*
- **Infusion Reactions** *[see Warnings and Precautions (5.3)]*
- **Depression and Suicidality** *[see Warnings and Precautions (5.4)]*
- **Malignancy** *[see Warnings and Precautions (5.5)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience with Intravenous Administration

Adults: The data described in Table 1 reflect exposure to BENLYSTA administered intravenously plus standard therapy compared with placebo plus standard therapy in 2,133 adult patients with SLE in 3 controlled trials (Trials 1, 2, and 3). Patients received BENLYSTA plus standard therapy at doses of 1 mg/kg (n=673), 4 mg/kg (n=111; Trial 1 only), or 10 mg/kg (n=674), or placebo plus standard therapy (n=675) intravenously over a 1-hour period on Days 0, 14, 28, and then every 28 days. In 2 of the trials (Trial 1 and Trial 3), treatment was given for 48 weeks, while in the other trial (Trial 2) treatment was given for 72 weeks *[see Clinical Studies (14.1 in full prescribing information)]*. Because there was no apparent dose-related increase in the majority of adverse events observed with BENLYSTA, the safety data summarized below are presented for the 3 intravenous doses pooled, unless otherwise indicated; the adverse reaction table displays the results for the recommended intravenous dose of 10 mg/kg compared with placebo.

The population had a mean age of 39 years (range: 18 to 75): 94% were female, and 52% were White. In these trials, 93% of patients treated with BENLYSTA plus standard therapy reported an adverse event compared with 92% treated with placebo plus standard therapy.

The most common serious adverse events were serious infections (6.0% and 5.2% in the groups receiving BENLYSTA and placebo plus standard therapy, respectively), some of which were fatal *[see Warnings and Precautions (5.1)]*.

The most commonly reported adverse events, occurring in ≥5% of patients in clinical trials, were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, and pharyngitis.

The proportion of patients who discontinued treatment due to any adverse reaction during the controlled clinical trials was 6.2% for patients receiving BENLYSTA plus standard therapy and 7.1% for patients receiving placebo plus standard therapy. The most common adverse reactions resulting in discontinuation of treatment (≥1% of patients receiving BENLYSTA or placebo) were infusion reactions (1.6% BENLYSTA and 0.9% placebo), lupus nephritis (0.7% BENLYSTA and 1.2% placebo), and infections (0.7% BENLYSTA and 1.0% placebo).

Adverse reactions, regardless of causality, occurring in at least 3% of patients with SLE who received BENLYSTA 10 mg/kg plus standard therapy and at an incidence at least 1% greater than that observed with placebo plus standard therapy in 3 controlled trials (Trials 1, 2, and 3) were: nausea 15% and 12%; diarrhea 12% and 9%; pyrexia 10% and 8%; nasopharyngitis 9% and 7%; bronchitis 9% and 5%; insomnia 7% and 5%; pain in extremity 6% and 4%; depression 5% and 4%; migraine 5% and 4%; pharyngitis 5% and 3%; cystitis 4% and 3%; leukopenia 4% and 2%; viral gastroenteritis 3% and 1%.

Infections: In the controlled clinical trials of BENLYSTA administered intravenously in adults with SLE, the overall incidence of infections was 71% in patients receiving BENLYSTA compared with 67% in patients receiving placebo. The most frequent infections (>5% of patients receiving BENLYSTA) were upper respiratory tract infection, urinary tract infection, nasopharyngitis, sinusitis, bronchitis, and influenza. Infections leading to discontinuation of treatment occurred in 0.7% of patients receiving BENLYSTA and 1.0% of patients receiving placebo. Serious infections occurred in 6.0% of patients receiving BENLYSTA and in 5.2% of patients receiving placebo. The most frequent serious infections included pneumonia, urinary tract infection, cellulitis, and bronchitis. Fatal infections occurred in 0.3% (4/1,458) of patients receiving BENLYSTA and in 0.1% (1/675) of patients receiving placebo.

In a randomized, double-blind, placebo-controlled, 104-week trial of active lupus nephritis in adults receiving BENLYSTA administered intravenously (N=448), the overall incidence of infections was 82% in patients receiving BENLYSTA compared with 76% in patients receiving placebo. Serious infections occurred in 14% of patients receiving BENLYSTA and in 17% of patients receiving placebo. Fatal infections occurred in 0.9% (2/224) of patients receiving BENLYSTA and in 0.9% (2/224) of patients receiving placebo.

In a randomized, double-blind, placebo-controlled, 52-week, postmarketing safety trial of BENLYSTA administered intravenously in adults with SLE (N=4,003), the incidence of serious infections was 3.7% in patients receiving BENLYSTA compared with 4.1% in patients receiving placebo. Serious infections leading to discontinuation of treatment occurred in 1.0% of patients receiving BENLYSTA and in 0.9% of patients receiving placebo. Fatal infections occurred in 0.45% (9/2,002) of patients receiving BENLYSTA and in 0.15% (3/2,001) of patients receiving placebo, where the incidence of all-cause mortality was 0.50% (10/2,002) in patients receiving BENLYSTA and 0.40% (8/2,001) in patients receiving placebo.

Depression and Suicidality: In controlled clinical trials of BENLYSTA administered intravenously in adults with SLE (N=2,133), psychiatric events were reported more frequently with BENLYSTA (16%) than with placebo (12%), primarily related to depression-related events (6.3% BENLYSTA; 4.7% placebo), insomnia (6.0% BENLYSTA; 5.3% placebo), and anxiety (3.9% BENLYSTA; 2.8% placebo). Serious psychiatric events were reported in 0.8% (12/1,458) of patients receiving BENLYSTA and 0.4% (3/675) of patients receiving placebo. Serious depression was reported in 0.4% (6/1,458) of patients receiving BENLYSTA and 0.1% (1/675) of patients receiving placebo. Two suicides (0.1%) were reported in patients receiving BENLYSTA (one with 10 mg/kg and one with 1 mg/kg).

In a randomized, double-blind, placebo-controlled, 52-week, postmarketing safety trial of BENLYSTA administered intravenously in adults with SLE (N=4,003), serious psychiatric events were reported in 1.0% (20/2,002) of patients receiving BENLYSTA and 0.3% (6/2,001) of patients receiving placebo. Serious depression was reported in 0.3% (7/2,002) of patients receiving BENLYSTA and in <0.1% (1/2,001) receiving placebo. The overall incidence of serious suicidal ideation or behavior or self-injury without suicidal intent was 0.7% (15/2,002) of patients receiving BENLYSTA and 0.2% (5/2,001) of patients receiving placebo. On the Columbia-Suicide Severity Rating Scale (C-SSRS), 2.4% (48/1,974) of patients receiving BENLYSTA reported suicidal ideation or behavior compared with 2.0% (39/1,988) of patients receiving placebo. No suicide was reported in either group.

The intravenous trials above did not exclude patients with a history of psychiatric disorders.

Black/African-American Patients: The safety of BENLYSTA 10 mg/kg administered intravenously plus standard therapy (n=331) compared with placebo plus standard therapy (n=165) in Black patients with SLE (Trial 4) was consistent with the known safety profile of BENLYSTA administered intravenously plus standard therapy in the overall population *[see Clinical Studies (14.1) of full prescribing information]*.

(continued on next page)

Benlysta (belimumab)

Lupus Nephritis: The safety of BENLYSTA 10 mg/kg administered intravenously plus standard therapy (n=224) compared with placebo plus standard therapy (n=224) was evaluated in adults with lupus nephritis for up to 104 weeks (Trial 5) *[see Clinical Studies (14.2) of full prescribing information]*. The adverse reactions observed were consistent with the known safety profile of BENLYSTA administered intravenously plus standard therapy in patients with SLE. Cases of myelosuppression, including febrile neutropenia, leukopenia, and pancytopenia, were observed in subjects who received induction therapy with cyclophosphamide followed by maintenance therapy with azathioprine, or mycophenolate.

Pediatric Patients: The safety of BENLYSTA administered intravenously plus standard therapy (n=53) compared with placebo plus standard therapy (n=40) was evaluated in 93 pediatric patients with SLE (Trial 6). The adverse reactions observed were consistent with those observed in adults *[see Clinical Studies (14.3) of full prescribing information]*.

6.2 Clinical Trials Experience with Subcutaneous Administration in Adults: The data described below reflect exposure to BENLYSTA administered subcutaneously plus standard therapy compared with placebo plus standard therapy in 836 patients with SLE in a controlled trial (Trial 7). In addition to standard therapy, patients received BENLYSTA 200 mg (n=556) or placebo (n=280) (2:1 randomization) once weekly for up to 52 weeks *[see Clinical Studies (14.4) of full prescribing information]*.

The overall population had a mean age of 39 years (range: 18 to 77), 94% were female, and 60% were White. In the trial, 81% of patients treated with BENLYSTA plus standard therapy reported an adverse event compared with 84% treated with placebo plus standard therapy. The proportion of patients who discontinued treatment due to any adverse reaction during the controlled clinical trial was 7.2% of patients receiving BENLYSTA plus standard therapy and 8.9% of patients receiving placebo plus standard therapy.

The safety profile observed for BENLYSTA administered subcutaneously plus standard therapy was consistent with the known safety profile of BENLYSTA administered intravenously plus standard therapy, with the exception of local injection site reactions.

Infections

In a controlled trial of BENLYSTA administered subcutaneously in adults with SLE (N=836), the overall incidence of infections was 55% in patients receiving BENLYSTA compared with 57% in patients receiving placebo (serious infections: 4.1% with BENLYSTA and 5.4% with placebo). The most commonly reported infections with BENLYSTA administered subcutaneously were similar to those reported with BENLYSTA administered intravenously. Fatal infections occurred in 0.5% (3/556) of patients receiving BENLYSTA and in no patients receiving placebo (0/280).

Depression and Suicidality

In a controlled trial of BENLYSTA administered subcutaneously in adults with SLE (N=836), which excluded patients with a history of psychiatric disorders, psychiatric events were reported in 6% of patients receiving BENLYSTA and 11% of patients receiving placebo. Depression-related events were reported in 2.7% (15/556) of patients receiving BENLYSTA and 3.6% (10/280) of patients receiving placebo. Serious psychiatric events were reported in 0.2% (1/556) of patients receiving BENLYSTA and in no patients receiving placebo. There were no serious depression-related events or suicides reported in either group. On the C-SSRS, 1.3% (7/554) of patients receiving BENLYSTA reported suicidal ideation or behavior compared with 0.7% (2/277) of patients receiving placebo.

Injection Site Reactions

In a controlled clinical trial of BENLYSTA administered subcutaneously in adults with SLE (N=836), the frequency of injection site reactions was 6.1% (34/556) for patients receiving BENLYSTA plus standard therapy and 2.5% (7/280) for patients receiving placebo plus standard therapy. These injection site reactions (most commonly pain, erythema, hematoma, pruritus, and induration) were mild to moderate in severity. The majority (94%) did not necessitate discontinuation of treatment.

6.3 Postmarketing Experience: The following adverse reactions have been identified during postapproval use of BENLYSTA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Fatal anaphylaxis *[see Warnings and Precautions (5.2)]*.

6.4 Immunogenicity: As with all therapeutic proteins, there is potential for immunogenicity. In Trials 2 and 3 (intravenous dosing in adults with SLE), anti-belimumab antibodies were detected in 4 of 563 (0.7%) patients receiving BENLYSTA 10 mg/kg and in 27 of 559 (4.8%) patients receiving BENLYSTA 1 mg/kg. The reported frequency for the group receiving 10 mg/kg may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentrations. Neutralizing antibodies were detected in 3 patients receiving BENLYSTA 1 mg/kg. Three patients with anti-belimumab antibodies experienced mild infusion reactions of nausea, erythematous rash, pruritus, eyelid edema, headache, and dyspnea; none of the reactions was life-threatening. In Trial 4 (intravenous dosing in adult Black patients), anti-belimumab antibodies were detected in 2 of 321 (0.6%) patients receiving BENLYSTA 10 mg/kg during the 52-week, placebo-controlled period. In Trial 5 (intravenous dosing in adults with lupus nephritis), there was no formation of anti-belimumab antibodies in 224 patients receiving BENLYSTA 10 mg/kg plus standard therapy during the 104-week, placebo-controlled period. In Trial 6 (intravenous dosing in pediatric patients with SLE), there was no formation of anti-belimumab antibodies in 53 patients receiving BENLYSTA 10 mg/kg plus standard therapy during the 52-week placebo-controlled period. In Trial 7 (subcutaneous dosing in adults with SLE), there was no formation of anti-belimumab antibodies in 556 patients receiving BENLYSTA 200 mg during the 52-week placebo-controlled period.

The clinical relevance of the presence of anti-belimumab antibodies is not known.

The data reflect the percentage of patients whose test results were positive for antibodies to belimumab in specific assays.

7 DRUG INTERACTIONS

Formal drug interaction studies have not been performed with BENLYSTA. In clinical trials, BENLYSTA was administered concomitantly with other drugs, including corticosteroids, antimalarials, immunomodulatory and immunosuppressive agents (including azathioprine, cyclophosphamide, methotrexate, and mycophenolate), angiotensin pathway antihypertensives, HMG-CoA reductase inhibitors (statins), and/or non-steroidal anti-inflammatory drugs (NSAIDs) without evidence of a clinically meaningful effect of these concomitant medications on belimumab pharmacokinetics. The effect of belimumab on the pharmacokinetics of other drugs has not been evaluated *[see Clinical Pharmacology (12.3) of full prescribing information]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to BENLYSTA during pregnancy. Healthcare professionals are encouraged to register patients by calling 1-877-681-6296.

Risk Summary: Available data on use of BENLYSTA in pregnant women, from observational studies, published case reports, and postmarketing surveillance, are insufficient to determine whether there is a drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with SLE *(see Clinical Considerations)*. Monoclonal antibodies, such as belimumab, are actively transported across the placenta during the third trimester of pregnancy and may affect immune response in the in utero-exposed infant *(see Clinical Considerations)*. In an animal combined embryo-fetal and pre- and post-natal development study with monkeys that received belimumab by intravenous administration, there was no evidence of fetal harm with exposures approximately 9 times (based on intravenous administration) and 20 times (based on subcutaneous administration) the exposure at the maximum recommended human dose (MRHD). Belimumab-related findings in monkey fetuses and/or infants included reductions of B-cell counts, reductions in the density of lymphoid tissue B-lymphocytes in the spleen and lymph nodes, and altered IgG and IgM titers. The no-adverse-effect-level (NOAEL) was not identified for these findings; however, they were reversible within 3 to 12 months after the drug was discontinued *(see Data)*. Based on animal data and the mechanism of action of belimumab, the immune system in infants of treated mothers may be adversely affected. It is unknown, based on available data, whether immune effects, if identified, are reversible *[see Clinical Pharmacology (12.1) of full prescribing information]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk: Pregnant women with SLE are at increased risk of adverse pregnancy outcomes, including worsening of the underlying disease, premature birth, miscarriage, and intrauterine growth restriction. Maternal lupus nephritis increases the risk of hypertension and preeclampsia/eclampsia. Passage of maternal autoantibodies across the placenta may result in adverse neonatal outcomes, including neonatal lupus and congenital heart block.

Fetal/Neonatal Adverse Reactions: Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to BENLYSTA in utero. Monitor an infant of a treated mother for B-cell reduction and other immune dysfunction *[see Warnings and Precautions (5.6) and Animal Data (in 8.1) of full prescribing information]*.

Data *[see Data (in 8.1) of full prescribing information]*.

8.2 Lactation

Risk Summary: No information is available on the presence of belimumab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BENLYSTA, and any potential adverse effects on the breastfed child from BENLYSTA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception: Following an assessment of benefit versus risk, if prevention of pregnancy is warranted, females of reproductive potential should use effective contraception during treatment and for at least 4 months after the final treatment.

8.4 Pediatric Use: Intravenous administration of BENLYSTA in patients with SLE is indicated in children aged 5 years and older. Determination of efficacy in pediatric patients was based on pharmacokinetic (PK) and efficacy results from a pediatric SLE study (Trial 6), as well as PK exposure and extrapolation of the established efficacy of BENLYSTA plus standard therapy from the Phase 3 intravenous studies in adults with SLE. A randomized, double-blind, placebo-controlled, PK, efficacy, and safety study (Trial 6) to evaluate intravenously administered BENLYSTA 10 mg/kg plus standard therapy compared with placebo plus standard therapy over 52 weeks was conducted in 93 pediatric patients with SLE. The proportion of pediatric patients achieving an SRI-4 response was higher in patients receiving BENLYSTA plus standard therapy compared with placebo plus standard therapy. Pediatric patients receiving BENLYSTA plus standard therapy also had a lower risk of experiencing a severe flare compared with the placebo plus standard therapy *[see Clinical Studies (14.3) of full prescribing information]*.

The adverse event profile in pediatric patients was consistent with the overall population in the Phase 3 studies in adults *[see Adverse Reactions (6.1)]*.

Pharmacokinetics were evaluated in a total of 53 pediatric patients and were consistent with the adult population *[see Clinical Pharmacology (12.3) of full prescribing information]*. The safety and effectiveness of BENLYSTA have not been established in pediatric patients younger than 5 years of age.

The safety and effectiveness of intravenous administration of BENLYSTA have not been established in pediatric patients with active lupus nephritis younger than 18 years of age.

The safety and effectiveness of subcutaneous administration of BENLYSTA have not been established in pediatric patients younger than 18 years of age.

8.5 Geriatric Use: Clinical studies of BENLYSTA did not include sufficient numbers of subjects aged 65 or older to determine whether they respond differently from younger subjects. Use with caution in elderly patients.

8.6 Renal Impairment: No dosage adjustment is recommended in patients with renal impairment.

8.7 Hepatic Impairment: No dosage adjustment is recommended in patients with hepatic impairment.

8.8 Racial Groups: In Trial 2 and Trial 3 (intravenous dosing), SLE Responder Index-4 (SRI-4) response rates were lower for Black patients receiving BENLYSTA plus standard therapy relative to Black patients receiving placebo plus standard therapy *[see Clinical Studies (14.1) of full prescribing information]*.

In Trial 4 (intravenous dosing), a 2:1 randomized, placebo-controlled trial in Black patients, SLE Responder Index (SRI-S2K) response rates were higher for Black patients receiving BENLYSTA plus standard therapy (49%) relative to Black patients receiving placebo plus standard therapy (42%). However, the treatment difference was not statistically significant *[see Clinical Studies (14.1) of full prescribing information]*.

In Trial 7 (subcutaneous dosing), SRI-4 response was 45% (26/58) in Black patients receiving BENLYSTA plus standard therapy compared with 39% (13/33) in Black patients receiving placebo plus standard therapy *[see Clinical Studies (14.4) of full prescribing information]*.

The safety profile of BENLYSTA in Black patients was consistent with the known safety profile of BENLYSTA administered in the overall population *[see Adverse Reactions (6.1)]*.

10 OVERDOSAGE

There is limited experience with overdosage of belimumab. Adverse reactions reported in association with cases of overdose have been consistent with those expected for belimumab.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility:

Long-term animal studies have not been performed to evaluate the carcinogenic potential of belimumab. Effects on male and female fertility have not been directly evaluated in animal studies.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use) of full prescribing information.

Serious Infections: Advise patients that BENLYSTA may decrease their ability to fight infections, and that serious infections, including some fatal ones, occurred in patients receiving BENLYSTA in clinical trials. Ask patients if they have a history of chronic infections and if they are currently on any therapy for an infection *[see Warnings and Precautions (5.1)]*. Instruct patients to tell their healthcare provider if they develop signs or symptoms of an infection.

Progressive Multifocal Leukoencephalopathy: Advise patients to contact their healthcare professional if they experience new or worsening neurological symptoms such as memory loss, confusion, dizziness or loss of balance, difficulty talking or walking, or vision problems *[see Warnings and Precautions (5.1)]*.

Hypersensitivity Reactions/Anaphylaxis and Infusion Reactions: Educate patients on the signs and symptoms of hypersensitivity reactions and infusion reactions. Instruct patients to immediately tell their healthcare provider if they experience symptoms of an allergic reaction during or after the administration of BENLYSTA. Inform patients to tell their healthcare provider about possible delayed reactions that may include a combination of symptoms such as rash, nausea, fatigue, muscle aches, headache, and/or facial swelling that may occur after administration of BENLYSTA *[see Warnings and Precautions (5.2, 5.3)]*.

Depression and Suicidality: Instruct patients to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts, or other mood changes *[see Warnings and Precautions (5.4)]*.

Immunizations: Inform patients that they should not receive live vaccines while taking BENLYSTA. Response to vaccinations could be impaired by BENLYSTA *[see Warnings and Precautions (5.6)]*.

Pregnancy Registry: Inform patients that there is a pregnancy registry to monitor fetal outcomes of pregnant women exposed to BENLYSTA *[see Use in Specific Populations (8.1)]*.

Pregnancy: Inform female patients of reproductive potential that BENLYSTA may impact the immune system in infants of treated mothers and to inform their prescriber of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

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The Second COVID-19 Wave in India

Continued from page 1

were resumed. Inevitably, once the transmission started, it spread like wildfire. Professor Ashish K. Jha, Dean of Brown School of Public Health, has called the *Kumbh Mela* (religious mega-gathering) the largest superspreader event in the world (4).

During the Indian winter, when the caseloads were low, the health system also rapidly de-escalated. Rather than further improve preparedness in anticipation of a possible second wave (as had occurred in other parts of the world), it shut down COVID-19 facilities and ignored the need to bolster intensive care services. This meant that when the inevitable wave hit with ferocity, and people started seeking hospital care in large numbers, beds were scarce, hospitals ran out of oxygen, and healthcare professionals were stretched far beyond their capabilities. This culminated in thousands of deaths that could have been prevented.

As the vaccine capital of the world, India was well poised to vaccinate its population. However, the sense of complacency and misinformation meant many people were unwilling to get vaccinated. The government played its part at the global level by committing to export vaccines as part of its *Vaccine Maitri* (vaccine diplomacy program) (5). Initially, vaccinations started in a phased manner, with the elderly and those with comorbidities prioritized, but as caseloads rose sharply, the government announced opening it up to all adults. The resulting clamor and failure to increase the supply to match demand led to a massive shortage of vaccines (6). There have been issues with production and supply as well—the vaccination rate came down to 1.6 million doses/day from a peak of 3.5 million doses/day. It is estimated that only about 8% of the population has received one dose of the vaccine (7). Vaccinating India out of the pandemic, as in Israel, the United States, and the United Kingdom, seems unrealistic in the near future unless the country ramps up production and/or gets help in obtaining adequate stockpiles very soon.

In this chaotic environment, desperation to seek any effective therapy and the lack of any clear authoritative evidence-based guidance are driving the use of low-quality care including several completely outlandish remedies. Despite weak evidence of their benefit, there have been desperate searches for plasma therapy, in addition to multiple antimicrobials. This has prompted many academics to appeal to government for responsible, evidence-based guidelines (8). It is common to see infected patients carrying prescriptions that have more than 10 drugs, encouraging profiteering and black marketing. Practitioners of alternative systems of medicine openly claim curative powers in remedies peddled by them.

Finally, major doubts have been raised about the reporting of cases and COVID-19 deaths. Epidemiologists and data modelers estimate that the actual number of daily cases could be 5–10 times the official figures, which at the time of writing, is around 400,000/day. Similarly, Professor Murad Banaji of Middlesex University, London, believes the actual death count could be in excess of 1 million, against the officially reported 240,000 (9).

With a country as densely populated as India, the virus has managed to spiral out of control due to the casual approach toward COVID-19-sensible behavior by the public, mismanagement by the administration, and lack of adequate healthcare facilities including hospital beds, oxygen supply, and vaccination, compounded by the government's haste in exporting medical resources to other countries. India has just about two intensive care unit (ICU) beds for every 100,000 people, compared to 29 in Germany (10).

Chaos in kidney care

The large-scale disruptions in dialysis and transplant services have been well documented (1). Some of these, in particular transplants, had just resumed when the second wave shut them down once again. Even though dialysis patients were included in the priority list for vaccinations, only a small portion has actually been vaccinated.

There have been a few examples of the community coming together and developing appropriate responses. A COVID-19 hemodialysis unit preparedness checklist designed by prominent nephrologists from around the country made dialysis practices during COVID-19 uniform across India (11). The city of Mumbai set up a project by the local government (Project Victory), which came up with a website to facilitate the coordination of care (https://covidialysis.in/) for COVID-19-positive or suspected patients. This significantly eased the pressure on treating nephrologists as well as patients and brought about a significant drop in the number of skipped dialysis sessions. In many communities, an informal network of providers including rural medical practitioners, frontline health workers, non-governmental organizations, and community self-help groups came together to meet with the chronic care needs of the people, including arranging medications and teleconsultations (12).

The ubiquitous shots of ghoulish orange glows of funeral pyres and news of the collapsing healthcare system, mountains of corpses, and the nationwide hunt for oxygen and other medical supplies remind us that this did not happen just over the past 15 months but was 50 years in the making. The systematic neglect of the healthcare system by the political and administrative class and failure of the population at large to make this a mainstream issue on which to ask for accountability from elected representatives have been assimilated in popular consciousness. Only those not familiar with the deficiencies of the system are shocked by what they are seeing. Hope is being expressed that maybe this will be the shock that will jolt the country into undertaking these much-needed reforms. If that were to happen, indeed, that would be a bright and welcome light at the end of this very long and dark tunnel. ■

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References

1. Ramachandran R, Jha V. Adding insult to injury: Kidney replacement therapy during COVID-19 in India. *Kidney Int* 2020; 98:238–239. doi: 10.1016/j.kint.2020.04.019
2. Vaidyanathan G. Coronavirus variants are spreading in India—what scientists know so far. *Nature* [published online ahead of print May 11, 2021]. doi: 10.1038/d41586-021-01274-7; https://www.nature.com/articles/d41586-021-01274-7
3. Bhattacharya S, et al. Coronavirus strain found in India is a 'variant of concern,' WHO says. B.1.617 becomes fourth variant so classified by agency, which says it may be more transmissible than some others. *The Wall Street Journal*. May 10, 2021. https://www.wsj.com/articles/coronavirus-strain-found-in-india-is-a-variant-of-concern-who-says-11620662311?mod=itp_wsj&yptr=yahoo
4. YouTube. Kumbh Mela Shahi Snans would be biggest super-spreaders in this pandemic's history—Dr. Ashish Jha. *The Wire*. May 6, 2021. https://www.youtube.com/watch?v=hSGASl_KTgk
5. Vinayak AJ. Vaccine Maitri: A Sanjeevini for the world. *The Hindu Business Line*. March 4, 2021. https://www.thehindubusinessline.com/news/variety/vaccine-maitri-a-sanjeevini-for-the-world/article33989241.ece
6. Alluri A. India's Covid vaccine shortage: The desperate wait gets longer. BBC News. May 1, 2021. https://www.status/1391725837729206279?s=20
7. Bhattacharya A, Shendruk A. India's Covid-19 vaccination program is alarmingly behind schedule. *Quartz India*. May 5, 2021. https://qz.com/india/2004984/how-long-until-indians-get-vaccinated/
8. Bhaumik S. (@DrSoumyadeepB) "Concerned clinicians, public health professionals & scientists from…." Twitter. May 10, 2021. https://twitter.com/DrSoumyadeepB/status/1391725837729206279?s=20
9. YouTube. Watch: 1 million Indians may have already died of COVID. *The Wire*. September 5, 2021. https://science.thewire.in/health/watch-1-million-indians-may-havealready-died-of-covid-murad-banaji-karan-thapar/
10. Vijayaraghavan BKT, et al. Challenges in the delivery of critical care in India during the COVID-19 pandemic. *J Intensive Care Soc* 2020; 0:1–7. doi: 10.1177/1751143720952590; https://doi.org/10.1177/1751143720952590
11. COVID-19 Kidney Health Action Group. Hemodialysis unit preparedness during and after COVID-19 pandemic. April 19, 2020; 1:1–8. https://www.georgeinstitute.org/sites/default/files/2020-04/hemodialysis-unit-preparedness-during-and-after-covid-19-pandemic.pdf
12. Gummidi B. Continuing dialysis in the face of the COVID-19 lockdown. The George Institute for Global Health. January 4, 2020. https://www.georgeinstitute.org/news/continuing-dialysis-in-the-face-of-the-covid-19-lockdown

Racism a Public Health Crisis

Continued from page 1

principles. It stated that the plan must "understand, address and dismantle racism, in order to undo how racism affects individual and population health and provide tools to engage actively and authentically with communities of color."

The Board of Health also plans to advocate for relevant policies that improve health in communities of color and build partnerships with other organizations confronting racism. Alejandro Diez, MD, associate professor and transplant nephrologist at The Ohio State University Wexner Medical Center, said the Columbus declarations "really opened up a lot of eyes and were a catalyst for looking inward."

The National League of Cities has been asked by at least 38 cities—compared to 20 in 2019—to help them develop racial equity plans, Soler Ossolinski said. While many of these programs are still in the planning stage, some of the declarations have mentioned various health conditions that disproportionately affect Black and/or Hispanic populations, including diabetes and hypertension, primary drivers of kidney diseases.

The declarations "matter because it now means someone is listening; someone is paying attention," said Maya Clark-Cutaia, PhD, RN, assistant professor at New York University Rory Meyers College of Nursing and an acute care nurse practitioner at Pennsylvania Hospital in Philadelphia.

"The problem with that is the lip service isn't enough," said Clark-Cutaia, who studies kidney disease and dialysis patients. "The reason these disparities have been perpetuated is because there's no action. It's going to take a lot more than declarations. We need investment in these communities. That's what's missing."

During the COVID-19 pandemic, kidney diseases have been in some cases a "perfect storm" of racial and ethnic health disparities; racism; disproportionate rates of diabetes, hypertension, and other comorbidities; and increased vulnerability to the coronavirus, Clark-Cutaia said.

"I feel like kidney disease patients are the embodiment of the many things that cause health disparities," she said.

Racial and ethnic minorities have higher rates of diabetes and hypertension than White Americans. In fact, Black Americans are 60% more likely than non-Hispanic White adults to have been diagnosed with diabetes, and non-Hispanic Black adults are 3.5 times more likely to be diagnosed with end-stage kidney disease compared to non-Hispanic White adults, according to the US Department of Health and Human Services (3). Black Americans are also more likely to get diagnosed later, be referred to a nephrologist later, and have longer kidney transplant waits, Clark-Cutaia said. A complex mixture of a person's social determinants of health—the conditions in which people are born, live, learn, work, play, worship, and age—affects disease risk and access to healthcare (4). Over the past year more cities and counties have recognized and acknowledged that structural racism affects a person's social determinants of health.

Clark-Cutaia says her Philadelphia kidney disease patients have unique vulnerabilities that are often out of their control. For example, they are instructed to cut down on their salt intake, but they tend to live in lower socioeconomic neighborhoods that are "food deserts," without supermarkets and affordable, nutritious food sources. These neighborhoods often have only convenience stores, with higher priced, high-sodium processed foods, an example of the structural problems that cities and counties have declared racism a public health crisis must address, Clark-Cutaia said.

Furthermore, adults in these communities often have lower education levels, which could make it difficult to understand or access complex nutrition guidelines. And those without cars often rely on the city bus system to go to a supermarket or to their doctor's and dialysis appointments. Diez pointed out that it can take some of his Columbus patients an hour and a half to get to an appointment by bus, including at least one bus transfer—a distance that takes only 30 minutes by car.

Then came COVID-19, adding to their risks and health disparities. Black Americans, American Indians, and Alaska Native and Hispanic Americans have disproportionately higher rates of COVID-19 cases, hospitalizations, and deaths (5). This does not surprise Clark-Cutaia because, she said, the communities in which they live have not addressed the social determinants of health that put them at greater risk. These adults are also more likely to be essential workers, such as grocery store employees and bus drivers, who cannot work from home and are more exposed to the virus. They may also live in multi-generational homes, which puts more people in their family at risk, Diez said.

"These are often the ones who prepare our food, clean our offices, stock our food at the supermarket," he said. "These are jobs that they depend on, and a lot of times you have one individual who the entire family depends on for income." While clinicians and researchers may point to racial and ethnic health disparities—and more and more, structural racism—individual racism also harms the health of racial and ethnic minorities. There are longstanding falsehoods that plague the care of these vulnerable populations, such as that Black people have a higher pain tolerance, Clark-Cutaia said. This belief does not recognize that race is a social construct with no biological basis. In addition, Black women, in particular, may be viewed as histrionic or as having a history of abuse of pain medicine.

In a 2016 study of 222 White medical students and residents, one-half reported that they believed at least one false statement about Black adults having higher pain tolerance. Participants who endorsed such false beliefs were more likely to show racial bias and inaccuracy in their pain treatment recommendations, according to the study, published in the *Proceedings of the National Academy of Sciences* (6).

In December 2020, a Black physician, Susan Moore, MD, died from COVID-19 after documenting her struggle to get proper medical care on social media. From her Indianapolis hospital bed, she explained in a Facebook video how a White male doctor said he was uncomfortable giving her more narcotics and suggested she be discharged. She also said she had to beg for remdesivir and for tests to be done. After complaining, she received more pain medication and was sent home. However, her case worsened, and she was taken to a new hospital only 12 hours after being discharged. She died about 2 weeks later (7).

Awareness of these stereotypes and unconscious biases can help nephrologists and other clinicians not fall prey to them—and step in when spotting other healthcare professionals acting on these falsehoods. In addition, "It's always good to approach a patient with empathy and humility," said Romita Mukerjee, MD, MHS, a nephrologist at a large private practice in the Raleigh, North Carolina, area.

Being more aware of the social determinants of health that affect patients is also important. "I think if there is a greater awareness of social determinants of health, that would improve empathy for the patient experience," Mukerjee said. "Instead of blaming patients, for example, for not following a healthy lifestyle or not showing up to their appointments the way they're supposed to or not taking their medications correctly, we would have a general understanding that there might be other life factors that play into some people's ability to take care of their health."

In Mukerjee's state, five counties, three health boards, and the North Carolina Healthcare Association (8) have declared racism a public health crisis, according to the National Association of Counties. (See what your county has done at www.naco.org/county-resources-race-equity-and-inclusion.) These declarations give validity to the problem, Mukerjee said. "Instead of it being an issue that just certain sections of the population have concerns about, it becomes more of a universal concern for the community, as well as for the larger healthcare system infrastructure in which we practice," she said.

"I think also, in a pragmatic way, declarations of this kind can have implications from a monetary standpoint, in terms of funding appropriate community resources and

Continued on page 10 >

Racism a Public Health Crisis

Continued from page 9

other public health interventions and more concrete structures that would allow for addressing racial disparities and health," she added. "So, I think, from a social and public health standpoint, these types of statements do have a lot of impact." ■

References

1. Franklin County Public Health. Franklin County Board of Health Declares Racism a Public Health Crisis. May 13, 2020. https://myfcph.org/franklin-county-board-of-health-declares-racism-a-public-health-crisis/
2. Tyson P, et al., sponsors. Resolution Declaring Racism a Public Health Crisis in Columbus (The City of Columbus City Council). 2021; 0095X-2020. https://www.columbus.gov/racismresolution/
3. US Department of Health and Human Services, Office of Minority Health. Diabetes and African Americans. December 19, 2019. https://minorityhealth.hhs.gov/omh/browse.aspx?lvl=4&lvlid=18
4. Office of Disease Prevention and Health Promotion. Social Determinants of Health. October 8, 2020. https://www.healthypeople.gov/2020/topics-objectives/topic/social-determinants-of-health
5. Artiga S, et al. Racial Disparities in COVID-19: Key Findings from Available Data and Analysis (Kaiser Family Foundation). August 17, 2020. https://www.kff.org/racial-equity-and-health-policy/issue-brief/racial-disparities-covid-19-key-findings-available-data-analysis/
6. Hoffman KM, et al. Racial bias in pain assessment and treatment recommendations, and false beliefs about biological differences between blacks and whites. *Proc Natl Acad Sci USA* 2016; 113:4296–4301. doi: 10.1073/pnas.1516047113
7. Associated Press. Black doctor dies of COVID after racist treatment complaints. December 25, 2020. https://apnews.com/article/race-and-ethnicity-indianapolis-media-social-media-coronavirus-pandemic-e9332a29f-d5a202664c4eae0989add10
8. Chambers S. North Carolina Healthcare Association Issues Statement on Racism as a Public Health Crisis (North Carolina Healthcare Association). November 17, 2020. https://www.ncha.org/2020/11/north-carolina-health-care-association-issues-statement-on-racism-as-a-public-health-crisis/

Did Roxadustat's Results Change from Blockbuster to Lackluster?

By Eric Seaborg

The news from FibroGen that roxadustat's safety profile is not as positive as it had previously reported considerably dampened enthusiasm for a drug that some had been awaiting with anticipation, according to several nephrologists.

Roxadustat is part of a new class of drugs, called hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs), for treating chronic kidney disease (CKD)-related anemia. HIF-PHIs have been touted as possibly safer replacements for the erythropoiesis-stimulating agents (ESAs) that have been mainstays for more than 30 years but are associated with cardiovascular risks.

The US Food and Drug Administration (FDA) surprised FibroGen and AstraZeneca, with whom the company has been collaborating in the drug's development, by asking for a meeting of its Cardiovascular and Renal Drugs Advisory Committee to review the company's new drug application for roxadustat. In turn, FibroGen stunned many observers when CEO Enrique Conterno announced in a press release on April 6, 2021: "As members of the senior management were preparing for the upcoming FDA Advisory Committee meeting, we became aware that the primary cardiovascular safety analyses included post-hoc changes to the stratification factors. We promptly decided to clarify this issue with the FDA and communicate with the scientific and investment communities."

The press release revealed that the company's previous evaluations had analyzed the drug's safety using "post-hoc stratification factors" rather than the proper "pre-specified stratification factors." FibroGen did not specify what the post-hoc changes in the stratification factors were, but the net effect was to remove roxadustat's evident safety advantage compared with the drugs it would presumably replace.

Previous publications had indicated that clinical trials had found roxadustat's safety to be superior to an ESA in incident dialysis patients, comparable to placebo in nondialysis patients, and comparable to an ESA in dialysis patients.

"All the superiority claims have now gone away … and the noninferiority claims, while not dramatically different, are a little bit worse," said Daniel W. Coyne, MD, professor of medicine at Washington University in St. Louis. He has been a site investigator for both roxadustat and daprodustat, another drug in the HIF-PHI class, and has been co-author on publications and abstracts for roxadustat. In a conflict-of-interest statement for the March 2021 *KN* article, "Novel Anemia Treatment: HIF-PH Inhibitors," Coyne stated he has been a consultant to the manufacturer of all three HIF-PHIs.

Losing their advantage

The lack of a safety advantage deals a significant blow to the drug's value as a replacement for ESAs, because it is the cardiovascular risks of ESAs that limit their use to patients on dialysis.

"I think this changes everything," Coyne told *ASN Kidney News*. "This means that they don't have a distinct advantage over our present standard of care, ESAs. It shifts the balance of what the role of these drugs is."

"We have all had safety concerns about the EPO [erythropoietin] analogs," said Katie Kwon, MD, FASN, a nephrologist in private practice at Lake Michigan Nephrology in St. Joseph, MI. "My thought process was, if this were safer than EPO and gave the same control of anemia, I would switch, for sure. I would not be excited to switch if it were equivalent, because I don't know how much it is going to cost. And it is a big deal to change up your protocols and learn the ins and outs of dosing a new drug. There is a significant investment of time and resources in that switch."

The NephJC podcast, Freely Filtered, devoted an edition to "The Roxadustat Statistical Shenanigans." One of the hosts, Swapnil Hiremath, MD, MPH, a staff nephrologist at Ottawa Hospital and associate professor of medicine at the University of Ottawa in Canada, said the original safety superiority numbers were "such a dramatic result [that] it was going to be a no-brainer that these drugs should be used. I was keen on using them. I am looking at them now and saying, 'I'm not sure I'll switch.' Now, I am [seeing them as] one more ESA."

Questions of credibility

In addition to the change in perception of the drug, the "statistical shenanigans" are leading to a large loss in credibility for FibroGen. Despite his involvement in research for the company, Coyne received no notice that it was about to issue what the company described as a "clarification." Coyne first heard about the press release while presenting at a National Kidney Foundation Spring Clinical Meetings symposium on the HIF-PHI class—when he received a question from the audience. "This deeply damages the reputation of FibroGen going forward," Coyne said. "I feel very misled, and I don't think there is any excuse for this. I don't know how this could happen accidentally."

"I am really shocked that a mistake of this magnitude was made," Kwon said. "If these drugs ultimately are approved, my evidence threshold for when I am going to feel comfortable using them is going to be quite a bit higher."

Roxadustat has been approved for use in Japan and China and had been considered to have the inside track to be the first in the class to gain FDA approval. The consensus of the speakers on the Freely Filtered podcast was that the drug had demonstrated efficacy, so they expected the FDA to approve it.

FibroGen said the revelation should not affect its application to the FDA, because "there is no change to the underlying data, or to the efficacy analyses from the Phase 3 program." That left observers all the more mystified about the reason for the presumed data manipulation, considering that the FDA would receive the raw data and make its own analysis and conclusions. Hiremath said the company had demonstrated "noninferiority…. That was good enough…. The FDA see[s] the raw data."

Still, the nephrology community will be watching the literature carefully for updates. At least one roxadustat paper "will be retracted and replaced with a corrected version," *KI Reports* Executive Editor Radha McLean said in an email to *ASN Kidney News*. "The authors are in the process of making the corrections" to the paper, "Pooled analysis of roxadustat for anemia in patients with kidney failure incident to dialysis" (1), which was published online on December 24, 2020. ASN retracted Abstract FR-OR131 [Pooled Efficacy and Cardiovascular (CV) Analyses of Roxadustat in the Treatment of Anemia in CKD Patients on and Not on Dialysis, submitted to ASN Kidney Week in 2019] (2). A statement on the ASN website reads: "This retraction is based on close review according to ASN meeting and peer-review policies, and this review identified significant concerns regarding the accuracy of the data presented at ASN Kidney Week 2019."

In two recent trials published in the *New England Journal of Medicine* (3, 4), the HIF-PHI vadadustat showed inferior outcomes in respect to cardiovascular events in CKD patients and noninferior outcomes in dialysis patients.

Coyne noted that the change in roxadustat's status could raise the stakes for the upcoming release of clinical trial results of the HIF-PHI daprodustat, given that the recent safety results from the other drug in the class, vadadustat, "looked inferior in the nondialysis patients vs. ESAs." Daprodustat trials "may turn out to be the tie-breaker" on the safety of this new class of drugs, he said. ■

References

1. Provenzano R, et al. Pooled analysis of roxadustat for anemia in patients with kidney failure incident to dialysis. *Kidney Int Rep* 2020; 6:613–623. doi: 10.1016/j.ekir.2020.12.018
2. Provenzano R, et al. Pooled efficacy and cardiovascular (CV) analyses of roxadustat in the treatment of anemia in CKD patients on and not on dialysis. ASN Kidney Week. November 8, 2019; FR-OR131. https://www.asn-online.org/education/kidneyweek/2019/program-abstract.aspx?controlId=3275139
3. Eckardt K-U, et al. Safety and efficacy of vadadustat for anemia in patients undergoing dialysis. *N Engl J Med* 2021; 384:1601–1612. doi: 10.1056/NEJMoa2025956
4. Chertow GM, et al. Vadadustat in patients with anemia and non-dialysis-dependent CKD. *N Engl J Med* 2021; 384:1589–1600. doi: 10.1056/NEJMoa2035938

What is the SARS-CoV-2 Vaccine Response in Patients Undergoing Hemodialysis?

By Nestor Toapanta and María José Soler

Chronic kidney disease is one of the risk factors that has been associated with higher risk of infection and mortality from SARS-CoV-2 (1, 2). The increased rate of SARS-CoV-2 infection has been related to the transportation and greater hospital exposure of patients (3, 4). In addition, the higher mortality rate has been, in part, ascribed to alterations in the immune system.

Vaccination against SARS-CoV-2 infection has raised hopes for the pandemic to end. Recent studies reported that the BNT162b2 (Pfizer-BioNTech) vaccine against SARS-CoV-2 is effective for symptomatic COVID-19 in the general population, being 94% after the second dose (5). However, little is known about the response in patients undergoing hemodialysis because these patients have not been included in clinical trials. Patients undergoing hemodialysis are known to have frequent infections, as well as a suboptimal response to vaccines, in part, due to alterations in both innate and adaptive immunity (6, 7) (Table 1).

Grupper et al. (8) evaluated the humoral response in 56 patients on hemodialysis against a control group composed of 95 healthcare workers after receiving two doses of the BNT162b2 vaccine (Pfizer-BioNTech). They demonstrated that dialysis patients developed a lower titer of anti-SARS-CoV-2 antibody than the control group, 21 days after vaccination (median dialysis patients 171 U/mL, interquartile range [IQR] 477.7 versus median controls 2500 U/mL, IQR 943.5), with an inverse correlation between age and immunoglobulin G6 (IgG6) levels (8). In another study with 81 patients on hemodialysis, 43 patients (53%) had an antibody titer lower than 200 U/mL, 22 patients (27%) had a titer lower than 29 U/mL, and 7 patients (9%) had no detectable antibodies at all (9). In concordance, Torreggiani et al. (10) demonstrated that about one-third of patients on hemodialysis develop neutralizing antibodies after the first dose of the BNT162b2 COVID-19 mRNA vaccine and that these are at low titers, as could be expected in a high-comorbidity cohort (median Charlson comorbidity index = 8).

A group from Israel (11) reported the following findings alter vaccination in 160 patients on chronic dialysis (127 hemodialysis and 33 peritoneal dialysis patients): 1) a lower response rate to the vaccine, 2) a lower anti-spike antibody level, and 3) a higher rate of COVID-19. Frantzen et al. (12), with the same vaccine, also demonstrated in a large population of hemodialysis patients (n = 244) that these patients are a hyporesponsive population with a 91% antibody-positivity rate, and only 60% of the patients presented an antibody level above 200 U/mL. Agur et al. (13) also evaluated seropositivity against the BNT162b2 vaccine (Pfizer-BioNTech) in 122 patients on hemodialysis and 22 patients on peritoneal dialysis who received two doses, 21 days apart, and a follow-up of up to 8 weeks after the second dose. These patients developed 93.4% antibodies at 36 days (IQR 32–40). Interestingly, a younger age was associated with higher antibody titers, whereas lack of response to the vaccine was associated with lower albumin and higher doses of iron sucrose administered (13). In this study, the seropositive response for SARS-CoV-2 anti-spike IgG at 2–6 weeks following the second dose of the BNT162b2 vaccination seems to be similar in hemodialysis and peritoneal dialysis patients (13). Lacson et al. (14) studied seropositivity after vaccination against SARS-CoV-2 infection in 186 patients on hemodialysis with two vaccines: BNT162b2/Pfizer (n = 148) and mRNA-1273/Moderna (n = 18). Overall, they did not find differences between the two vaccines. In addition, the seropositive rate was 165/186 (88.7%), with 70% at maximum titer with IgG levels, although in patients who had previously had the SARS-CoV-2 infection, the seropositivity was 100% (97% with IgG levels at the maximum titer) (14).

The evidence, to date, suggests that the majority of patients on hemodialysis seroconvert after the administration of the two doses of the vaccine (80%–96%); however, advanced age plays an important role in the development of antibodies. With the consideration that the population on hemodialysis is mostly elderly, it is convenient to study whether they require a third dose of the vaccine, especially in those patients who have not had COVID-19. In addition, the inclusion of these patients in clinical trials to evaluate their immunogenicity against the vaccine is an unmet need. To date, the studies on the effectivity of the SARS-CoV-2 vaccination in dialysis patients have been focused on the antibody response, and there is a clear gap of knowledge on its effectivity in terms of COVID-19 infection and severity of the disease. Currently, studies to assess long-term efficacy and safety of SARS-CoV-2 vaccination in patients on dialysis or after kidney transplantation are ongoing. ■

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References

1. Ortiz A, et al. Chronic kidney disease is a key risk factor for severe COVID-19: A call to action by the ERA-EDTA. *Nephrol Dial Transplant* 2021; 36:87–94. doi: 10.1093/ndt/gfaa314
2. Zúñiga J, et al. SARS-CoV-2 infection in patients with chronic kidney disease on haemodialysis. Evolution of SARS-CoV-2 CRP. [Article in Spanish.] *Nefrología* [published online ahead of print January 28, 2021]. doi: 10.1016/j.nefro.2020.12.008; https://www.sciencedirect.com/science/article/pii/S021169952100014X?via%3Dihub
3. Rincón A, et al. The keys to control a COVID-19 outbreak in a haemodialysis unit. *Clin Kidney J* 2020; 13:542–549. doi: 10.1093/CKJ/SFAA119
4. Hsu CM, et al. COVID-19 among US dialysis patients: Risk factors and outcomes from a national dialysis provider. *Am J Kidney Dis* 2021; 77:748–756.e1. doi: 10.1053/j.ajkd.2021.01.003
5. Dagan N, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med* 2021; 384:1412–1423. doi: 10.1056/nejmoa2101765
6. Lim WH, et al. Uremia impairs monocyte and monocyte-derived dendritic cell function in hemodialysis patients. *Kidney Int* 2007; 72:1138–1148. doi: 10.1038/sj.ki.5002425
7. Eleftheriadis T, et al. Infections in hemodialysis: A concise review. Part II: Blood transmitted viral infections. *Hippokratia* 2011; 15:120–126. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3209673/
8. Grupper A, et al. Humoral response to the Pfizer BNT162b2 vaccine in patients undergoing maintenance hemodialysis. *Clin J Am Soc Nephrol* [published online ahead of print April 6, 2021]. doi: 10.2215/cjn.03500321; https://cjasn.asnjournals.org/content/early/2021/04/05/CJN.03500321
9. Simon B, et al. Hemodialysis patients show a highly diminished antibody response after COVID-19 mRNA vaccination compared to healthy controls. *medRxiv* [preprint published online ahead of print March 26, 2021]. doi: https://doi.org/10.1101/2021.03.26.21254259; https://www.medrxiv.org/content/10.1101/2021.03.26.21254259v1
10. Torreggiani M, et al. Neutralizing SARS-CoV-2 antibody response in dialysis patients after the first dose of the BNT162b2 mRNA COVID-19 vaccine: The war is far from being won. *Kidney Int* [published online ahead of print April 20, 2021]. doi: 10.1016/j.kint.2021.04.010; https://www.kidney-international.org/article/S0085-2538(21)00395-1/fulltext
11. Yanay NB, et al. Experience with SARS-COV-2 BNT162b2 mRNA vaccine in dialysis patients. *Kidney Int* [published online ahead of print April 20, 2021]. doi: 10.1016/j.kint.2021.04.006; https://www.kidney-international.org/article/S0085-2538(21)00390-2/fulltext
12. Frantzen L, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in a hemodialysis cohort. *Nephrol Dial Transplant* [published online ahead of print April 24, 2021]. doi: 10.1093/ndt/gfab165; https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfab165/6251363
13. Agur T, et al. Antibody response to mRNA SARS-CoV-2 vaccine among dialysis patients—a prospective cohort study. *Nephrol Dial Transplant* [published online ahead of print April 11, 2021]. doi: 10.1093/ndt/gfab155; https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfab155/6220326
14. Lacson Jr E, et al. Immunogenicity of SARS-CoV-2 vaccine in dialysis. *medRxiv* [preprint published online ahead of print April 13, 2021]. doi: 10.1101/2021.04.08.21254779; https://www.medrxiv.org/content/10.1101/2021.04.08.21254779v1

Table 1. Studies demonstrating response to the vaccine against SARS-CoV-2 in hemodialysis patients after the second dose

Study	No. of patients on HD	Age	Measure of antibody time, days	Seroconversion, %
Grupper et al. (8)	56	74 ± 11	30 (27–34)	96.0
Simon et al. (9)	81	67 (34–86)	21	80.0
Torreggiani et al. (10)	101	69 ± 15	21	35.0*
Frantzen et al. (12)	244	76 ± 13	30	91.0
Agur et al. (13)	122	72 ± 12	36 (32–40)	93.4
Lacson et al. (14)	186	68 ± 12	23 ± 8	88.7

*Determinations of antibodies at 21 days after the first dose. HD, hemodialysis.

Identifying, Confronting, and Addressing Systemic Racism in US Nephrology

By Crystal A. Gadegbeku, Tod Ibrahim, Anupam Agarwal, and Susan E. Quaggin

In the United States, people who are Black or African American, Hispanic or Latinx, Indigenous or Native American, Asian American, and Native Hawaiian or other Pacific Islanders (NHPIs) are underpaid, financially disadvantaged, and underrepresented in corporate leadership and government. When compared to White Americans, minoritized people have higher rates of unemployment, have been denied opportunities to build wealth, are more likely to have mortgage applications rejected, face higher debt for student loans, and are less likely to have the same educational opportunities.

Besides experiencing discrimination and being poorer with fewer professional opportunities than White Americans, Black and Latinx Americans are less likely to have health insurance, have less access to health care, and experience lower-quality care when they do have access. They also have higher rates of kidney diseases, asthma, cancer, cardiovascular diseases, diabetes, HIV/AIDS, hypertension, and obesity, to name a few chronic diseases. The COVID-19 pandemic has accentuated and exacerbated these health disparities and inequities: Black, Latinx, and Indigenous people are more likely to be infected by and die from the virus, whereas White Americans disproportionately received more vaccinations in the early stages of the rollout (1).

Addressing these disparities and inequities requires identifying and confronting racism on a systemic level. Health status closely correlates with racism and socioeconomic status (as does allostatic load), which is further stagnated by a lack of upward mobility through multiple generations. In addition to health and health care, these social determinants of health include economic stability, social and community context, neighborhood and built environment, and education.

Unfortunately, the educational system in the United States (including undergraduate and graduate medical education) disadvantages people who are Black, Latinx, Native American, and NHPIs. Black Americans are currently 13.4% of the US population, but racism undermines their opportunity to pursue professions like medicine where few apply (8.4%), matriculate (6.2%), match into residency programs (5.1%), work in academic medicine (3.6%), or reach the rank of full professor (1.9%) (Table 1). From 1970 to 2020, the percentage of Black Americans graduating from US medical schools has not changed, whereas, by comparison, the percentage of women has increased from 8.4% to 49.6% (2).

The Association of American Medical Colleges defines "underrepresented in medicine" (UIM) as "those racial and ethnic populations that are underrepresented in the medical profession relative to their numbers in the general population" (3). Nephrology has a higher percentage of UIM fellows than most other internal medicine specialties, particularly cardiology, gastroenterology, hematology/oncology, pulmonary and critical care medicine, and rheumatology (4). "With the exception of rheumatology, the subspecialties with the lowest percentages of UIM fellows were also the largest fellowships and the more procedural specialties."

As illustrated in Table 2, US medical schools need to quadruple the number of Latinx and double the number of Black medical students to begin to make medicine more representative. Until this important goal is accomplished, every medical specialty is competing to attract a limited number of underrepresented students into their residency and fellowship positions. How limited? Of the 19,938 graduates of US medical schools in 2019, only 1,238 and 1,063 identified as Black or Latinx, respectively (5).

The situation is equally troubling for PhDs. Less than 2% of the PhDs who receive funding from the National Institutes of Health (NIH) are Black, Latinx, Native American, or NHPI researchers. As was asserted in a recent editorial, "The NIH director and leadership must recognize that its previous approaches, most of which have focused on filling the 'pipeline' without simultaneously addressing our profession's systemic racism, have failed" (6). It is impossible to have a leaky pipe when no pipeline exists, so it is not surprising that fewer underrepresented individuals receive funding for their research, hold key leadership positions, or become endowed professors.

Taken together, these sobering facts contribute to the current disparities and inequities we face in nephrology: Of the more than 37 million adults with kidney diseases in the United States, a disproportionate number are Black, Latinx, Native American, Asian American, and NHPIs. The kidney health consequences these Americans face are particularly horrifying (Table 3). To advance kidney health, the American Society of Nephrology (ASN) must address systemic racism that results in health-related disparities and inequities in social determinants of health.

For the past decade, ASN has focused on promoting diversity and inclusiveness within the society to enhance the nephrology profession and the lives of people with kidney diseases through improved health care, research, and education. ASN supports two Harold Amos Medical Faculty Development Program Scholars from historically disadvantaged backgrounds, provides travel support for 25 ASN members each year to attend the National Institute of Diabetes and Digestive and Kidney Diseases' Network of Minority Health Research Investigators Annual Workshop, and requires implicit/unconscious bias training for the society's leaders and staff. Later this year, ASN will initiate a loan mitigation pilot program, funding six nephrology fellows annually from minority populations.

ASN fully recognizes the need to do more to address inequities that negatively impact the kidney community. Therefore, building on these initiatives, ASN in 2021 is prioritizing opportunities to address health disparities and influence social determinants of health in the United States and throughout the world, particularly in populations at risk for and overburdened with kidney diseases; highlighting specific health-equity issues that should be addressed on a policy level; working to achieve optimal care for all people at risk for and overburdened with kidney diseases; and helping to dismantle racist structures that impact social determinants of health and lead to health disparities and inequities.

This summer, the National Kidney Foundation (NKF)-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases will inform the kidney community and other stakeholders on how to move forward with an inclusive, equitable measurement of kidney function that recognizes race as a social, not a biological, construct (7). Through this process, NKF and ASN have ensured that any change in eGFR reporting carefully considers the multiple social and clinical implications, be based on rigorous science, and be part of a national conversation about uniform reporting of eGFR within, between, and among health care delivery systems. ASN is proud that the kidney community is taking the lead in critically evaluating the use of race in this clinical algorithm, likely forging a path for other specialties to follow in addressing this issue.

Identifying, confronting, and addressing racism in health care, in general, and kidney medicine, in particular, will require a wide-ranging approach and partnerships with myriad stakeholders beyond the kidney community. For example, ASN agrees with "The Moral Determinants of Health," which include having the United States (and many other democracies) ratify "the basic human rights treaties and conventions of the international community," stating in statute "health care as a human right" (and a wise investment of resources to promote wellness that fosters opportunity for people to contribute meaningfully to society), "restoring US leadership to reverse climate change," "achieving radical reform of the US criminal justice system," "ending policies of exclusion and achieving compassionate immigration reform," "ending hunger and homelessness," and promoting "order, dignity, and equity to US democratic institutions and ensuring the right of every single person's vote to count equally" (8).

As a first step toward achieving these goals, the American College of Physicians (ACP) in January 2021 unveiled "A Comprehensive Policy Framework to Understand and Address Disparities and Discrimination in Health and Health Care" (9). This approach includes recommendations to "create safe, inclusive, and supportive educational and workplace environments"; "address disparities in coverage, access, and quality of care for racial and ethnic minorities"; and change "criminal justice and law enforcement policies and practices that result in racial and ethnic disparities in interactions, sentencing, and incarceration and disproportionate harm to these communities."

As a member of the ACP Council of Specialty Societies, ASN looks forward to working closely with ACP to help implement this framework. ASN and ACP are also members of the Council of Medical Specialty Societies (CMSS), a coalition that includes 45 medical societies representing more than 800,000 US physicians. CMSS has partnered with the Accreditation Council for Graduate Medical Education to launch "Equity Matters: A Diversity, Equity, Inclusion, and Antiracism Initiative for Physicians and Medical Leadership."

The United States offers tremendous opportunities, hope, and audacity difficult to match elsewhere. A promising future for this country, however, depends on overcoming systemic racism today for all Americans to enjoy healthy and happy lives. ■

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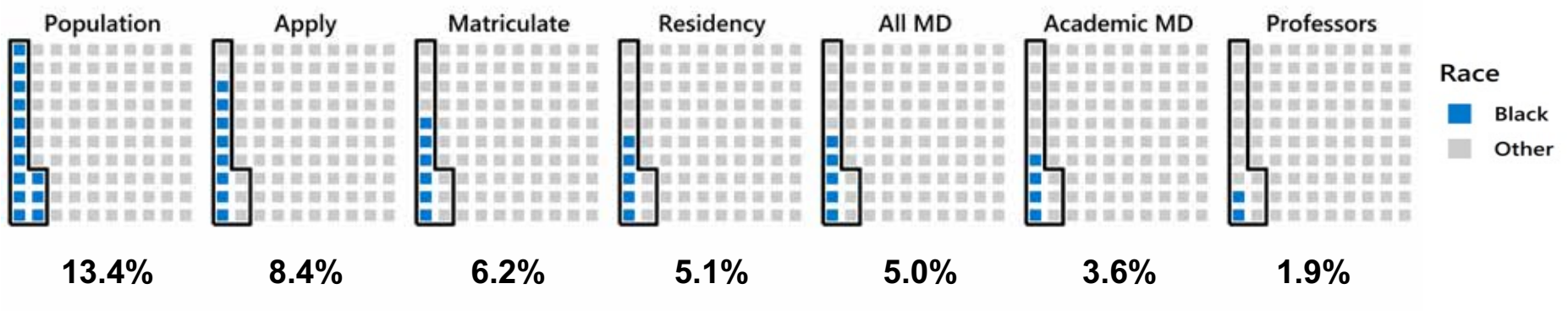
References

1. Tai DBG, et al. The disproportionate impact of COVID-19 on racial and ethnic minorities in the United States. *Clin Infect Dis* 2021; 72:703–706. doi: 10.1093/cid/ciaa815
2. Campbell KM, et al. Projected estimates of African American medical graduates of closed historically Black medical schools. *JAMA Netw Open* 2020; 3:e2015220. doi: 10.1001/jamanetworkopen.2020.15220
3. Association of American Medical Colleges. Underrepresented in Medicine Definition. Accessed May 24, 2021. https://www.aamc.org/what-we-do/equity-diversity-inclusion/underrepresented-in-medicine
4. Santhosh L, Babik JM. Trends in racial and ethnic diversity in internal medicine subspecialty fellowships from 2006 to 2018. *JAMA Netw Open* 2020; 3:e1920482. doi: 10.1001/jamanetworkopen.2019.20482
5. Association of American Medical Colleges. Diversity in Medicine: Facts and Figures 2019. Figure 13. Percentage of U.S. medical school graduates by race/ethnicity (alone), academic year 2018–2019. Accessed May 24, 2021. https://www.aamc.org/data-reports/workforce/interactive-data/figure-13-percentage-us-medical-school-graduates-race/ethnicity-alone-academic-year-2018-2019
6. Stevens KR, et al. Fund Black scientists. Cell 2021; 184:561–565. doi: 10.1016/j.cell.2021.01.011
7. Delgado C, et al. Reassessing the inclusion of race in diagnosing kidney diseases: An interim report from the NKF-ASN Task Force. *J Am Soc Nephrol* [published online ahead of print April 9, 2021]. doi: 10.1681/ASN.2021010039; https://jasn.asnjournals.org/content/early/2021/05/04/ASN.2021010039
8. Berwick DM. The moral determinants of health. *JAMA* 2020; 324:225–226. doi: 10.1001/jama.2020.11129
9. Serchen J, et al. A comprehensive policy framework to understand and address disparities and discrimination in health and health care: A policy paper from the American College of Physicians. *Ann Intern Med* 2021; 174:529–532. doi: 10.7326/M20-7219

Table 1. Black and African Americans in academic medicine



United States Census Bureau. QuickFacts United States. July 1, 2019. https://www.census.gov/quickfacts/fact/table/US/PST045219

Centers for Disease Control and Prevention. COVID Data Tracker. Demographic trends of COVID-19 cases and deaths in the US reported to CDC. https://covid.cdc.gov/covid-data-tracker/#demographics

Kaiser Family Foundation (KFF). Poverty rate by race/ethnicity. https://www.kff.org/other/state-indicator/poverty-rate-by-raceethnicity/?currentTimeframe=0&sortModel=%7B%22colId%22:%22Location%22,%22sort%22:%22asc%22%7D

Association of American Medical Colleges. Diversity in Medicine: Facts and Figures 2019. Figure 18. Percentage of all active physicians by race/ethnicity, 2018. https://www.aamc.org/data-reports/workforce/interactive-data/figure-18-percentage-all-active-physicians-race/ethnicity-2018

Association of American Medical Colleges. Diversity in Medicine: Facts and Figures 2019. Figure 13. Percentage of U.S. medical school graduates by race/ethnicity (alone), academic year 2018–2019. Accessed May 24, 2021. https://www.aamc.org/data-reports/workforce/interactive-data/figure-13-percentage-us-medical-school-graduates-race/ethnicity-alone-academic-year-2018-2019

Pivert K, et al. 2019 Nephrology Fellow Survey—Results and Insights. Washington, DC: ASN Alliance for Kidney Health, 2019. https://www.asn-online.org/education/training/workforce/Nephrology_Fellow_Survey_Report_2019.pdf

Table 2. The US population and US medical school graduates by race and ethnicity*

	US population		US medical school graduates in 2019
	2020	2030	
White	60.1%	55.8%	54.6%
Hispanic or Latinx	18.5%	21.0%	5.3%
Black or African American	13.4%	12.8%	6.2%
Asian American	5.9%	6.7%	21.6%
Multiracial	2.8%	2.8%	8.0%
Indigenous or Native American	1.3%	0.7%	0.2%
Native Hawaiian or other Pacific Islanders	0.2%	0.2%	0.1%

*Does not equal 100% due to rounding and other counting issues.

Association of American Medical Colleges. Diversity in Medicine: Facts and Figures 2019. Figure 13. Percentage of U.S. medical school graduates by race/ethnicity (alone), academic year 2018–2019. Accessed May 24, 2021. https://www.aamc.org/data-reports/workforce/interactive-data/figure-13-percentage-us-medical-school-graduates-race/ethnicity-alone-academic-year-2018-2019

United States Census Bureau. 2017 National Population Projections Tables: Main Series. Accessed May 24, 2021. https://www.census.gov/data/tables/2017/demo/popproj/2017-summary-tables.html

PBS News Hour. 3 ways that the U.S. population will change over the next decade. January 2, 2020. Accessed May 24, 2021. https://www.pbs.org/newshour/nation/3-ways-that-the-u-s-population-will-change-over-the-next-decade

Table 3. Kidney health disparities and inequities in the United States: A partial list

1	Black people comprise 13.4% of the US population but 33% of the nation's population on dialysis for kidney failure.
2	Kidney failure prevalence is about 3.5 times greater in Black people, 2.7 times greater in Native Hawaiians and Pacific Islanders (NHPIs), 1.5 times greater in Latinx people, and 1.4 times greater in Native Americans than in White Americans.
3	Kidney failure is increasing among Native Americans at an alarming rate (nearly 10% between 2017 and 2018 alone), while decreasing among White Americans during the past decade.
4	People who are Black, Latinx, Native American, and NHPI are significantly less likely than their White counterparts to receive any kidney care before kidney failure, missing key opportunities for intervention.
5	The median age of initiating dialysis is younger for NHPIs (57 years old) than for Whites (65 years old).
6	Black, Latinx, Native American, and NHPI people on dialysis are significantly less likely than their White counterparts to receive a kidney transplant and are also less likely to receive a living donor kidney transplant (the optimal type of transplant) than Whites.
7	Even though NHPIs experience better survival for kidney transplants, they have substantially lower transplant rates compared with Whites.
8	Black Americans have disproportionately high rates of kidney transplant (allograft) failure compared to White Americans, with up to a 60% higher risk of allograft failure.
9	When compared to White Americans, Black Americans are less likely to be placed on the transplant waiting list and, once on it, experience disparities in the time it takes to receive a kidney.
10	Every racial/ethnic minority group in the United States is significantly less likely to be treated with home dialysis than White Americans, and demographic and clinical characteristics are insufficient to explain this differential use: Home dialysis is 40% to 50% lower among Black and Latinx people compared to Whites.

Now approved for the treatment of adults with active lupus nephritis...

START WITH A STRONG FIRST LINE

Indications

LUPKYNIS is indicated in combination with a background immunosuppressive therapy regimen for the treatment of adult patients with active lupus nephritis (LN). *Limitations of Use:* Safety and efficacy of LUPKYNIS have not been established in combination with cyclophosphamide. Use of LUPKYNIS is not recommended in this situation.

Important Safety Information

BOXED WARNINGS: MALIGNANCIES AND SERIOUS INFECTIONS

Increased risk for developing malignancies and serious infections with LUPKYNIS or other immunosuppressants that may lead to hospitalization or death.

CONTRAINDICATIONS: LUPKYNIS is contraindicated in patients taking strong CYP3A4 inhibitors because of the increased risk of acute and/or chronic nephrotoxicity, and in patients who have had a serious/severe hypersensitivity reaction to LUPKYNIS or its excipients.

WARNINGS AND PRECAUTIONS

Lymphoma and Other Malignancies: Immunosuppressants, including LUPKYNIS, increase the risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to increasing doses and duration of immunosuppression rather than to the use of any specific agent.

Serious Infections: Immunosuppressants, including LUPKYNIS, increase the risk of developing bacterial, viral, fungal, and protozoal infections (including opportunistic infections), which may lead to serious, including fatal, outcomes.

Nephrotoxicity: LUPKYNIS, like other calcineurin inhibitors (CNIs), may cause acute and/or chronic nephrotoxicity. The risk is increased when CNIs are concomitantly administered with drugs associated with nephrotoxicity.

Hypertension: Hypertension is a common adverse reaction of LUPKYNIS therapy and may require antihypertensive therapy.

Neurotoxicity: LUPKYNIS, like other CNIs, may cause a spectrum of neurotoxicities: severe include posterior reversible encephalopathy syndrome (PRES), delirium, seizure, and coma; others include tremor, paresthesia, headache, and changes in mental status and/or motor and sensory functions.

Hyperkalemia: Hyperkalemia, which may be serious and require treatment, has been reported with CNIs, including LUPKYNIS. Concomitant use of agents associated with hyperkalemia may increase the risk for hyperkalemia.

Lupkynis™ (voclosporin) capsules 7.9 mg

Using LUPKYNIS™ (voclosporin) in combination with MMF and steroids can transform your first-line regimen[1,a,b]

- ✓ Significantly greater complete renal response rates with LUPKYNIS vs standard of care alone
- ✓ Faster proteinuria reductions than standard of care alone
- ✓ Outcomes achieved with a low-dose steroid regimen
- ✓ Novel CNI with no drug level monitoring required[1,2]

[a]Complete renal response was achieved in 40.8% of patients with LUPKYNIS and 22.5% with control. Proteinuria reductions (UPCR ≤0.5 mg/mg) were achieved at a median time of 169 days with LUPKYNIS vs 372 days with control.[1]

[b]Complete renal response was defined as a confirmed UPCR of ≤0.5 mg/mg; eGFR ≥60 mL/min/1.73 m^2 or no confirmed decrease from baseline in eGFR of >20% or no treatment- or disease-related eGFR-associated event at time of assessment; presence of sustained, low-dose steroids (≤10 mg prednisone from Weeks 44-52); and no administration of rescue medications. Proteinuria reduction was based on time to UPCR of ≤0.5 mg/mg.[1]

CNI=calcineurin inhibitor; eGFR=estimated glomerular filtration rate; MMF=mycophenolate mofetil; standard of care=MMF + steroids; UPCR=urine protein/creatinine ratio.

See how LUPKYNIS can impact your appropriate patients with lupus nephritis at LUPKYNISpro.com

QTc Prolongation: LUPKYNIS prolongs the QTc interval in a dose-dependent manner when dosed higher than the recommended lupus nephritis therapeutic dose. The use of LUPKYNIS in combination with other drugs that are known to prolong QTc may result in clinically significant QT prolongation.

Immunizations: Avoid the use of live attenuated vaccines during treatment with LUPKYNIS. Inactivated vaccines noted to be safe for administration may not be sufficiently immunogenic during treatment with LUPKYNIS.

Pure Red Cell Aplasia: Cases of pure red cell aplasia (PRCA) have been reported in patients treated with another CNI immunosuppressant. If PRCA is diagnosed, consider discontinuation of LUPKYNIS.

Drug-Drug Interactions: Avoid co-administration of LUPKYNIS and strong CYP3A4 inhibitors or with strong or moderate CYP3A4 inducers. Reduce LUPKYNIS dosage when co-administered with moderate CYP3A4 inhibitors. Reduce dosage of certain P-gp substrates with narrow therapeutic windows when co-administered.

ADVERSE REACTIONS

The most common adverse reactions (≥3%) were glomerular filtration rate decreased, hypertension, diarrhea, headache, anemia, cough, urinary tract infection, abdominal pain upper, dyspepsia, alopecia, renal impairment, abdominal pain, mouth ulceration, fatigue, tremor, acute kidney injury, and decreased appetite.

SPECIFIC POPULATIONS

Pregnancy/Lactation: May cause fetal harm. Advise not to breastfeed.

Renal Impairment: Not recommended in patients with baseline eGFR ≤45 mL/min/1.73 m^2 unless benefit exceeds risk. If used in this population, reduce LUPKYNIS dose.

Hepatic Impairment: For mild or moderate hepatic impairment, reduce LUPKYNIS dose. Avoid use with severe hepatic impairment.

Please see Brief Summary of Prescribing Information including Boxed Warning on adjacent pages.

References: 1. LUPKYNIS [package insert]. Rockville, MD: Aurinia Pharma U.S., Inc., 2021. **2.** Kuglstatter A, Mueller F, Kusznir E, et al. Structural basis for the cyclophilin A binding affinity and immunosuppressive potency of E-ISA247 (voclosporin). *Acta Crystallogr D Biol Crystallogr.* 2011;67(pt 2):119-123.

Aurinia™

Lupkynis™ (voclosporin) capsules 7.9 mg

LUPKYNIS™ (voclosporin) capsules, BRIEF SUMMARY
SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

BOXED WARNINGS: MALIGNANCIES AND SERIOUS INFECTIONS

Increased risk for developing malignancies and serious infections with LUPKYNIS or other immunosuppressants that may lead to hospitalization or death.

INDICATIONS AND USAGE

LUPKYNIS is indicated with a background immunosuppressive therapy regimen for the treatment of adult patients with active lupus nephritis (LN). Limitations of Use: Safety and efficacy of LUPKYNIS have not been established in combination with cyclophosphamide. Use of LUPKYNIS is not recommended in this situation.

CONTRAINDICATIONS

LUPKYNIS is contraindicated in patients taking strong CYP3A4 inhibitors because these medications can significantly increase exposure to LUPKYNIS, which may increase the risk of acute and/or chronic nephrotoxicity, and in patients who have had a serious/severe hypersensitivity reaction to LUPKYNIS or its excipients.

WARNINGS AND PRECAUTIONS

Lymphoma and Other Malignancies: Immunosuppressants, including LUPKYNIS, increase the risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

Serious Infections: Immunosuppressants, including LUPKYNIS, increase the risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections. These infections may lead to serious, including fatal, outcomes. Viral infections reported include cytomegalovirus and herpes zoster infections.

Nephrotoxicity: LUPKYNIS, like other calcineurin inhibitors (CNIs), can cause acute and/or chronic nephrotoxicity. The risk is increased when CNIs are concomitantly administered with drugs associated with nephrotoxicity. Consider the risks and benefits of LUPKYNIS treatment in light of the patient's treatment response and risk of worsening nephrotoxicity, including in the following situations:
1) Longer treatment duration beyond one year. Safety and efficacy of LUPKYNIS have not been established beyond one year.
2) Co-administration with drugs associated with nephrotoxicity. The risk for acute and/or chronic nephrotoxicity is increased when LUPKYNIS is concomitantly administered with drugs associated with nephrotoxicity.

Hypertension: Hypertension is a common adverse reaction of LUPKYNIS therapy and may require antihypertensive therapy.

Neurotoxicity: Like other CNIs, LUPKYNIS can cause neurotoxicities. The most severe ones include posterior reversible encephalopathy syndrome (PRES), delirium, seizure, and coma; others include tremor, paresthesia, headache, mental status changes, and changes in motor and sensory functions.

Hyperkalemia: Hyperkalemia, which may be serious and require treatment, has been reported with CNIs including LUPKYNIS. Concomitant use of agents associated with hyperkalemia may increase the risk for hyperkalemia.

QTc Prolongation: LUPKYNIS prolongs the QTc interval in a dose-dependent manner after single dose administration at a dose higher than the recommended lupus nephritis therapeutic dose. The use of LUPKYNIS in combination with other drugs that are known to prolong QTc may result in clinically significant QT prolongation.

Immunizations: Avoid the use of live attenuated vaccines during treatment with LUPKYNIS. Inactivated vaccines noted to be safe for administration may not be sufficiently immunogenic during treatment with LUPKYNIS.

Pure Red Cell Aplasia: Cases of pure red cell aplasia (PRCA) have been reported in patients treated with another CNI immunosuppressant. If PRCA is diagnosed, consider discontinuation of LUPKYNIS.

ADVERSE REACTIONS

Clinical Trials Experience

A total of 355 patients with LN were treated with voclosporin in the Phase 2 and 3 clinical studies of whom 224 were exposed for at least 48 weeks. A total of 267 patients received at least 1 dose of LUPKYNIS 23.7 mg twice a day with 184 exposed for at least 48 weeks. A total of 88 patients received at least 1 dose of voclosporin 39.5 mg twice a day with 40 exposed for 48 weeks. Patients received background treatment with MMF 2 g daily and an IV bolus of corticosteroids followed by a pre-specified oral corticosteroid taper dosing schedule.

Adverse Reactions in ≥3% of Patients Treated with LUPKYNIS 23.7 mg BID and ≥2% Higher than Placebo in Studies 1 and 2

Adverse Reaction	LUPKYNIS 23.7 mg twice a day (n=267)	Placebo (n=266)
Glomerular filtration rate (GFR) decreased*	26%	9%
Hypertension	19%	9%
Diarrhea	19%	13%
Headache	15%	8%
Anemia	12%	6%
Cough	11%	2%
Urinary tract infection	10%	6%
Abdominal pain upper	7%	2%
Dyspepsia	6%	3%
Alopecia	6%	3%
Renal Impairment*	6%	3%
Abdominal Pain	5%	2%
Mouth ulceration	4%	1%
Fatigue	4%	1%
Tremor	3%	1%
Acute kidney injury*	3%	1%
Decreased appetite	3%	1%

**GFR decreased was the most frequently reported renal adverse reaction. Other renal adverse reactions were renal impairment, acute kidney injury, blood creatinine increased, azotemia, renal failure, oliguria, and proteinuria.*

Other adverse reactions reported in less than 3% of patients in the LUPKYNIS 23.7 mg group and at a 2% higher rate than in the placebo group through Week 48/52 included gingivitis and hypertrichosis. Studies 1 and 2 were integrated to represent safety through 48/52 weeks for placebo (n=266), LUPKYNIS 23.7 mg twice a day (n=267), and voclosporin 39.5 mg twice a day (n=88). Exposure adjusted incidence rates were adjusted by study for all the adverse events reported in this section.

DRUG INTERACTIONS

Effect of Other Drugs on LUPKYNIS

Strong and Moderate CYP3A4 Inhibitors: Voclosporin is a sensitive CYP3A4 substrate. Co-administration with strong or moderate CYP3A4 inhibitors increases voclosporin exposure, which may increase the risk of LUPKYNIS adverse reactions. Co-administration of LUPKYNIS with strong CYP3A4 inhibitors (e.g., ketoconazole,

itraconazole, clarithromycin) is contraindicated. Reduce LUPKYNIS dosage when co-administered with moderate CYP3A4 inhibitors (e.g., verapamil, fluconazole, diltiazem). Avoid food or drink containing grapefruit when taking LUPKYNIS.

Strong and Moderate CYP3A4 Inducers: Voclosporin is a sensitive CYP3A4 substrate. Co-administration with strong or moderate CYP3A4 inducers decreases voclosporin exposure, which may decrease the efficacy of LUPKYNIS. Avoid co-administration of LUPKYNIS with strong or moderate CYP3A4 inducers.

Effect of LUPKYNIS on Other Drugs

Certain P-gp Substrates

Voclosporin is a P-gp inhibitor. Co-administration of voclosporin increases exposure of P-gp substrates, which may increase the risk of adverse reactions of these substrates. For certain P-gp substrates with a narrow therapeutic window, reduce the dosage of the substrate as recommended in its prescribing information, if needed.

OATP1B1 Substrates

The effect of LUPKYNIS on OATP1B1 substrates (e.g., statins) has not been studied clinically. However, voclosporin is an OATP1B1 inhibitor in vitro, and information suggests an increase in the concentration of these substrates is possible. Monitor for adverse reactions of OATP1B1 substrates when used concomitantly with LUPKYNIS.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Avoid use of LUPKYNIS in pregnant women. The available data on the use of LUPKYNIS in pregnant patients are insufficient to determine whether there is a drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with systemic lupus erythematosus (SLE). LUPKYNIS may be used in combination with a background immunosuppressive therapy regimen that includes mycophenolate mofetil (MMF). MMF used in pregnant women and men whose female partners are pregnant can cause fetal harm (major birth defects and miscarriage). Refer to the MMF prescribing information for more information on its use during pregnancy. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk: Pregnant women with SLE are at increased risk of adverse pregnancy outcomes, including worsening of the underlying disease, premature birth, miscarriage, and intrauterine growth restriction. Maternal LN increases the risk of hypertension and preeclampsia/eclampsia. Passage of maternal autoantibodies across the placenta may result in adverse neonatal outcomes, including neonatal lupus and congenital heart block.

Lactation

There are no available data on the presence of voclosporin in human milk, the effects on the breastfed infant, or the effects on milk production. Voclosporin is present in milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Given the serious adverse reactions seen in adult patients treated with LUPKYNIS such as increased risk of serious infections, advise patients that breastfeeding is not recommended during treatment and for at least 7 days after the last dose of LUPKYNIS (approximately 6 elimination half-lives).

Females and Males of Reproductive Potential

LUPKYNIS may be used in combination with a background immunosuppressive therapy regimen that includes MMF. If LUPKYNIS is administered with MMF, the information for MMF regarding pregnancy testing, contraception, and infertility also applies to this combination regimen. Refer to MMF prescribing information for additional information.

Pediatric Use: The safety and efficacy of LUPKYNIS in pediatric patients has not been established.

Geriatric Use: Clinical studies of LUPKYNIS did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal Impairment

Use of LUPKYNIS is not recommended in patients with a baseline eGFR ≤45 mL/min/1.73 m^2 unless the benefit exceeds the risk. If used in patients with severe renal impairment at baseline, LUPKYNIS should be used at a reduced dose. No dosage adjustment is recommended in patients with mild or moderate renal impairment at baseline. Monitor eGFR closely. After initiating therapy, dosing adjustments should be made based on eGFR.

Hepatic Impairment

Reduce LUPKYNIS dosage in patients with mild/moderate hepatic impairment. Avoid LUPKYNIS in patients with severe hepatic impairment.

OVERDOSAGE

Symptoms of accidental overdose may include tremor, headache, nausea and vomiting, infections, tachycardia, urticaria, lethargy, and increases in blood urea nitrogen, serum creatinine, and alanine aminotransferase levels. General supportive measures and symptomatic treatment are recommended in cases of overdose.

To report SUSPECTED ADVERSE REACTIONS, contact Aurinia Pharma U.S., Inc. at 1-833-672-0028 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

This brief summary is based on LUPKYNIS Prescribing Information (FPI-0009) issued January 2021.

Additional information can be found at LUPKYNISpro.com.

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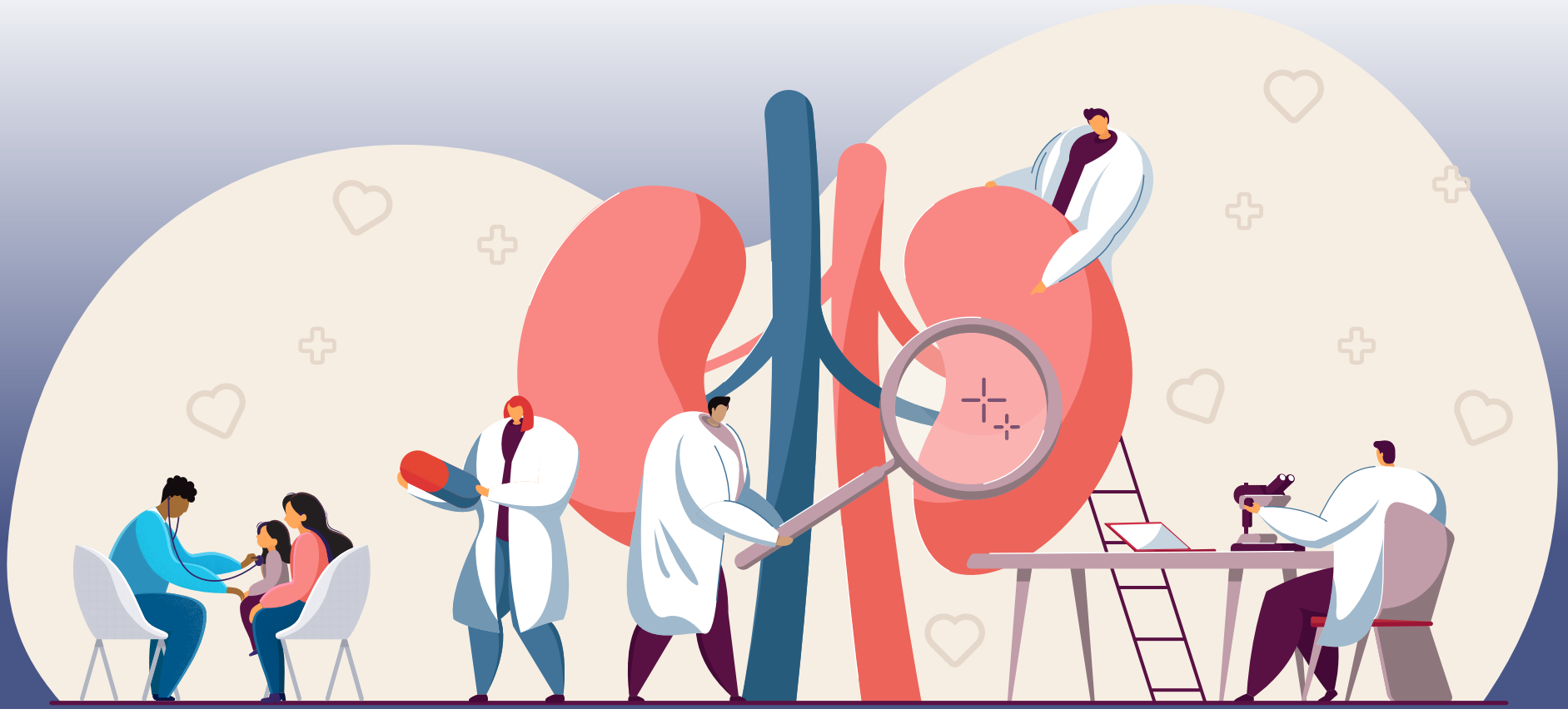

Kids and Kidneys

A Journey of Joy and Discovery

By Ray Bignall

There are five reasons why I'm a pediatric nephrologist, but they might not all be the reasons you'd think. After all, my renal block in medical school was certainly not my favorite, and my clinical nephrology exposure was limited. I heard the stories—"To be a nephrologist, you have to be the smartest doctor in the hospital."—and since I never saw myself as "the smartest," I didn't think the field was for me. But by the end of my month on pediatric nephrology as a first-year resident, a confluence of inspiring events and the encouragement of supportive mentors had changed my life and altered my career path forever.

Now at Nationwide Children's Hospital, medical students and residents learn a new reason for my career choice each day of the week when I am the attending on our service. It's a fun way to encourage young learners to consider a career in pediatric nephrology, but it's also a wonderful reminder about what this dynamic subspecialty has to offer.

First, I am a nephrologist because of my mentors. As a first-year resident, I lacked confidence on rounds and struggled with "imposter syndrome" (1). A dedicated group of enthusiastic and supportive faculty mentors took the time to build my confidence and encourage me to be bolder in my medical decision-making. Comments like "Dr. Bignall, you're writing excellent notes," from Dr. Bradley Dixon, and "I love your plan—that's exactly what I would have done," from Dr. Stuart Goldstein, enabled me to dedicate less time to perseverating over the mechanics of inpatient rounds and more time to the development of robust differential diagnoses and plans of care. Their support was essential in prompting me to join the small but steadfast ranks of the roughly 1100 board-certified pediatric nephrologists in the United States (2), and such mentorship will be key to inspiring the next generation of pediatric nephrologists as well.

Second, I am a nephrologist today because of my patients; they inspire and teach me on a daily basis. No other profession affords such variety of pathologies, the ability to follow the traverse of electrolytes through the nephron, facilitate the gift of life through organ donation, bring balance to the forces of oncotic and hydrostatic pressures in nephrotic syndrome, and discover new genes that unlock the promise of new cures for disease. And for children with kidney disease, there is the added thrill of contributing to their growth and development for the rest of their life. With such a breadth of opportunities, pediatric nephrology is an easy sell.

Third, I learned that nephrologists get to go on field trips: we are needed in all facets and venues of child health! Our expertise is required in emergency departments and intensive care units. We direct chronic dialysis programs that give patients with kidney failure a lifeline of hope. We deliver life-saving acute dialysis in settings that range from the operating rooms of quaternary care academic children's hospitals to the humble abodes of remote villages around the world. We establish relationships with patients in the outpatient clinic and in our communities that result in lasting and powerful human connections. And we do all of this while delivering world-class care for some of the most complex diseases in the smallest of patients. What a gift!

Fourth, and speaking of gifts, we offer children the gift of life. There is no greater thrill than calling a parent to share the news of an available organ for their child's transplant or receiving a graduation invitation for a patient living (and thriving!) with glomerular disease. Pediatric nephrologists share in this gift through myriad medical, surgical, diagnostic, and therapeutic breakthroughs taking place across our field. Innovations in kidney genetics, neonatal nephrology, pediatric transplant, and acute dialysis are just some of the advances discussed in this issue, contributing to the culture of discovery that improves the lives of so many children and their families.

Finally, pediatric nephrology offers opportunities for service and advocacy. In no other field of medicine is one's physical health more closely connected to one's social, psychological, or environmental well-being, and advocating for healthcare justice is essential to our work. Children living with kidney disease face tremendous obstacles to health if they are also impacted by poverty, food insecurity, housing instability, environmental injustice, or systemic racism and discrimination. In this issue, you will read about pediatric nephrologists who are answering the call, leveraging our work as kidney health professionals to fight for justice and equity in medicine and society.

It is our hope that these pieces will propel you to consider not only the many advances in the field but also the incredible opportunities for this field to inspire the next generation of nephrologists. ■

O. N. Ray Bignall II, MD, FAAP, FASN, is Director, Kidney Health Advocacy and Community Engagement, Division of Nephrology and Hypertension, Nationwide Children's Hospital, and Assistant Professor of Pediatrics, The Ohio State University College of Medicine, Columbus, OH. Dr. Bignall serves as Chair of the ASN Health Care Justice Committee.

References

1. Mullangi S, Jagsi R. Imposter syndrome: Treat the cause, not the symptom. *JAMA* 2019; 322:403–404. doi: 10.1001/jama.2019.9788
2. The American Board of Pediatrics. Pediatric subspecialists ever certified. ABP Certification Management System. March 2020. https://www.abp.org/content/pediatric-subspecialists-ever-certified

Fellows First

Advancing a Legacy: Advocacy in Pediatric Nephrology

By Kaye Brathwaite, Jill Krissberg, and Alex Kula

For pediatric nephrologists, the feeling of walking into a pediatric dialysis unit is like no other. On any given day, we get to see patients playing with a new toy, singing their favorite song, or working hard on their homework. With our observation of children on dialysis playing and smiling, it's easy to forget the toll dialysis takes on them and their family. Many families uproot their lives or drive hours back and forth for each session because the nearest pediatric unit is hundreds of miles from home. Young children face disruption in their education and social lives during developmentally vulnerable times. Patients struggle with keeping up with their schoolwork, learning to take pills, and finding foods they like that fit their dietary restrictions, all while coping with a chronic illness.

The American Society of Pediatric Nephrology (ASPN) is the primary professional society for pediatric nephrologists in the United States. Although many components of the ASPN share a common goal with those of the ASN, children with chronic kidney disease (CKD) have unique needs that differ from those of adults and thus require their own voice. ASPN's mission is to provide that voice for the needs of children affected by kidney diseases and the providers, nurses, nutritionists, and other specialists who care for them.

An important part of the ASPN mission is the John E. Lewy Fund for Children's Health (JELF) Advocacy Scholars Program, which was started in 2009 in honor of John E. Lewy's dedication to advocacy, science, and education in pediatric nephrology. Dr. Lewy was a major figure and a lifetime advocate for pediatric nephrology. He served as president of ASPN, where he fought for health equity, research dissemination, and improving access to care for children with kidney disease. His relationship with regulatory and governmental figures laid the groundwork for the ongoing advocacy efforts of the ASPN. Today, JELF scholars continue in his legacy and are recruited bi-annually to pursue their own passion for advocacy, their patients, and nephrology.

JELF scholars learn how to be advocates through formal curricula and hands-on legislative skills. They participate in the annual American Academy of Pediatrics (AAP) Legislative Conference to formally learn advocacy skills. The scholars also learn about legislative policy and regulatory processes, public insurance programs, health disparities, and racism in healthcare—all through the lens of the pediatric nephrologist. They then practice these skills alongside other experts in the field by participating in regular advocacy Capitol Hill days, and in similar fashion to the ASN's Policy and Advocacy Committee Internship Program, JELF scholars serve as trainee members of the ASPN's Public Policy Committee to stay up to date on and guide new policies that affect pediatric kidney patients. They participate in advocacy in a complimentary and coordinated function with the ASN, most specifically by participating in the Annual Kidney Community Advocacy Day, co-sponsored by ASN, the National Kidney Foundation (NKF), and the American Association of Kidney Patients (AAKP). Held each fall, this event brings together dozens of kidney health advocacy groups and institutions to advocate about specific topics with elected officials in Washington, DC. All these components together help teach scholars about the needs of the pediatric and adult kidney health communities and how to actualize change in these arenas.

Since there are similarities in the issues affecting patients with kidney disease in adults and children, and because childhood kidney disease is often chronic and extends into adulthood, it is important that the JELF scholars work in conjunction with ASN on advocacy issues. For example, both children and adults benefit from advocacy efforts to provide equitable care, target disparities in access to kidney transplantation, and dismantle racial bias in clinical practice. More recently, this included removal of race from kidney function estimation equations and support of anti-racism and diversity in nephrology. During the height of the COVID-19 pandemic, JELF scholars continued their important work via virtual forums and advocated for COVID-19-specific legislation: research funding focusing on COVID-19 and its associated kidney outcomes and health disparities and expansion of telehealth services. Similar to adult nephrology, pediatric nephrology is facing a severe workforce shortage. Scholars advocate for increasing and diversifying the nephrology workforce—an initiative important to both adult and pediatric providers.

In addition, JELF scholars continue to strive to highlight the specific needs of pediatric patients with kidney disease. Currently, pediatric patients with end-stage kidney disease are the only children covered by Medicare insurance. Thus, scholars meet with leadership in the Centers for Medicare & Medicaid Services (CMS) to understand the payment process, to increase reimbursement for pediatric nephrologists, and to highlight the unique needs of pediatric patients and their providers, such as limited access to age-appropriate kidney replacement therapy, a need for specialized personnel (e.g., child life specialists, dieticians, teachers), and expertise in running dialysis units that cater to children. Scholars also meet with officials from the National Institutes of Health (NIH) on areas relevant to pediatric nephrology to discuss continued support of research of this special population and to help recruit to the workforce (Table 1).

JELF also incorporates its scholarship on a local level by contributing to advocacy efforts at home institutions. Often inspired by the patients seen in their clinics, scholars are particularly driven to improve health equity and access to care for children living with kidney disease. For example, the current work of one senior JELF scholar focuses on understanding and addressing food insecurity in children with kidney disease and how to effectively connect much-needed resources to patients.

All scholars are paired with a mentor throughout their 2-year term to aid in development and implementation of their advocacy goals. This mentorship also helps cater new skills to future work after completion of the program. JELF scholars become expert advocates in the pediatric kidney disease community—often continuing their roles in public policy, with some going on to work in governmental roles after this unique training. As with education and research, advocacy through public policy is an area that is much needed to develop the field of pediatric nephrology, particularly given the difficulty of getting pediatric-specific needs heard among the millions of adult patients living with kidney disease.

All patients treated as children with CKD will inevitably grow to become adults with CKD. Moreover, many of the origins of adult-onset CKD begin in childhood. As such, the work of JELF scholars is both separate and complimentary to parallel advocacy efforts through ASN. The JELF Advocacy Scholars Program will train future advocates who will see to the unique needs of our youngest patients with CKD while developing new strategies to reduce the number, and severity, of adults with CKD. ■

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All the authors are JELF Scholars and report no disclosures.

JELF scholars continue to strive to highlight the specific needs of pediatric patients with kidney disease.

Table 1. Overview of JELF Scholars Program and advocacy agenda

Didactics	AAP Legislative Conference JELF Scholars Curriculum
Hands-on skills training	ASN & ASPN Advocacy Day Meetings with CMS/NIH Public Policy Committee members Op-Ed writing
Nephrology advocacy	Immunosuppressive Drug Act Living Donor Protection Act NIH research funding
Pediatrics advocacy	Access to care Medicaid/Children's Health Insurance Program (CHIP) Vaccinations
Pediatric nephrology advocacy	Loan forgiveness Workforce shortage Medicare reimbursement

Acute Care Pediatric Nephrology
WHAT CAN I DO?

By Nadia McLean, Shina Menon, and Stuart L. Goldstein

The call was one received ever so often, for this fledgling nephrology service on the small island: A newborn with no urine output and a startlingly high blood urea nitrogen and creatinine. He had become edematous and would soon need a ventilator. There was no antenatal ultrasound, as is the norm in these rural parts. A few calls are made to the capital: their wards are full. "It's you and me, baby" is the thought that runs through the young nephrologist's head as she makes her way to the hospital neonatal ICU. What are her options? She recalls similar discussions during her fellowship training abroad, but it wasn't the dilemma of what could be offered; it was the ethical considerations of futility in starting kidney replacement therapy. In a well-established nephrology program, one could have these elevated and cerebral discussions. What would be the quality of life of this baby should we start dialysis? What modality would be best for his antenatally diagnosed condition? In her small rural hospital where she is the nephrology service, without a cadre of dietitians, nurses, neonatologists, and patient care coordinators at her disposal, the question is "What can I do?"

Nourse et al. in the recently published International Society for Peritoneal Dialysis (ISPD) guidelines for peritoneal dialysis in acute kidney injury noted that acute peritoneal dialysis has a similar track record to other kidney replacement therapies. Peritoneal dialysis remains cost and resource effective, thus remaining the preferred modality for lower middle income countries (LMIC) (1). According to the World Health Organization, the burden of end stage kidney disease (ESKD) in LMIC may approach that of high-income countries (HIC), and low socioeconomic status may be associated with higher rates of ESKD. Despite the need, most patients receiving kidney replacement therapy live in HIC (2). In fact, as recently as 2020, Qarni et al. noted the inequity in access to kidney replacement therapy, particularly as it related to acute and chronic peritoneal dialysis (3).

In addition to easily accessible, low cost, and less complex methods of kidney replacement therapy, collaboration and access to information often form the backbone of delivery of care to these often complex and critically ill patients. Junior faculty returning to LMIC do not often have the benefit of in-house consultation with a multidisciplinary team or with expert senior faculty members. However, although the current pandemic has separated us physically, it has had the fortunate side effect of bridging the information gap that previously existed. Specialists in LMIC are now able to access up-to-date information and international expertise and to commiserate on complex cases once they have a wifi connection. Opportunities also exist for expanded, cross-national collaboration and education that can serve to mutually benefit nephrologists who practice in variably resourced settings and in different parts of the world.

In the future, through ongoing collaboration, education, and advocacy, our young nephrologist may not have to wonder "What can I do?" but should be able to ask, "Who can I call for help?" ■

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References

1. Nourse P, et al. ISPD guidelines for peritoneal dialysis in acute kidney injury: 2020 update (pediatrics). *Perit Dial Intl* 41:139–157. doi:10.1177/0896860820982120
2. White SL, et al. How can we achieve global equity in provision of renal replacement therapy? *Bulletin of the World Health Organization* 2008; 86:229–237.
3. Qarni B. (2020-Supplement, January). Kidney care in low- and middle-income countries. *Clin Nephrol* 93:21–30. doi:10.5414/CNP92S104

Neonatal Nephrology
A Growing Problem in Need of an Innovative Solution

By Michelle Starr, Tahagod Mohamed, Katherine Twombley, and Keia Sanderson

Kidney disease in premature infants and critically ill neonates is a growing problem. One in 10 children is born prematurely each year (1). In these neonates, improvements in neonatal intensive care have increased survival and shifted focus to long-term outcomes. Kidney-related outcomes are increasingly recognized in this population (2). Children born prematurely have a 3-fold increased risk of chronic kidney disease (CKD) and a 1.5-fold increased risk of end-stage kidney disease over the life course compared to children born full term (2, 3). This clinical problem will continue to grow as more survive prematurity into adulthood.

Neonates admitted to the neonatal intensive care unit (NICU) may be inherently at increased risk of CKD (4, 5). In those born prematurely, this risk is thought to result from disrupted nephrogenesis, resulting in a lower nephron number. In addition, acute kidney injury (AKI) occurs in up to 30% of high-risk neonates admitted to the NICU from both intrinsic factors (including low nephron number, low glomerular filtration rate [GFR], and tubular immaturity) and extrinsic factors (such as increased insensible losses and nephrotoxic medications) (6, 7). Infants who survive NICU admission and had an episode of AKI are at increased risk for repeated episodes of AKI as well as CKD (8). All patients, including infants, surviving an episode of AKI should have long-term monitoring for CKD. Unfortunately, the diagnosis of AKI remains underrecognized, made in only 10%–30% of neonates (9). The reasons for under-diagnosis are complicated but likely related to underrecognized, subtle changes in serum creatinine that reflect significant alterations in GFR and a lack of awareness of neonatal AKI definitions (10). Without clinical recognition of the impact of preterm birth and AKI on CKD risk, many neonates are not identified for long-term kidney follow-up, reducing providers' ability to identify CKD early. Children are not routinely screened for kidney disease, and those who develop CKD often do not experience symptoms until the kidney damage is severe and irreversible. Healthcare costs increase fourfold with a late-stage CKD diagnosis (11, 12).

One potential solution to this gap in AKI diagnoses and follow-up after preterm birth and AKI is increasing nephrology integration into the NICU. Studies show programs that integrate early pediatric nephrologist consultation into the NICU improve AKI diagnosis (13). There are multiple models that have been implemented successfully, including nephrology consults on all NICU patients with AKI identified by electronic medical record review (Riley Children's Hospital). Some centers lead weekly NICU nephrology rounds in which all neonates with AKI are evaluated by a nephrologist (Nationwide Children's Hospital). Other centers have developed local guidelines for neonatologists to support AKI recognition and consultation with pediatric nephrology (Medical University of South Carolina and University of North Carolina).

No matter the model, we strongly believe that the integration of pediatric nephrology providers into NICUs improves the recognition and management of AKI and increases follow-up of patients at high risk for future CKD. The importance of neonatal nephrology integration is especially valuable in the NICU where the diagnosis of AKI is challenging. A Neonatal Nephrology Program emphasizes early referral to a nephrology clinic and facilitates discussion of kidney health monitoring, early identification of CKD, and risk reduction. Early identification of pediatric patients with CKD is essential to slow the progression of kidney disease, as it allows for the initiation of treatment to improve kidney function into adulthood. ■

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References

1. Horbar JD, et al. Mortality and neonatal morbidity among infants 501 to 1500 grams from 2000 to 2009. *Pediatrics* 2012; 129:1019–1026. doi: 10.1542/peds.2011-3028
2. Eriksson JG, et al. Prenatal growth and CKD in older adults: Longitudinal findings from the Helsinki Birth Cohort Study, 1924–1944. *Am J Kidney Dis* 2018; 71:20–26. doi: 10.1053/j.ajkd.2017.06.030
3. Vikse BE, et al. Low birth weight increases risk for end-stage renal disease. *J Am Soc Nephrol* 2008; 19:151–157. doi: 10.1681/ASN.2007020252
4. Carmody JB, Charlton JR. Short-term gestation, long-term risk: Prematurity and chronic kidney disease. *Pediatrics* 2013; 131:1168–1179. doi: 10.1542/peds.2013-0009
5. Sanderson KR, et al. Albuminuria, hypertension, and reduced kidney volumes in adolescents born extremely premature. *Front Pediatr* 2020; 8:230. doi: 10.3389/fped.2020.00230
6. Jetton JG, et al. Incidence and outcomes of neonatal acute kidney injury (AWAKEN): A multicentre, multinational, observational cohort study. *Lancet Child Adolesc Health* 2017; 1:184–194. doi: 10.1016/S2352-4642(17)30069-X
7. Selewski DT, et al. Neonatal acute kidney injury. *Pediatrics* 2015; 136:e463–e473. doi: 10.1542/peds.2014-3819
8. Mammen C, et al. Long-term risk of CKD in children surviving episodes of acute kidney injury in the intensive care unit: A prospective cohort study. *Am J Kidney Dis* 2012; 59:523–530. doi: 10.1053/j.ajkd.2011.10.048
9. Carmody JB, et al. Recognition and reporting of AKI in very low birth weight infants. *Clin J Am Soc Nephrol* 2014; 9:2036–2043. doi: 10.2215/CJN.05190514
10. Kent AL, et al. Neonatal acute kidney injury: A survey of neonatologists' and nephrologists' perceptions and practice management. *Am J Perinatol* 2018; 35:1–9. doi: 10.1055/s-0037-1604260
11. Mitsnefes MM. Cardiovascular disease in children with chronic kidney disease. *J Am Soc Nephrol* 2012; 23:578–585. doi: 10.1681/ASN.2011111115
12. Elshahat S, et al. The impact of chronic kidney disease on developed countries from a health economics perspective: A systematic scoping review. *PLoS One* 2020; 15:e0230512. doi: 10.1371/journal.pone.0230512
13. Starr MC, et al. Improving the recognition and reporting of acute kidney injury in the Neonatal Intensive Care Unit. *J Perinatol* 2020; 40:1301–1307. doi: 10.1038/s41372-020-0725-y

Pediatric Dialysis Care: A Brief Update

By Shweta Shah and Sarah J. Swartz

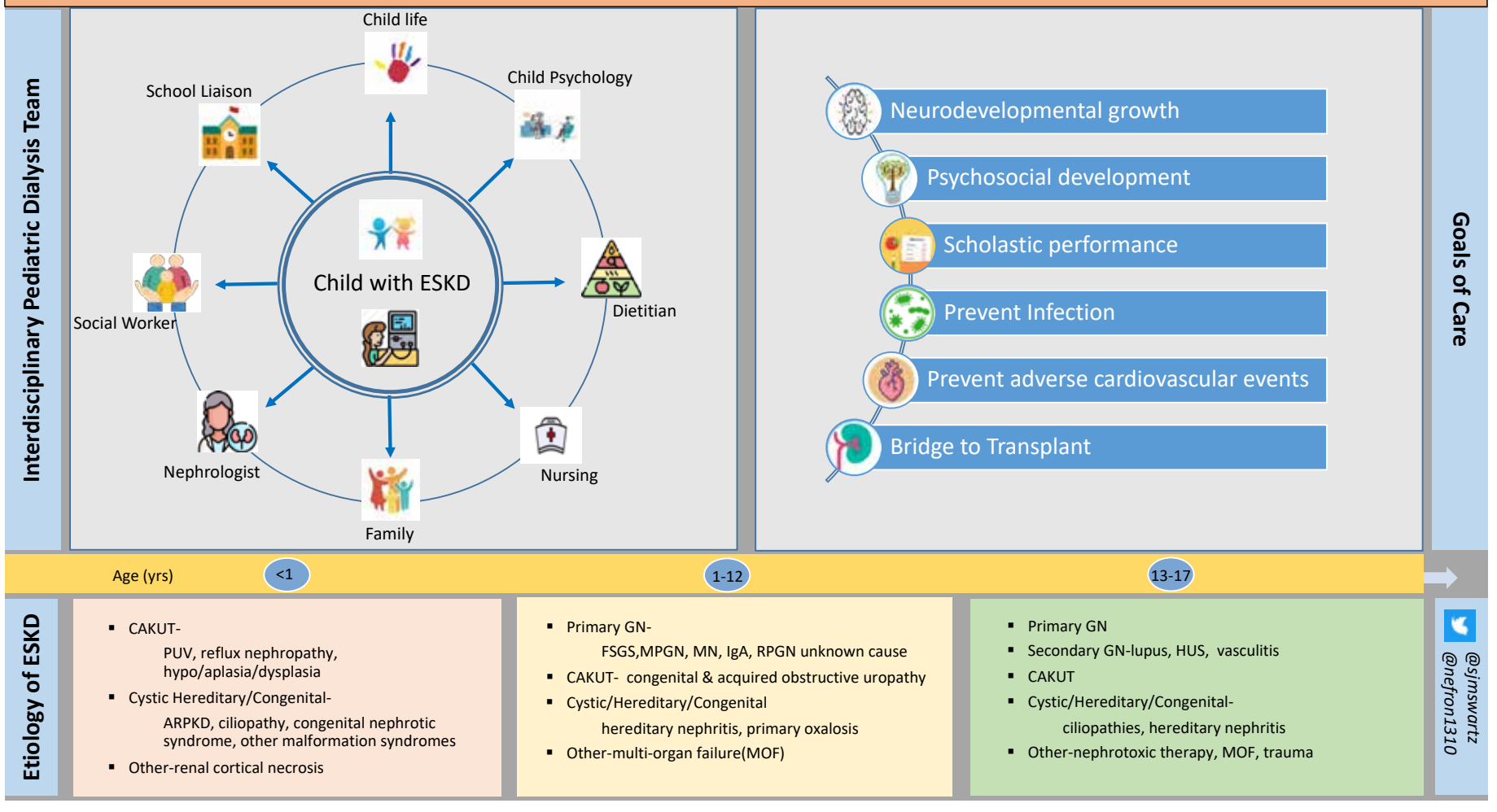
Although the number of children with end-stage kidney disease (ESKD) is small compared to adults, their management can pose a unique challenge due to variability in size and their complex medical, growth, and maturational needs, as well as caregiver involvement. The adjusted incidence of ESKD in children has remained relatively unchanged from 2014 to 2018, ~11.5 per million population, whereas prevalence has increased, with close to 71% of the pediatric ESKD population receiving kidney transplant (1). Racial disparities are noted in modality of treatment, with White children twice as likely to receive a kidney transplant as Black children, and the latter more likely to receive hemodialysis (HD) over peritoneal dialysis (PD). Hispanic-Latino children are also less likely to receive kidney transplant and initiate HD more often than PD compared to non-Hispanic children.

Congenital abnormalities of the kidney and urinary tract (CAKUT) remain the primary etiology for kidney failure in infants and young children, whereas etiology is more varied in the adolescent age group, with a higher prevalence of glomerulonephritis and tubulointerstitial diseases. In comparison, diabetes, neoplasms and tumors, and hypertensive/large vessel disease are relatively uncommon causes of incident ESKD in children (1). Adjusted mortality has declined in recent years, with the primary cause of death being cardiovascular disease (25%) followed by infection (13.3%). Hard cardiovascular endpoints (such as stroke, myocardial infarction, and death) have low incidence in the pediatric ESKD population; therefore, surrogate markers like left-ventricular hypertrophy, pulse-wave velocity, and carotid-intimal thickness are often used in outcome-based research studies (2).

The prevention of infection is imperative for children on dialysis. Infections are not only a leading cause of mortality for children with ESKD but also lead to increased morbidity, posing an important risk factor for PD failure or the need for HD access replacement with potential loss of a vascular access site.

Focused on increasing implementation of standardized best care practices initially for pediatric PD patients and later pediatric HD patients, the Standardizing Care to Improve Outcomes in Pediatric End Stage Renal Disease (SCOPE)

Figure 1. Pediatric Dialysis Care: A Brief Update



PUV, posterior urethral valve; ARPKD, autosomal-recessive polycystic kidney disease; GN, glomerulonephritis; FSGS, focal segmental glomerulosclerosis; MPGN, membrano proliferative GN; MN, membranous nephropathy; IgA, immunoglobulin A; RPGN, rapidly progressive GN; HUS, hemolytic uremic syndrome.

Continued on page 22

Pediatric Dialysis Care

Continued from page 21

Collaborative was developed. Together, the pediatric dialysis community in collaboration with North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), Children's Hospital Association (CHA), and Making Dialysis Safer for Patient Coalition launched a national multicenter North American quality improvement effort. Currently, there are 53 pediatric dialysis centers participating in the initiative implementing best practice bundles focused on PD catheter insertion, PD catheter care and follow-up, PD training, and HD catheter/arteriovenous fistula (AVF) care.

With the use of a multidisciplinary team approach, which includes engagement of families/caregivers, and quality improvement methodology to increase implementation of these best care bundle practices, the SCOPE Collaborative has been able to improve patient outcomes. SCOPE centers have achieved not only increased implementation of and maintained high levels of compliance with PD-related best care practices but also ongoing and sustained reduction in infection rates over 7 years since inception, with a decrease in annualized peritonitis rates from 0.53 infections per patient-year pre-launch to 0.38 at 36 months and 0.30 at 84 months post-launch (3). They have also successfully demonstrated improvement in catheter care bundle compliance for HD and a significant reduction in the rate of catheter-associated bloodstream infection (CA-BSI) in children on maintenance HD (4).

Children with ESKD represent an especially vulnerable subset of the overall ESKD population. Their care is different from their adult counterparts. Pediatric ESKD care is centered on promoting growth and development while minimizing potential complications, recognizing an ongoing and future need for specialized medical care as these children continue into adulthood. Children with ESKD require special attention to nutritional needs and optimal management of dialysis, anemia, and bone-mineral health to foster appropriate growth and maturation. Fundamental to their care is an interdisciplinary team with pediatric expertise that includes medical providers and a social worker, dietitian, nurse, child life specialist, quality-of-life coordinator, school liaison, and psychologist dedicated to promoting the medical, psychosocial, and scholastic growth of children on dialysis. The social worker, quality-of-life coordinator, and school liaison work closely with families and school districts to ensure individualized learning plans and obtain accommodations and additional resources to promote scholastic growth. Mental health providers play a key role in providing coping skills and support during this vulnerable period. A child life specialist interacts directly with the child for support and engagement during dialysis sessions and clinic visits as well as preparation for procedures such as fistula creation and cannulation (Figure 1). Different media, such as pets, music, and art therapy, are also often used to assist with emotional expression and improve mood and adherence during therapy. Members of this team, with the adult caregivers and inclusion of the children in a developmentally appropriate manner, help define goals of care and guide medical decision-making (5).

Continued advances in dialysis care and prevention of complications related to ESKD and dialysis have led to better survival for pediatric patients on dialysis. Hence, the focus on their pediatric care is crucial for their future potential productivity as adults. ■

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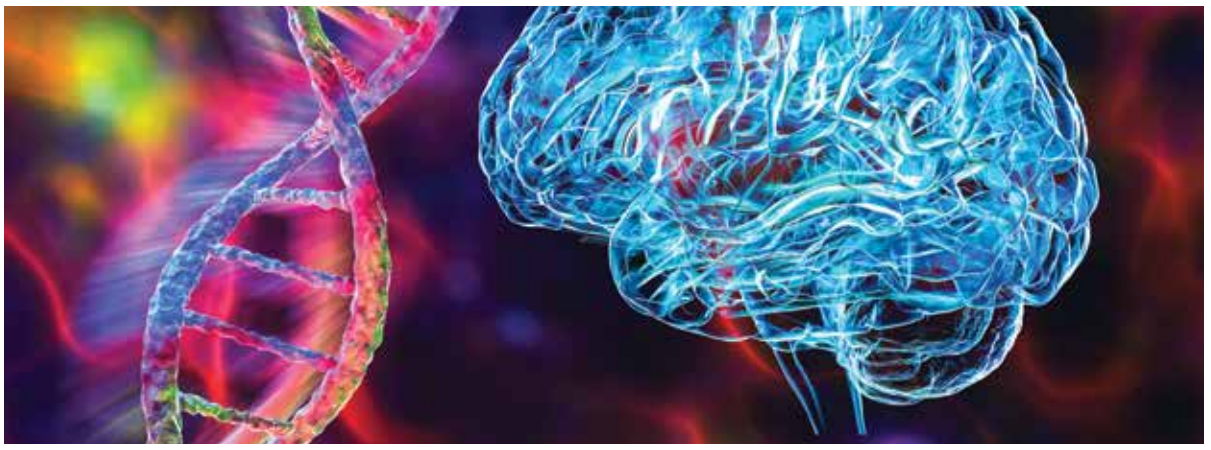
References

1. United States Renal Data System. *USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2020. https://adr.usrds.org/2020
2. Querfeld U, Schaefer F. Cardiovascular risk factors in children on dialysis: An update. *Pediatr Nephrol* 2020; 35:41–57. doi: 10.1007/s00467-018-4125-x
3. Marsenic O, et al. Tunneled hemodialysis catheter care practices and blood stream infection rate in children: Results from the SCOPE Collaborative. *Pediatr Nephrol* 2020; 35:135–143. doi: 10.1007/s00467-019-04384-7
4. Neu AM, et al. Continued reduction in peritonitis rates in pediatric dialysis centers: Results of the Standardizing Care to Improve Outcomes in Pediatric End Stage Renal Disease (SCOPE) Collaborative. *Pediatr Nephrol* [published online ahead of print March 1, 2021]. doi: 10.1007/s00467-021-04924-0; https://link.springer.com/article/10.1007/s00467-021-04924-0
5. Chand DH, et al. Dialysis in children and adolescents: The pediatric nephrology perspective. *Am J Kidney Dis* 2017; 69:278–286. doi: 10.1053/j.ajkd.2016.09.023

Targeting the Molecular Mechanisms of Tuberous Sclerosis

By Oded Volovelsky and Bradley Dixon



Since the completion of the Human Genome Project in 2003, an expanding understanding of the genetic basis of diseases has allowed us to target disease mechanisms at the molecular level. One example of the application of precision medicine in nephrology targets the mammalian target of rapamycin (mTOR) complex in the multisystem disease of tuberous sclerosis (TSC). Affecting roughly 1 in 6000 live births, TSC is a rare but significant cause of kidney disease in children (1). About one-half of patients with TSC are at risk of chronic kidney disease, which is the leading cause of morbidity and mortality in adults with TSC. The kidney manifestations of TSC are characterized by angiomyolipomas, benign tumors with risk of life-threatening hemorrhage, and cystic kidney disease ranging from a single cyst to polycystic kidney disease gradually encroaching upon and replacing healthy renal parenchyma.

Previously, the care of patients with TSC relied on repeated embolizations and surgical resections to remove angiomyolipomas and suspected malignant lesions in the kidney. A wealth of data (2, 3) has demonstrated the efficacy of targeting the mTOR complex in patients with TSC, where mTOR is constitutively overactive due to loss-of-function mutations in *TSC1* and *TSC2*, in which their protein products hamartin and tuberin, respectively, serve to gate mTOR activity. Treatment with mTOR inhibitors, by inhibiting the constitutively overactive complex, decreases the kidney disease burden of angiomyolipoma as well as neurological manifestations of TSC including subependymal giant cell astrocytomas (SEGAs) and seizures (4, 5). Current recommendations direct use of this targeted intervention of mTOR inhibitors in enlarging lesions, thereby directly treating the molecular pathomechanism and sparing surrounding kidney tissue from surgical disruption and injury (6).

Recent efforts have also explored the efficacy of targeting the mTOR complex to reduce the cystic kidney disease associated with TSC, both with retrospective clinical data (7) and more recently in an animal model of TSC cystic kidney disease (8). This recent study provides experimental evidence for the efficacy of mTOR inhibitors administered during pregnancy in preventing the onset of postnatal TSC cystic kidney disease. Despite this beneficial effect of maternal mTOR inhibition on cyst formation in the offspring, non-mTOR-related pathways seem to contribute to cystogenesis, with inflammation playing a central role in the progression of the disease.

In contrast to much accumulated medical knowledge on the deleterious effects of mutations in *TSC1* and *TSC2*, reduced mTOR level by losing a single copy of the *TSC1* gene in mouse models has been shown to be beneficial in kidney development by sustaining nephron progenitor cells and increasing nephron number (9). This apparent paradox of the simultaneously detrimental and beneficial effects of a genetic alteration urges caution that even with our most precise insight on the molecular mechanisms of disease, targeted treatments may still have unanticipated consequences. As such, it is humbling to remember that the clinical application of precision medicine, although holding great promise in the individualized treatment of patients with kidney disease, is indeed still in its formative youth. ■

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References

1. Davis PE, et al. Presentation and diagnosis of tuberous sclerosis complex in infants. *Pediatrics* 2017; 140:e20164040. doi: 10.1542/peds.2016-4040
2. Bissler JJ, et al. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. *N Engl J Med* 2008; 358:140–151. doi: 10.1056/NEJMoa063564
3. Bissler JJ, et al. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): A multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2013; 381:817–824. doi: 10.1016/S0140-6736(12)61767-X
4. Franz DN, et al. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): A multicentre, randomised, placebo-controlled phase 3 trial. *Lancet* 2013; 381:125–132. doi: 10.1016/S0140-6736(12)61134-9
5. French JA, et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): A phase 3, randomised, double-blind, placebo-controlled study. *Lancet* 2016; 388:2153–2163. doi: 10.1016/S0140-6736(16)31419-2
6. Kingswood JC, et al. Review of the tuberous sclerosis renal guidelines from the 2012 Consensus Conference: Current data and future study. *Nephron* 2016; 134:51–58. doi: 10.1159/000448293
7. Siroky BJ, et al. Improvement in renal cystic disease of tuberous sclerosis complex after treatment with mammalian target of rapamycin inhibitor. *J Pediatr* 2017; 187:318–322.e2. doi: 10.1016/j.jpeds.2017.05.015
8. Nechama M, et al. Rapamycin and dexamethasone during pregnancy prevent tuberous sclerosis complex-associated cystic kidney disease. *JCI Insight* 2020; 5:e136857. doi: 10.1172/jci.insight.136857
9. Volovelsky O, et al. Hamartin regulates cessation of mouse nephrogenesis independently of mTOR. *Proc Natl Acad Sci USA* 2018; 115:5998–6003. doi: 10.1073/pnas.1712955115

Cooperation and Collaboration:
Lessons from and for Pediatric Nephrology

By Charles Varnell, Jr., and Aviva M. Goldberg

The success of Wikipedia, Airbnb, and Uber and the increasing influence of social media show the strength of decentralizing knowledge, the power of collaboration, and the ways we find community in modern times (1). Despite the rise of this "sharing economy," in the United States and Canada, healthcare systems remain areas of centralized power and expertise. Pediatric nephrology, fortunately, has shown to be a field amenable to collaboration at all levels, and the last year has increased the opportunities for this work.

Former US Surgeon General C. Everett Koop once said, "Drugs don't work in patients who do not take them." This recognition in pediatric nephrology has led to growing attention toward how medication adherence directly affects clinical outcomes for our patients and how health disparities affect adherence. Randomized controlled trials, like the TAKE-IT (Transplant Regimen Adherence for Kidney Recipients by Engaging Information Technologies) study in pediatric kidney transplant (Figure 1) and the MAESTRO-Tx (Medication Adherence Enhancing Strategies in Solid Organ Transplantation) and MAGIC (Myoblast Autologous Grafting in Ischaemic Cardiomyopathy) studies in adult solid organ transplant, provide the evidence that addressing barriers to medication adherence through targeted interventions improves outcomes. Like medication adherence, transition from pediatric to adult care requires a holistic approach to barriers and opportunities that come with our patients achieving developmental milestones and increasing independence. By getting to the "why" of what our patients do and do not do, we can test interventions that can influence those behaviors. Such research is only possible, however, with the continued collaboration that has defined much of the most successful work in this field.

Due to the relative rarity of many pediatric kidney diseases, no center is able to produce significant generalizable knowledge alone. Our field has long recognized this dilemma and has sought to collaborate to answer the questions of how to provide optimal care. Following the lead of early collaborations, like the International Study of Kidney Disease in Children (ISKDC) and the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), multiple research and improvement networks have been created to advance the care of children with kidney diseases (Table 1). These networks were started within specific aspects of pediatric nephrology care, and they use the power of large data collection and registries to provide benchmarking and identify gaps in care along with quality improvement methods to advance outcomes and inform the development and spread of best practices. This collaborative spirit is present as part of the culture of pediatric nephrologists around the world. There are also several international pediatric nephrology Listservs that exist to share knowledge, help with challenging cases, and disseminate best practices for questions brought to the group.

The necessity to literally meet people where they are means that we now know much more about how our patients . . . live and what is most important to them.

The COVID-19 pandemic has, as one of its very few silver linings, given us the impetus and opportunity to collaborate more effectively among centers and through previously novel means of communication. One year ago, few of us would have spent our days in virtual communication with patients, local partners, or cross-country collaborators, but this is now routine. The necessity to literally meet people where they are means that we now know much more about how our patients and colleagues live and what is most important to them. These lessons can allow us to ensure our ongoing collaborations are likewise nimble—collaborating on solutions to shared problems and responding in real-time to data and trends. Most important, such work ensures that ultimately our work serves to improve the lives of children with kidney diseases, whether they are on the exam table or on the other side of our screens. ■

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Dr. Varnell is on the QI/IT committee for the Improving Renal Outcomes Collaborative and is on the IT subcommittee for NAPRTCS. Dr. Goldberg reports no conflicts of interest.

Reference

1. Hamari J, et al. The sharing economy: Why people participate in collaborative consumption. *J Assoc Inf Sci Technol* 2016; 67:2047–2059. doi: 10.1002/asi.23552

Table 1. Networks to advance the care of children with kidney diseases

Research/Improvement networks	Clinical focus
Chronic Kidney Disease in Children (CKiD)	Chronic kidney disease
Glomerular Disease Learning Network (GLEAN)	Glomerular disease
Improving Renal Outcomes Collaborative (IROC)	Transplant
Neonatal Kidney Collaborative (NKC)	Neonatal kidney disease
Nephrotoxic Injury Negated by Just-in-time Action (NINJA)	Acute kidney injury
Standardized Care to Improve Outcomes in Pediatric Endstage Kidney Disease (SCOPE)	Dialysis

Continued on page 24 ›

Cooperation and Collaboration

Continued from page 23

Figure 1

Clinic-based Intervention to Promote Medication Adherence in Kidney Transplant Recipients

Kidney News

Teen Adherence in Kidney Transplant, Effectiveness of Intervention Trial (TAKE-IT)
Unblinded, parallel arm RCT

8 Kidney Transplant centers

February 2012 – May 2016

11-24 years

Prevalent Kidney Transplant recipients
≥ 3 months post-transplantation
n = 169

RANDOMIZATION

Intervention group
n = 81
- *Coaching*
- *Action-focused problem solving*
- *Feedback on adherence*
- *Text, email, visual cue dose reminders*

Control group
n = 88
- *Non-specific support (Coach actively listened)*
- *Adherence was not discussed*

PRIMARY OUTCOMES

	INTENTION TO TREAT	AS TREATED
	Intervention (vs. control)	
"Taking" adherence *Proportion of prescribed doses of immunosuppressive medications taken*	**1.66** (1.15-2.39) *p=0.006*	**1.70** (1.18-2.45) *p=0.004*
"Timing" adherence *Proportion of doses of immunosuppressive medications taken between 1 hour before and 2 hours after the prescribed time of administration*	**1.74** (1.21-2.50) *p=0.003*	**1.78** (1.24-2.55) *p=0.002*

***Odds ratio (95% CI)**

⚠ **Lack of electronic adherence day for some (potential bias)**

⚠ **Low statistical power for clinical outcomes**

Conclusions The multicomponent TAKE-IT intervention resulted in significantly better medication adherence than the control condition. Better medication adherence may result in improved graft outcomes but this will need to be demonstrated in larger studies.

Foster BJ, Pai ALH, Zelikovsky N, et al. ***A Randomized Trial of a Multicomponent Intervention to Promote Medication Adherence: The Teen Adherence in Kidney Transplant Effectiveness of Intervention Trial (TAKE-IT).*** Am J Kidney Dis. 2018 Jul;72(1):30-41

Visual Abstract by Edgar Lerma, MD, FASN

Pediatric Onco-Nephrology: A Long-Overdue Conversation

By Sai Sudha Mannemuddhu

How many times were you consulted on or followed up on a child with cancer with one of the following issues: hypertension, acute kidney injury, proteinuria, hematuria, fluid and electrolyte imbalances, tumor lysis syndrome, kidney and urinary tract infections, kidney tumor, on nephrotoxic medications, stem cell or bone marrow transplant, thrombotic microangiopathy, or chronic kidney disease (CKD)? All the time, right? With advances in cancer therapies and development of novel treatments like CD19-targeted chimeric antigen receptor T cell (CAR-T) therapy and vascular endothelial growth factor (VEGF)-targeted therapy, challenges have only increased. Since the first onco-nephrology forum at ASN Kidney Week in 2012, there have been several publications and conferences on this topic, leading to the emergence of onco-nephrology as a medical subspecialty, but the idea of pediatric onco-nephrology is still fledgling.

The survival of children and adolescents with cancer has improved significantly over the past 50 years, with 5-year survival rates of 83%–85% in 2008–2014, compared to 58%–68% in the mid-1970s. This begs the question, what will the long-term kidney function be in these young adult populations who were exposed to a variety of therapies that are potentially nephrotoxic?

The survival of children and adolescents with cancer has improved significantly over the past 50 years.

To answer this question, Green et al. (1) conducted a prospective study on a patient population from St. Jude Children's Research Hospital, aiming to define the prevalence of and risk factors for impaired kidney function. Based on the St. Jude Lifetime Cohort Study (SJLIFE) eligibility criteria (Figure 1), 2753 patients, who were followed for a median of 23.2 years, were selected for this study. Investigators quantified kidney function by measuring serum creatinine, urine protein (qualitative), estimated glomerular filtration rate, and quantified exposure to a variety of cancer treatments such as chemotherapy, radiation therapy, and surgery. In this cohort, the prevalence of CKD stages 3–5 was 2% (~0.4% in a 30- to 39-year-old population in Tennessee), and proteinuria was 6%. At an older age at evaluation, hypertension, cumulative doses of alkylating or platinating agents, usage of calcineurin inhibitors (CNIs), an increase in volume or dose of radiation, or nephrectomy increased the odds for CKD in this population. Similarly, Knijnenburg, et al. (2) showed that in a European childhood cancer survivor cohort, the prevalence of CKD stage 2 or above, proteinuria, and hypertension was 5%, 15%, and 15%, respectively.

Kidney injury is not uncommon in childhood cancer survivors, and development of new protocols and screening guidelines aids in early diagnosis and treatment of CKD in this population. This highlights the importance of pediatric onco-nephrology and drives the attitude from "why" to "now." ■

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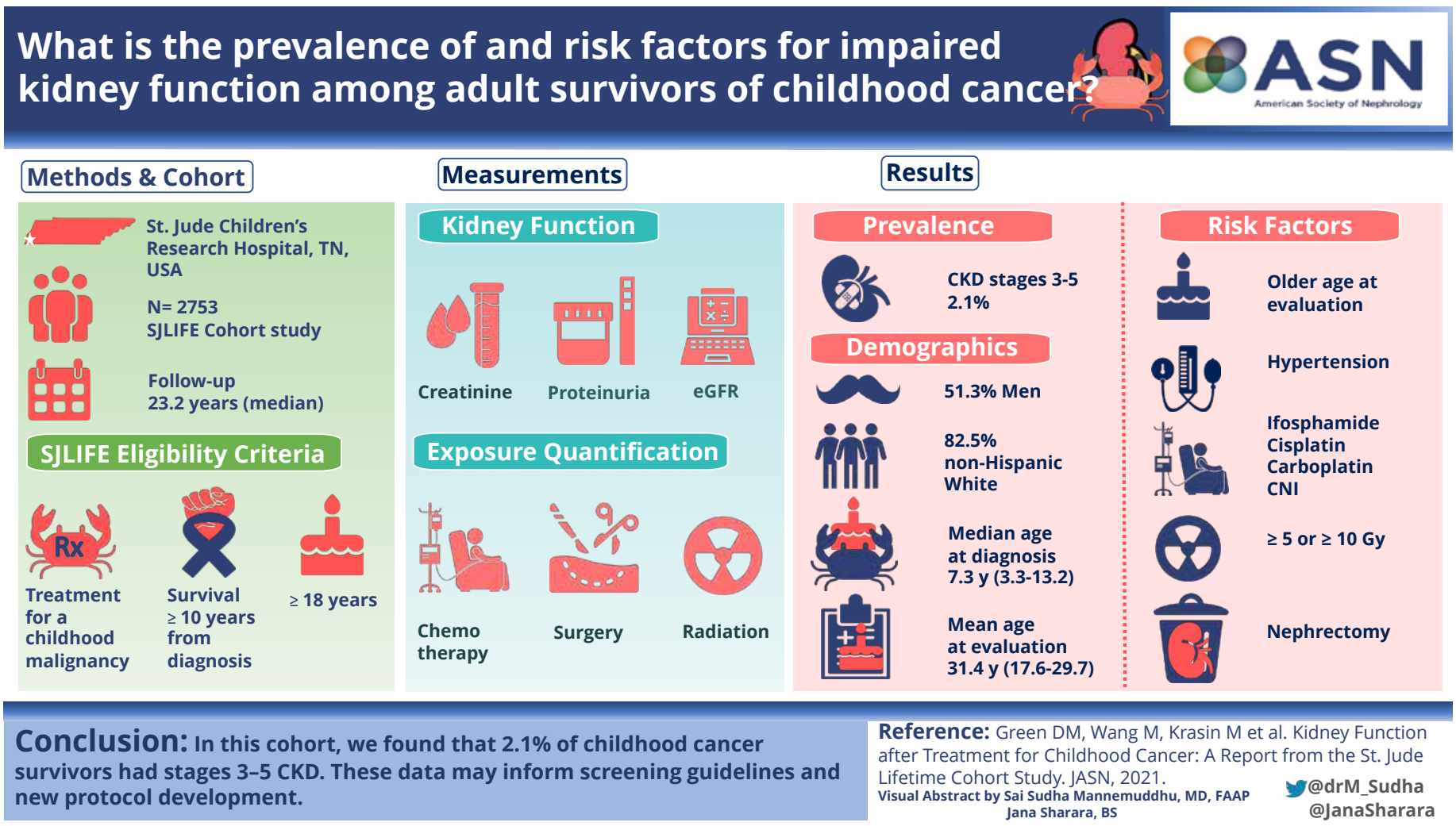
Visual Abstract (Figure 1) co-creator Jana Sharara, BS, is a second-year medical student at the Lebanese American University, Lebanon.

The author and Visual Abstract creators declare no disclosures/conflicts of interest related to the work.

References

1. Green MG, et al. Kidney function after treatment for childhood cancer: A report from the St. Jude Lifetime Cohort Study. *J Am Soc Nephrol* 2021; 32:983–993. doi: 10.1681/ASN.2020060849
2. Knijnenburg SL, et al. Renal dysfunction and elevated blood pressure in long-term childhood cancer survivors. *Clin J Am Soc Nephrol* 2012; 7:1416–1427. doi: 10.2215/CJN.09620911

Figure 1



Combination of Albuminuria and Kidney Function Predicts CKD Risk

The combination of increased urinary albumin-creatinine ratio (UACR) and decreased estimated glomerular filtration rate (eGFR) is strongly associated with an increased risk of advanced chronic kidney disease (CKD), reports a UK population-based study in the *American Journal of Kidney Diseases*.

The analysis included more than 91,319 UK primary care patients, identified from the Clinical Practice Research Datalink between 2000 and 2015. Mean eGFR was 72.6 mL/min/1.73 m^2 and median UACR 9.7 mg/g; 77.7% of patients had diabetes.

Patterns of change in UACR and eGFR—a 30% or greater increase, stable, or a 30% or greater decrease—were analyzed over a 3-year exposure window. The main outcome of interest was the occurrence of advanced CKD, defined as a sustained eGFR of less than 30 mL/min/1.73 m^2. Kidney failure, cardiovascular disease, and all-cause mortality were analyzed as secondary outcomes. Greater increases in UACR and greater decreases in eGFR were both associated with older age, history of cardiovascular disease, and use of renin-angiotensin system blockers or other antihypertensive drugs.

Risk of advanced CKD was higher in patients with a 30% or greater increase in UACR, hazard ratio (HR) 1.78, and in those with a 30% or greater decrease in eGFR, HR 7.53 (compared to stable values). For the combination of increased UACR and decreased eGFR, the HR was 15.15 (compared to stable values for both). For kidney failure, the associated HR was 16.68. The combination improved discrimination of advanced CKD better than either measure alone; the magnitude of improvement was greater for eGFR than for UACR.

Changes in eGFR and UACR have been evaluated separately as alternative outcomes in kidney trials. However, little is known about their combined value as a surrogate for progression to kidney failure.

This large population-based study finds that increased UACR plus decreased eGFR is strongly associated with the risk of advanced CKD as well as kidney failure [Neuen BL, et al. Changes in GFR and albuminuria in routine clinical practice and the risk of kidney disease progression. *Am J Kidney Dis*, published online ahead of print April 22, 2021. doi: 10.1053/j.ajkd.2021.02.335; https://www.ajkd.org/article/S0272-6386(21)00562-X/fulltext].

Comorbid Kidney Disease Increases Risk of Severe COVID-19

Patients with comorbid kidney disease and those on continuous renal replacement therapy (CRRT) are at increased risk of severe COVID-19, concludes a meta-analysis in *Clinical and Experimental Medicine*.

A systematic review of the literature was performed to identify studies providing information on comorbid chronic kidney disease (CKD), acute kidney injury (AKI), and CRRT and outcomes of hospitalized patients with laboratory-confirmed COVID-19. The meta-analysis included data from 29 observational studies including a total of 15,017 COVID-19 patients. The studies were published through August 2020, with 20 studies performed in China and 6 in the United States. Severe COVID-19 was defined in terms of intensive care unit (ICU) admission, oxygen saturation less than 90%, invasive mechanical ventilation, and in-hospital death.

Overall, 11.6% of patients had prevalent AKI, 9.7% had CKD, and 2.58% were receiving CRRT. On analysis of 13,278 patients from 22 studies, comorbid CKD was associated with increased odds of severe COVID-19: pooled odds ratio (OR) 1.7.

Based on 16 studies, including 3693 patients, comorbid CKD was associated with increased odds of severe COVID-19: OR 8.28. Meta-analysis of 3946 patients from 17 studies showed a significant association between CRRT and severe COVID-19: OR 16.90. Although pandemic COVID-19 primarily affects the lungs, kidney manifestations may also occur through unknown but likely multifactorial mechanisms. This meta-analysis of data available through August 2020 shows that AKI, CKD, and CRRT use are common among hospitalized patients with COVID-19 and are also associated with increased odds of severe disease [Singh J, et al. Kidney disease and COVID-19 disease severity—systematic review and meta-analysis. *Clin Exp Med*, published online ahead of print April 23, 2021. doi: 10.1007/s10238-021-00715-x; https://link.springer.com/article/10.1007/s10238-021-00715-x].

Change the story with FARXIGA

A BREAKTHROUGH THERAPY FOR CKD[1,2*]

THE FIRST THERAPY APPROVED IN 20 YEARS TO HELP DELAY THE WORSENING OF CKD IN PATIENTS AT RISK OF PROGRESSION, WITH AND WITHOUT T2D[1]

farxiga® (dapagliflozin) 10mg tablets

HELP PROTECT YOUR PATIENTS WITH CKD AT RISK OF PROGRESSION FROM DIALYSIS AND CV DEATH[1,3]

- **39%** RRR in the primary composite of sustained eGFR decline, ESKD, and CV or renal death[1,3†]
- **31%** RRR in all-cause mortality[1,3‡]

*The FDA granted its "Breakthrough Therapy" designation to FARXIGA in their review of FARXIGA in CKD.[2]
†14.5% vs 9.2% with placebo in adults with eGFR ≤75 to ≥25 mL/min/1.73 m^2; HR 0.61 (95% CI: 0.51–0.72); *P*<0.0001.[1,3]
‡6.8% vs 4.7% with placebo in adults with eGFR ≤75 to ≥25 mL/min/1.73 m^2; HR 0.69 (95% CI: 0.53–0.88); *P*=0.0035.[1,3]

Study design: DAPA-CKD was a randomized, double-blind, placebo-controlled, multicenter clinical trial of 4304 adults with eGFR 25-75 mL/min/1.73 m^2, and UACR 200-5000 mg/g, with or without T2D, randomly assigned to receive FARXIGA (10 mg once daily) or placebo for a median follow-up of 2.4 years.[3]

INDICATIONS AND LIMITATIONS OF USE for FARXIGA® (dapagliflozin)

FARXIGA is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular (CV) disease or multiple CV risk factors
- to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction
- to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression

FARXIGA is not recommended for patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.

FARXIGA is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m^2. FARXIGA is likely to be ineffective in this setting based upon its mechanism of action.

FARXIGA is not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of immunosuppressive therapy for kidney disease. FARXIGA is not expected to be effective in these populations.

IMPORTANT SAFETY INFORMATION

Contraindications

- Prior serious hypersensitivity reaction to FARXIGA
- Patients on dialysis

Warnings and Precautions

- **Ketoacidosis in Diabetes Mellitus** has been reported in patients with type 1 and type 2 diabetes receiving FARXIGA. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. Some cases were fatal. Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue FARXIGA, evaluate and treat promptly. Before initiating FARXIGA, consider risk factors for ketoacidosis. Patients on FARXIGA may require monitoring and temporary discontinuation in situations known to predispose to ketoacidosis
- **Volume Depletion:** FARXIGA can cause intravascular volume depletion which may manifest as symptomatic hypotension or acute transient changes in creatinine. Acute kidney injury requiring hospitalization and dialysis has been reported in patients with type 2 diabetes receiving SGLT2 inhibitors, including FARXIGA. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating FARXIGA in these patients, assess volume status and renal function. After initiating therapy, monitor for signs and symptoms of hypotension and renal function
- **Urosepsis and Pyelonephritis:** SGLT2 inhibitors increase the risk for urinary tract infections (UTIs) and serious UTIs have been reported with FARXIGA. Evaluate for signs and symptoms of UTIs and treat promptly
- **Hypoglycemia:** FARXIGA can increase the risk of hypoglycemia when coadministered with insulin and insulin secretagogues. Consider lowering the dose of these agents when coadministered with FARXIGA
- **Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):** Rare but serious, life-threatening cases have been reported in patients with diabetes mellitus receiving SGLT2 inhibitors including FARXIGA. Cases have been reported in females and males. Serious outcomes have included hospitalization, surgeries, and death. Assess patients presenting with pain or tenderness, erythema, swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment and discontinue FARXIGA
- **Genital Mycotic Infections:** FARXIGA increases the risk of genital mycotic infections, particularly in patients with prior genital mycotic infections. Monitor and treat appropriately

Adverse Reactions

In a pool of 12 placebo-controlled studies, the most common adverse reactions (≥5%) associated with FARXIGA 5 mg, 10 mg, and placebo respectively were female genital mycotic infections (8.4% vs 6.9% vs 1.5%), nasopharyngitis (6.6% vs 6.3% vs 6.2%), and urinary tract infections (5.7% vs 4.3% vs 3.7%).

Use in Specific Populations

- **Pregnancy:** Advise females of potential risk to a fetus especially during the second and third trimesters
- **Lactation:** FARXIGA is not recommended when breastfeeding

DOSING

To improve glycemic control, the recommended starting dose is 5 mg orally once daily. Dose can be increased to 10 mg orally once daily for additional glycemic control.

For all other indications, the recommended dose is 10 mg orally once daily.

Please see Brief Summary of Prescribing Information on adjacent pages.

*You are encouraged to report negative side effects of AstraZeneca prescription drugs to the FDA. Visit **www.FDA.gov/medwatch** or call 1-800-FDA-1088.*

CI=confidence interval; CKD=chronic kidney disease; DAPA-CKD=Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease; eGFR=estimated glomerular filtration rate; FDA=Food and Drug Administration; HR=hazard ratio; NYHA=New York Heart Association; SGLT2i=sodium-glucose cotransporter 2 inhibitor; RRR=relative risk reduction; T2D=type 2 diabetes; UACR=urine albumin-to-creatinine ratio.

References: 1. FARXIGA® (dapagliflozin) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2021. **2.** FARXIGA granted Breakthrough Therapy Designation in US for chronic kidney disease [press release]. Published October 2, 2020. Accessed March 17, 2021. https://www.astrazeneca-us.com/media/press-releases/2020/farxiga-granted-breakthrough-therapy-designation-in-us-for-chronic-kidney-disease.html **3.** Heerspink HJL et al. *N Engl J Med.* 2020;383(15):1436-1446.

AstraZeneca

FARXIGA® (dapagliflozin) tablets, for oral use

Initial U.S Approval: 2014

BRIEF SUMMARY of PRESCRIBING INFORMATION.

For complete prescribing information, consult official package insert.

INDICATIONS AND USAGE

FARXIGA (dapagliflozin) is indicated:

- As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular disease or multiple cardiovascular risk factors.
- To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction.
- To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.

Limitations of Use

- FARXIGA is not recommended for patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.
- FARXIGA is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m^2. FARXIGA is likely to be ineffective in this setting based upon its mechanism of action.
- FARXIGA is not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of immunosuppressive therapy for kidney disease. FARXIGA is not expected to be effective in these populations.

DOSAGE AND ADMINISTRATION

Prior to Initiation of FARXIGA

Assess renal function prior to initiation of FARXIGA therapy and then as clinically indicated *[see Warnings and Precautions (5.2) in the full Prescribing Information]*.

Assess volume status and, if necessary, correct volume depletion prior to initiation of FARXIGA *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.5, 8.6) in the full Prescribing Information]*.

Recommended Dosage

See Table 1 for dosage recommendations based on estimated glomerular filtration rate (eGFR).

Table 1: Recommended Dosage

eGFR (mL/min/1.73 m^2)	Recommended Dose
eGFR 45 or greater	To improve glycemic control, the recommended starting dose is 5 mg orally once daily. Dose can be increased to 10 mg orally once daily for additional glycemic control*. For all other indications, the recommended starting dose is 10 mg orally once daily.
eGFR 25 to less than 45	10 mg orally once daily*.
eGFR less than 25	Initiation is not recommended, however patients may continue 10 mg orally once daily to reduce the risk of eGFR decline, ESKD, CV death and hHF.
On dialysis	Contraindicated.

* FARXIGA is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m^2. FARXIGA is likely to be ineffective in this setting based upon its mechanism of action.

hHF: hospitalization for heart failure, CV: Cardiovascular, ESKD: End Stage Kidney Disease.

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to FARXIGA, such as anaphylactic reactions or angioedema *[see Adverse Reactions (6.1) in the full Prescribing Information]*.
- Patients on dialysis *[see Use in Specific Populations (8.6) in the full Prescribing Information]*.

WARNINGS AND PRECAUTIONS

Ketoacidosis in Patients with Diabetes Mellitus

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in patients with type 1 and type 2 diabetes mellitus receiving sodium-glucose cotransporter 2 (SGLT2) inhibitors, including FARXIGA *[see Adverse Reactions (6.1) in the full Prescribing Information]*. In placebo-controlled trials of patients with type 1 diabetes mellitus, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. Fatal cases of ketoacidosis have been reported in patients taking FARXIGA. FARXIGA is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (1) in the full Prescribing Information]*.

Patients treated with FARXIGA who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels as ketoacidosis associated with FARXIGA may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, FARXIGA should be discontinued, the patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid, and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized, and the institution of treatment was delayed because the presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis, such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating FARXIGA, consider factors in the patient history that may predispose to ketoacidosis, including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

For patients who undergo scheduled surgery, consider temporarily discontinuing FARXIGA for at least 3 days prior to surgery *[see Clinical Pharmacology (12.2, 12.3) in the full Prescribing Information]*.

Consider monitoring for ketoacidosis and temporarily discontinuing FARXIGA in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting FARXIGA. Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue FARXIGA and seek medical attention immediately if signs and symptoms occur.

Volume Depletion

FARXIGA can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including FARXIGA. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating FARXIGA in patients with one or more of these characteristics, assess volume status and renal function. Monitor for signs and symptoms of hypotension, and renal function after initiating therapy.

Urosepsis and Pyelonephritis

Serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization have been reported in patients receiving SGLT2 inhibitors, including FARXIGA. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated *[see Adverse Reactions (6) in the full Prescribing Information]*.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. FARXIGA may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions (6.1) in the full Prescribing Information]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when these agents are used in combination with FARXIGA.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Reports of necrotizing fasciitis of the perineum (Fournier's Gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including FARXIGA. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with FARXIGA presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue FARXIGA, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections

FARXIGA increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections *[see Adverse Reactions (6.1) in the full Prescribing Information]*. Monitor and treat appropriately.

ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Ketoacidosis in Patients with Diabetes Mellitus *[see Warnings and Precautions (5.1) in the full Prescribing Information]*
- Volume Depletion *[see Warnings and Precautions (5.2) in the full Prescribing Information]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions (5.3) in the full Prescribing Information]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) *[see Warnings and Precautions (5.5) in the full Prescribing Information]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.6) in the full Prescribing Information]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

FARXIGA has been evaluated in clinical trials in patients with type 2 diabetes mellitus, in patients with heart failure, and in patients with chronic kidney disease. The overall safety profile of FARXIGA was consistent across the studied indications. Severe hypoglycemia and diabetic ketoacidosis (DKA) were observed only in patients with diabetes mellitus.

Clinical Trials in Patients with Type 2 Diabetes Mellitus

Pool of 12 Placebo-Controlled Studies for FARXIGA 5 and 10 mg for Glycemic Control

The data in Table 1 is derived from 12 glycemic control placebo-controlled studies in patients with type 2 diabetes mellitus ranging from 12 to 24 weeks. In 4 studies FARXIGA was used as monotherapy, and in 8 studies FARXIGA was used as add-on to background antidiabetic therapy or as combination therapy with metformin *[see Clinical Studies (14.1) in the full Prescribing Information]*.

These data reflect exposure of 2338 patients to FARXIGA with a mean exposure duration of 21 weeks. Patients received placebo (N=1393), FARXIGA 5 mg (N=1145), or FARXIGA 10 mg (N=1193) once daily. The mean age of the population was 55 years and 2% were older than 75 years of age. Fifty percent (50%) of the population were male; 81% were White, 14% were Asian, and 3% were Black or African American. At baseline, the population had diabetes for an average of 6 years, had a mean hemoglobin A1c (HbA1c) of 8.3%, and 21% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired in 92% of patients and moderately impaired in 8% of patients (mean eGFR 86 mL/min/1.73 m^2).

Table 2 shows common adverse reactions associated with the use of FARXIGA. These adverse reactions were not present at baseline, occurred more commonly on FARXIGA than on placebo, and occurred in at least 2% of patients treated with either FARXIGA 5 mg or FARXIGA 10 mg.

Table 2: Adverse Reactions in Placebo-Controlled Studies of Glycemic Control Reported in ≥2% of Patients Treated with FARXIGA

Adverse Reaction	% of Patients		
	Pool of 12 Placebo-Controlled Studies		
	Placebo N=1393	FARXIGA 5 mg N=1145	FARXIGA 10 mg N=1193
Female genital mycotic infections*	1.5	8.4	6.9
Nasopharyngitis	6.2	6.6	6.3
Urinary tract infections†	3.7	5.7	4.3
Back pain	3.2	3.1	4.2
Increased urination‡	1.7	2.9	3.8
Male genital mycotic infections§	0.3	2.8	2.7

Table 2: Adverse Reactions in Placebo-Controlled Studies of Glycemic Control Reported in ≥2% of Patients Treated with FARXIGA (cont'd)

Adverse Reaction	% of Patients		
	Pool of 12 Placebo-Controlled Studies		
	Placebo N=1393	FARXIGA 5 mg N=1145	FARXIGA 10 mg N=1193
Nausea	2.4	2.8	2.5
Influenza	2.3	2.7	2.3
Dyslipidemia	1.5	2.1	2.5
Constipation	1.5	2.2	1.9
Discomfort with urination	0.7	1.6	2.1
Pain in extremity	1.4	2.0	1.7

* Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for females: vulvovaginal mycotic infection, vaginal infection, vulvovaginal candidiasis, vulvovaginitis, genital infection, genital candidiasis, fungal genital infection, vulvitis, genitourinary tract infection, vulval abscess, and vaginitis bacterial. (N for females: Placebo=677, FARXIGA 5 mg=581, FARXIGA 10 mg=598).

† Urinary tract infections include the following adverse reactions, listed in order of frequency reported: urinary tract infection, cystitis, *Escherichia* urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection, and prostatitis.

‡ Increased urination includes the following adverse reactions, listed in order of frequency reported: pollakiuria, polyuria, and urine output increased.

§ Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for males: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection male, penile infection, balanoposthitis, balanoposthitis infective, genital infection, and posthitis. (N for males: Placebo=716, FARXIGA 5 mg=564, FARXIGA 10 mg=595).

Pool of 13 Placebo-Controlled Studies for FARXIGA 10 mg for Glycemic Control

FARXIGA 10 mg was also evaluated in a larger glycemic control placebo-controlled study pool in patients with type 2 diabetes mellitus. This pool combined 13 placebo-controlled studies, including 3 monotherapy studies, 9 add-on to background antidiabetic therapy studies, and an initial combination with metformin study. Across these 13 studies, 2360 patients were treated once daily with FARXIGA 10 mg for a mean duration of exposure of 22 weeks. The mean age of the population was 59 years and 4% were older than 75 years. Fifty-eight percent (58%) of the population were male; 84% were White, 9% were Asian, and 3% were Black or African American. At baseline, the population had diabetes for an average of 9 years, had a mean HbA1c of 8.2%, and 30% had established microvascular disease. Baseline renal function was normal or mildly impaired in 88% of patients and moderately impaired in 11% of patients (mean eGFR 82 mL/min/1.73 m^2).

Volume Depletion

FARXIGA causes an osmotic diuresis, which may lead to a reduction in intravascular volume. Adverse reactions related to volume depletion (including reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension) in patients with type 2 diabetes mellitus for the 12-study and 13-study, short-term, placebo-controlled pools and for the DECLARE study are shown in Table 3 *[see Warnings and Precautions (5.2)]*.

Table 3: Adverse Reactions Related to Volume Depletion* in Clinical Studies in Patients with Type 2 Diabetes Mellitus with FARXIGA

	Pool of 12 Placebo-Controlled Studies			Pool of 13 Placebo-Controlled Studies		DECLARE Study	
	Placebo	FARXIGA 5 mg	FARXIGA 10 mg	Placebo	FARXIGA 10 mg	Placebo	FARXIGA 10 mg
Overall population N (%)	N=1393 5 (0.4%)	N=1145 7 (0.6%)	N=1193 9 (0.8%)	N=2295 17 (0.7%)	N=2360 27 (1.1%)	N=8569 207 (2.4%)	N=8574 213 (2.5%)
Patient Subgroup n (%)							
Patients on loop diuretics	n=55 1 (1.8%)	n=40 0	n=31 3 (9.7%)	n=267 4 (1.5%)	n=236 6 (2.5%)	n=934 57 (6.1%)	n=866 57 (6.6%)
Patients with moderate renal impairment with eGFR ≥30 and <60 mL/min/ 1.73 m^2	n=107 2 (1.9%)	n=107 1 (0.9%)	n=89 1 (1.1%)	n=268 4 (1.5%)	n=265 5 (1.9%)	n=658 30 (4.6%)	n=604 35 (5.8%)
Patients ≥65 years of age	n=276 1 (0.4%)	n=216 1 (0.5%)	n=204 3 (1.5%)	n=711 6 (0.8%)	n=665 11 (1.7%)	n=3950 121 (3.1%)	n=3948 117 (3.0%)

* Volume depletion includes reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension.

Hypoglycemia

The frequency of hypoglycemia by study in patients with type 2 diabetes mellitus *[see Clinical Studies (14.1) in the full Prescribing Information]* is shown in Table 4. Hypoglycemia was more frequent when FARXIGA was added to sulfonylurea or insulin *[see Warnings and Precautions (5.4) in the full Prescribing Information]*.

Table 4: Incidence of Severe Hypoglycemia* and Hypoglycemia with Glucose < 54 mg/dL† in Controlled Glycemic Control Clinical Studies in Patients with Type 2 Diabetes Mellitus

	Placebo/Active Control	FARXIGA 5 mg	FARXIGA 10 mg
Monotherapy (24 weeks)	**N=75**	**N=64**	**N=70**
Severe [n (%)]	0	0	0
Glucose <54 mg/dL [n (%)]	0	0	0
Add-on to Metformin (24 weeks)	**N=137**	**N=137**	**N=135**
Severe [n (%)]	0	0	0
Glucose <54 mg/dL [n (%)]	0	0	0
Add-on to Glimepiride (24 weeks)	**N=146**	**N=145**	**N=151**
Severe [n (%)]	0	0	0
Glucose <54 mg/dL [n (%)]	1 (0.7)	3 (2.1)	5 (3.3)
Add-on to Metformin and a Sulfonylurea (24 Weeks)	**N=109**	**-**	**N=109**
Severe [n (%)]	0	-	0
Glucose <54 mg/dL [n (%)]	3 (2.8)	-	7 (6.4)

Table 4: Incidence of Severe Hypoglycemia* and Hypoglycemia with Glucose < 54 mg/dL† in Controlled Glycemic Control Clinical Studies in Patients with Type 2 Diabetes Mellitus (cont'd)

	Placebo/Active Control	FARXIGA 5 mg	FARXIGA 10 mg
Add-on to Pioglitazone (24 weeks)	**N=139**	**N=141**	**N=140**
Severe [n (%)]	0	0	0
Glucose <54 mg/dL [n (%)]	0	1 (0.7)	0
Add-on to DPP4 inhibitor (24 weeks)	**N=226**	**–**	**N=225**
Severe [n (%)]	0	–	1 (0.4)
Glucose <54 mg/dL [n (%)]	1 (0.4)	–	1 (0.4)
Add-on to Insulin with or without other OADs‡ (24 weeks)	**N=197**	**N=212**	**N=196**
Severe [n (%)]	1 (0.5)	2 (0.9)	2 (1.0)
Glucose <54 mg/dL [n (%)]	43 (21.8)	55 (25.9)	45 (23.0)

* Severe episodes of hypoglycemia were defined as episodes of severe impairment in consciousness or behavior, requiring external (third party) assistance, and with prompt recovery after intervention regardless of glucose level.

† Episodes of hypoglycemia with glucose <54 mg/dL (3 mmol/L) were defined as reported episodes of hypoglycemia meeting the glucose criteria that did not also qualify as a severe episode.

‡ OAD = oral antidiabetic therapy.

In the DECLARE study *[see Clinical Studies (14.2) in the full Prescribing Information]*, severe events of hypoglycemia were reported in 58 (0.7%) out of 8574 patients treated with FARXIGA and 83 (1.0%) out of 8569 patients treated with placebo.

Genital Mycotic Infections

In the glycemic control trials, genital mycotic infections were more frequent with FARXIGA treatment. Genital mycotic infections were reported in 0.9% of patients on placebo, 5.7% on FARXIGA 5 mg, and 4.8% on FARXIGA 10 mg, in the 12-study placebo-controlled pool. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with FARXIGA 10 mg. Infections were more frequently reported in females than in males (see Table 1). The most frequently reported genital mycotic infections were vulvovaginal mycotic infections in females and balanitis in males. Patients with a history of genital mycotic infections were more likely to have a genital mycotic infection during the study than those with no prior history (10.0%, 23.1%, and 25.0% versus 0.8%, 5.9%, and 5.0% on placebo, FARXIGA 5 mg, and FARXIGA 10 mg, respectively). In the DECLARE study *[see Clinical Studies (14.2) in the full Prescribing Information]*, serious genital mycotic infections were reported in <0.1% of patients treated with FARXIGA and <0.1% of patients treated with placebo. Genital mycotic infections that caused study drug discontinuation were reported in 0.9% of patients treated with FARXIGA and <0.1% of patients treated with placebo.

Hypersensitivity Reactions

Hypersensitivity reactions (e.g., angioedema, urticaria, hypersensitivity) were reported with FARXIGA treatment. In glycemic control studies, serious anaphylactic reactions and severe cutaneous adverse reactions and angioedema were reported in 0.2% of comparator-treated patients and 0.3% of FARXIGA-treated patients. If hypersensitivity reactions occur, discontinue use of FARXIGA; treat per standard of care and monitor until signs and symptoms resolve.

Ketoacidosis in Patients with Diabetes Mellitus

In the DECLARE study *[see Warnings and Precautions (5.1) and Clinical Studies (14.2) in the full Prescribing Information]*, events of diabetic ketoacidosis (DKA) were reported in 27 out of 8574 patients in the FARXIGA-treated group and 12 out of 8569 patients in the placebo group. The events were evenly distributed over the study period.

Laboratory Tests

Increases in Serum Creatinine and Decreases in eGFR

Initiation of SGLT2 inhibitors, including FARXIGA causes a small increase in serum creatinine and decrease in eGFR. These changes in serum creatinine and eGFR generally occur within two weeks of starting therapy and then stabilize regardless of baseline kidney function. Changes that do not fit this pattern should prompt further evaluation to exclude the possibility of acute kidney injury *[see Warnings and Precautions (5.2) in the full Prescribing Information]*. In two studies that included patients with type 2 diabetes mellitus with moderate renal impairment, the acute effect on eGFR reversed after treatment discontinuation, suggesting acute hemodynamic changes may play a role in the renal function changes observed with FARXIGA.

Increase in Hematocrit

In the pool of 13 placebo-controlled studies of glycemic control, increases from baseline in mean hematocrit values were observed in FARXIGA-treated patients starting at Week 1 and continuing up to Week 16, when the maximum mean difference from baseline was observed. At Week 24, the mean changes from baseline in hematocrit were –0.33% in the placebo group and 2.30% in the FARXIGA 10 mg group. By Week 24, hematocrit values >55% were reported in 0.4% of placebo-treated patients and 1.3% of FARXIGA 10 mg-treated patients.

Increase in Low-Density Lipoprotein Cholesterol

In the pool of 13 placebo-controlled studies of glycemic control, changes from baseline in mean lipid values were reported in FARXIGA-treated patients compared to placebo-treated patients. Mean percent changes from baseline at Week 24 were 0.0% versus 2.5% for total cholesterol, and -1.0% versus 2.9% for LDL cholesterol in the placebo and FARXIGA 10 mg groups, respectively. In the DECLARE study *[see Clinical Studies (14.2) in the full Prescribing Information]*, mean changes from baseline after 4 years were 0.4 mg/dL versus -4.1 mg/dL for total cholesterol, and -2.5 mg/dL versus -4.4 mg/dL for LDL cholesterol, in FARXIGA-treated and the placebo groups, respectively.

Decrease in Serum Bicarbonate

In a study of concomitant therapy of FARXIGA 10 mg with exenatide extended-release (on a background of metformin), four patients (1.7%) on concomitant therapy had a serum bicarbonate value of less than or equal to 13 mEq/L compared to one each (0.4%) in the FARXIGA and exenatide-extended release treatment groups *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

DAPA-HF Heart Failure Study

No new adverse reactions were identified in the DAPA-HF heart failure study.

DAPA-CKD Chronic Kidney Disease Study

No new adverse reactions were identified in the DAPA-CKD study in patients with chronic kidney disease.

Postmarketing Experience

Additional adverse reactions have been identified during postapproval use of FARXIGA in patients with diabetes mellitus. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Ketoacidosis
- Acute Kidney Injury
- Urosepsis and Pyelonephritis
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
- Rash

DRUG INTERACTIONS

Positive Urine Glucose Test

Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on animal data showing adverse renal effects, FARXIGA is not recommended during the second and third trimesters of pregnancy.

Limited data with FARXIGA in pregnant women are not sufficient to determine drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes and untreated heart failure in pregnancy *(see Clinical Considerations)*.

In animal studies, adverse renal pelvic and tubule dilatations, that were not fully reversible, were observed in rats when dapagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy, at all doses tested; the lowest of which provided an exposure 15-times the 10 mg clinical dose *(see Data)*.

The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes with a HbA1c greater than 7% and has been reported to be as high as 20 to 25% in women with HbA1c greater than 10%. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

Dapagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg/kg/day, increased kidney weights and increased the incidence of renal pelvic and tubular dilatations at all dose levels. Exposure at the lowest dose tested was 15-times the 10 mg clinical dose (based on AUC). The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within a 1-month recovery period.

In a prenatal and postnatal development study, dapagliflozin was administered to maternal rats from gestation day 6 through lactation day 21 at doses of 1, 15, or 75 mg/kg/day, and pups were indirectly exposed *in utero* and throughout lactation. Increased incidence or severity of renal pelvic dilatation was observed in 21-day-old pups offspring of treated dams at 75 mg/kg/day (maternal and pup dapagliflozin exposures were 1415-times and 137-times, respectively, the human values at the 10 mg clinical dose, based on AUC). Dose-related reductions in pup body weights were observed at greater or equal to 29-times the 10 mg clinical dose (based on AUC). No adverse effects on developmental endpoints were noted at 1 mg/kg/day (19-times the 10 mg clinical dose, based on AUC). These outcomes occurred with drug exposure during periods of renal development in rats that corresponds to the late second and third trimester of human development.

In embryofetal development studies in rats and rabbits, dapagliflozin was administered throughout organogenesis, corresponding to the first trimester of human pregnancy. In rats, dapagliflozin was neither embryolethal nor teratogenic at doses up to 75 mg/kg/day (1441-times the 10 mg clinical dose, based on AUC). Dose related effects on the rat fetus (structural abnormalities and reduced body weight) occurred only at higher dosages, equal to or greater than 150 mg/kg (more than 2344-times the 10 mg clinical dose, based on AUC), which were associated with maternal toxicity. No developmental toxicities were observed in rabbits at doses up to 180 mg/kg/day (1191-times the 10 mg clinical dose, based on AUC).

Lactation

Risk Summary

There is no information regarding the presence of dapagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Dapagliflozin is present in the milk of lactating rats *(see Data)*. However, due to species specific differences in lactation physiology, the clinical relevance of these data are not clear. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in breastfed infants, advise women that use of FARXIGA is not recommended while breastfeeding.

Data

Dapagliflozin was present in rat milk at a milk/plasma ratio of 0.49, indicating that dapagliflozin and its metabolites are transferred into milk at a concentration that is approximately 50% of that in maternal plasma. Juvenile rats directly exposed to dapagliflozin showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

Pediatric Use

Safety and effectiveness of FARXIGA in pediatric patients under 18 years of age have not been established.

Geriatric Use

No FARXIGA dosage change is recommended based on age.

A total of 1424 (24%) of the 5936 FARXIGA-treated patients were 65 years and older and 207 (3.5%) patients were 75 years and older in a pool of 21 double-blind, controlled, clinical studies assessing the efficacy of FARXIGA in improving glycemic control in type 2 diabetes mellitus. After controlling for level of renal function (eGFR), efficacy was similar for patients under age 65 years and those 65 years and older. In patients ≥65 years of age, a higher proportion of patients treated with FARXIGA for glycemic control had adverse reactions of hypotension *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1) in the full Prescribing Information]*.

In both the DAPA-HF and DAPA-CKD studies, safety and efficacy were similar for patients age 65 years and younger and those older than 65. In the DAPA-HF study, 2714 (57%) out of 4744 patients with HFrEF were older than 65 years. In the DAPA-CKD study, 1818 (42%) out of 4304 patients with CKD were older than 65 years.

Renal Impairment

FARXIGA was evaluated in 4304 patients with chronic kidney disease (eGFR 25 to 75 mL/min/1.73 m^2) in the DAPA-CKD study. FARXIGA was also evaluated in 1926 patients with an eGFR of 30 to 60 mL/min/1.73 m^2 in the DAPA-HF study. The safety profile of FARXIGA across eGFR subgroups in these studies was consistent with the known safety profile *[see Adverse Reactions (6.1) and Clinical Studies (14.3 and 14.4) in the full Prescribing Information]*.

FARXIGA was evaluated in two glycemic control studies that included patients with type 2 diabetes mellitus with moderate renal impairment (an eGFR of 45 to less than 60 mL/min/1.73 m^2 *[see Clinical Studies (14.1) in the full Prescribing Information]*, and an eGFR of 30 to less than 60 mL/min/1.73 m^2, respectively). Patients with diabetes and renal impairment using FARXIGA may be more likely to experience hypotension and may be at higher risk for acute kidney injury secondary to volume depletion. In the study of patients with an eGFR 30 to less than 60 mL/min/1.73 m^2, 13 patients receiving FARXIGA experienced bone fractures compared to none receiving placebo. Use of FARXIGA for glycemic control in patients without established CV disease or CV risk factors is not recommended when eGFR is less than 45 mL/min/1.73 m^2 *[see Dosage and Administration (2.2) in the full Prescribing Information]*.

Efficacy and safety studies with FARXIGA did not enroll patients with an eGFR less than 25 mL/min/1.73 m^2. FARXIGA is contraindicated in patients on dialysis.

Hepatic Impairment

No dose adjustment is recommended for patients with mild, moderate, or severe hepatic impairment. However, the benefit-risk for the use of dapagliflozin in patients with severe hepatic impairment should be individually assessed since the safety and efficacy of dapagliflozin have not been specifically studied in this population *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

OVERDOSAGE

There were no reports of overdose during the clinical development program for FARXIGA.

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ supportive measures as dictated by the patient's clinical status. The removal of dapagliflozin by hemodialysis has not been studied.

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President Biden Proposes Advanced Research Projects Agency for Health (ARPA-H)

The president's request for fiscal year (FY) 2022 emphasized the Biden-Harris administration's strong support of and commitment to medical research and scientific innovation. While the president's complete budget will not be finalized by the start of the annual congressional appropriations process, typical during a presidential transition, the administration's proposal for discretionary funding in FY22 still provides useful insight into key administration priorities.

The administration proposed increasing the budget of the National Institutes of Health (NIH) to $51 billion, a $9 billion increase over FY21 levels (1). A significant portion of that increase would go to establishing the Advanced Research Projects Agency for Health (ARPA-H); President Biden first showed signs of supporting such an agency in 2019 on the presidential campaign trail. ARPA-H is envisioned to be housed within NIH and command a budget of $6.5 billion to "provide significant increases in direct Federal research and development spending in health" (2). ARPA-H's creation would be one of the largest increases in scientific research funding by the government in decades (3).

This new agency is believed to be charged with aggressively pursuing high-risk, high-reward technologies and therapies similar to the military's Defense Advanced Research Projects Agency (DARPA), after which it was modeled. While much still needs to be learned about ARPA-H as it is created, President Biden described the agency during his joint address to Congress on April 28, 2021, stating, "It would have a singular purpose: To develop breakthroughs to prevent, detect, and treat diseases like Alzheimer's, diabetes, and cancer" (4).

As ARPA-H is developed, ASN will advocate to the White House and NIH that sufficient resources be dedicated to programs within the agency that address kidney diseases and the needs of kidney patients. ASN will also continue to engage the Biden-Harris administration and Congress to advocate for federal agencies and programs that promote translational research and prioritize medical and scientific innovation such as NIH and ARPA-H during the congressional appropriations process.

ASN will continue to provide updates on the policies and priorities of the Biden-Harris administration that affect kidney health professionals and the patients they treat. ■

1. https://www.sciencemag.org/news/2021/04/biden-s-first-budget-request-goes-big-science
2. https://www.whitehouse.gov/wp-content/uploads/2021/04/FY2022-Discretionary-Request.pdf
3. https://www.statnews.com/2021/04/28/biden-pitches-new-health-agency-to-end-cancer/
4. https://www.whitehouse.gov/briefing-room/speeches-remarks/2021/04/29/remarks-by-president-biden-in-address-to-a-joint-session-of-congress/

Members of Congress Call for Organ Transplant System to Align with Patient Needs

By Zach Kribs

Members of the US Congress House Committee on Oversight and Reform called for urgency to increase the availability of organs for transplant and improve care for patients during a May 4, 2021, hearing on the US organ transplant system. Led by Committee Chair Raja Krishnamoorthi of Illinois and Ranking Member Michael Cloud of Texas, the hearing featured testimony from patients, organ donors, and transplant professionals and at times impassioned exchanges between members of the committee and Organ Procurement Organization (OPO) leadership.

"It is a very exhausting process waiting for a transplant," said Tonya Ingram, a hearing witness and patient on the waitlist for a kidney transplant. "Because of my rare blood type, being on the list could mean that I have to wait 10 years before I can receive a transplant. Ten years is a very long time for anyone…and to know that I won't have a kidney until then is a very daunting and heavy thing."

LaQuayia Goldring, a patient witness also on the waitlist for kidney transplant, provided testimony while receiving dialysis. "I can't miss dialysis, ever. Even when COVID-19 hit, I still had to come. And of course, I'm grateful for the opportunity to come to dialysis, and that it's keeping me alive, but it isn't easy."

The hearing follows recent finalization of the OPO Conditions for Coverage rule, which implements objective, verifiable, and standardizable metrics to assess the performance of OPOs. OPOs are a collection of 58 government contractors charged with the critical role of tracking potential organ donors, working with donors and donor families to obtain a consent-driven donation, and transporting the organ to the donor-recipient hospital.

"Given their central role in the transplant process, OPOs need to strive for perfection in their public mission," said Rep. Krishnamoorthi. "Unfortunately, they've been falling short. For years, OPOs have faced no outside incentive to perform. They evaded public scrutiny, refusing to reveal data showing their success and failure, hiding behind a wall of jargon and obfuscation. Each OPO enjoys a regional monopoly, under the law, with no competition, whatsoever."

The rule, staunchly supported by ASN, was established under the joint leadership of both the Trump and Biden administrations and many members of Congress. Rep. Cloud remarked that it was "refreshing" to work with congressional colleagues in a bipartisan manner, noting that "finalization and implementation of this rule [are important steps]" and that Congress "must scrutinize the system in its entirety, in order to truly bring about meaningful reform," as "OPOs are not the only actor in the system and, certainly, not the only problem."

In written testimony provided to the committee, ASN President Susan Quaggin, MD, FASN, stated: "Improving our organ transplant system will require improvement of many different, interconnected, and too often fragmented, systems, including OPO performance, streamlining government oversight of the US transplant system, cutting 'red tape' surrounding the regulation of transplant centers, and above all else, ensuring that the US organ transplant system is built around and aligned with the needs of patients first."

Putting patients first, in particular patients of color who are disproportionately affected by the failures of the current system, was a persistent theme throughout the hearing. "As a former transplant nurse … I personally treated and counseled patients suffering through chronic and severe illnesses," said Rep. Cori Bush of Missouri. "Black and Brown patients are more likely to suffer from illnesses like kidney failure and less likely to get an organ transplant. For them, the promise of receiving an organ is, too often, delayed or denied because there aren't enough organs available. I've watched this system fail dying patients time and time again. I've watched the system fail young people, older adults and far too many Black and Brown people. Our failing organ donation system is a death sentence for thousands. My time treating transplant patients has stayed with me, and I cannot overstate the urgency of this issue. We must do everything in our power to fix this system."

"Black Americans are three times more likely than white Americans to have a kidney failure, said Rep. Hank Johnson of Georgia." Despite this, Black kidney patients are less likely to be identified as transplant candidates, less likely to be put on a wait list, and less likely to receive a transplant."

The move to increase transparency and accountability was applauded by many, including US House Committee on Oversight and Reform Chairwoman Carolyn Maloney of New York. Rep. Maloney expanded on the need for transparency in the transplant system, highlighting that "UNOS [United Network for Organ Sharing], the entity that manages the US transplant list, under contract with the government, stores valuable OPO data. But UNOS prohibits OPOs from sharing performance data with the public and only allows some data to be distributed publicly." Maloney stated simply that "Because OPOs provide a public service, their data should be public."

Rep. Katie Porter of California, a longtime champion for reforming the transplant system, also expanded on the importance of transparent and standardizable data, bringing out her signature whiteboard to illustrate her point to Association of Organ Procurement Organizations (AOPO) CEO Steve Miller. Highlighting pitfalls of the now-replaced metric, which allowed OPOs to define the denominator to which they are held accountable, Porter criticized AOPO for "defending a system in which OPO B looks like [it's] much worse than OPO A. But in reality, it could just be the case that OPO B is going after every possible donor, regardless of race, regardless of whether it's hard, regardless of whether [it] may not get turned down, regardless of whether or not it might be easy."

Members of Congress made it clear that the hearing was only the start of their work to reform the transplant system for patients. Porter stated: "Thousands of patients waiting on a life-saving organ cannot wait while the AOPO lobbies and tries to stop rules and procedures, just to make it simply clear whether an OPO is doing the life-saving work of retrieving organs and putting them into patients in need." Krishnamoorthi warned that any effort to avoid congressional scrutiny would not succeed, stating, "This committee is on the case, and we're not going away. We're actually going to accelerate our efforts and we're going to pursue this, as far as we can."

As to what the result of increased congressional oversight and access to transplants would mean for patients, Ingram said, "For me, it kind of boils down to the simple fact of keeping people alive and just … what that holds. Like, we get to sit here right now, and this is living …. Essentially the gift of being able to have an organ is to be able to engage in and live this beautiful full life."

A full recording of the hearing can be found on the Oversight and Reform Committee's website at https://oversight.house.gov/legislation/hearings/the-urgent-need-to-reform-the-organ-transplantation-system-to-secure-more. ■

Only one calcimimetic lowers and maintains key sHPT lab values with IV administration you control[1]

Not an actual Parsabiv® vial.
The displayed vial is for illustrative purposes only.

Measure corrected serum calcium prior to initiation of Parsabiv®. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with Parsabiv®. Measure PTH 4 weeks after initiation or dose adjustment of Parsabiv®. Once the maintenance dose has been established, measure PTH per clinical practice.

Worsening Heart Failure: In Parsabiv® clinical studies, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. Closely monitor patients treated with Parsabiv® for worsening signs and symptoms of heart failure.

Upper Gastrointestinal Bleeding: In clinical studies, 2 patients treated with Parsabiv® in 1253 patient years of exposure had upper gastrointestinal (GI) bleeding at the time of death. The exact cause of GI bleeding in these patients is unknown and there were too few cases to determine whether these cases were related to Parsabiv®.

Patients with risk factors for upper GI bleeding, such as known gastritis, esophagitis, ulcers or severe vomiting, may be at increased risk for GI bleeding with Parsabiv®. Monitor patients for worsening of common Parsabiv® GI adverse reactions and for signs and symptoms of GI bleeding and ulcerations during Parsabiv® therapy.

Adynamic Bone: Adynamic bone may develop if PTH levels are chronically suppressed.

Adverse Reactions: In clinical trials of patients with secondary HPT comparing Parsabiv® to placebo, the most common adverse reactions were blood calcium decreased (64% vs. 10%), muscle spasms (12% vs. 7%), diarrhea (11% vs. 9%), nausea (11% vs. 6%), vomiting (9% vs. 5%), headache (8% vs. 6%), hypocalcemia (7% vs. 0.2%), and paresthesia (6% vs. 1%).

Please see Brief Summary of full Prescribing Information on adjacent page.

IV = intravenous; sHPT = secondary hyperparathyroidism; PTH = parathyroid hormone; P = phosphate; cCa = corrected calcium.

Reference: 1. Parsabiv® (etelcalcetide) prescribing information, Amgen.

Indication

Parsabiv® (etelcalcetide) is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

Limitations of Use:

Parsabiv® has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with CKD who are not on hemodialysis and is not recommended for use in these populations.

Important Safety Information

Contraindication: Parsabiv® is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including face edema and anaphylactic reaction, have occurred.

Hypocalcemia: Parsabiv® lowers serum calcium and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause QT interval prolongation and ventricular arrhythmia. Patients with conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to Parsabiv®. Closely monitor corrected serum calcium and QT interval in patients at risk on Parsabiv®.

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to Parsabiv®. Monitor corrected serum calcium in patients with seizure disorders on Parsabiv®.

Concurrent administration of Parsabiv® with another oral calcimimetic could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to Parsabiv® should discontinue cinacalcet for at least 7 days prior to initiating Parsabiv®. Closely monitor corrected serum calcium in patients receiving Parsabiv® and concomitant therapies known to lower serum calcium.

Parsabiv® (etelcalcetide) Injection for intravenous use

2.5mg/0.5mL | 5mg/1mL | 10mg/2mL

Visit **ParsabivHCP.com** for more information.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Parsabiv®
(etelcalcetide) Injection for intravenous use
2.5mg/0.5mL | 5mg/1mL | 10mg/2mL

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

PARSABIV is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

Limitations of Use:

PARSABIV has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with chronic kidney disease who are not on hemodialysis and is not recommended for use in these populations.

CONTRAINDICATIONS

Hypersensitivity

PARSABIV is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including face edema and anaphylactic reaction, have occurred with PARSABIV *[see Adverse Reactions (6) in PARSABIV full prescribing information].*

WARNINGS AND PRECAUTIONS

Hypocalcemia

PARSABIV lowers serum calcium *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]* and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause paresthesias, myalgias, muscle spasms, seizures, QT interval prolongation, and ventricular arrhythmia.

QT Interval Prolongation and Ventricular Arrhythmia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). In these studies, the incidence of a maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]*. Patients with congenital long QT syndrome, history of QT interval prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to PARSABIV. Closely monitor corrected serum calcium and QT interval in patients at risk receiving PARSABIV.

Seizures

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to PARSABIV. Monitor corrected serum calcium in patients with seizure disorders receiving PARSABIV.

Risk of Hypocalcemia with Other Serum Calcium Lowering Products

Concurrent administration of PARSABIV with another oral calcium-sensing receptor agonist could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to PARSABIV should discontinue cinacalcet for at least 7 days prior to initiating PARSABIV *[see Dosage and Administration (2.4) in PARSABIV full prescribing information]*. Closely monitor corrected serum calcium in patients receiving PARSABIV and concomitant therapies known to lower serum calcium.

Monitoring Serum Calcium and Patient Education

Measure corrected serum calcium prior to initiation of PARSABIV. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with PARSABIV *[see Dosage and Administration (2.2) in PARSABIV full prescribing information]*. Educate patients on the symptoms of hypocalcemia and advise them to contact a healthcare provider if they occur.

Management of Hypocalcemia

If corrected serum calcium falls below the lower limit of normal or symptoms of hypocalcemia develop, start or increase calcium supplementation (including calcium, calcium-containing phosphate binders, and/or vitamin D sterols or increases in dialysate calcium concentration). PARSABIV dose reduction or discontinuation of PARSABIV may be necessary *[see Dosage and Administration (2.2) in PARSABIV full prescribing information]*.

Worsening Heart Failure

In clinical studies with PARSABIV, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. In clinical studies, heart failure requiring hospitalization occurred in 2% of PARSABIV-treated patients and 1% of placebo-treated patients. Reductions in corrected serum calcium may be associated with congestive heart failure, however, a causal relationship to PARSABIV could not be completely excluded. Closely monitor patients treated with PARSABIV for worsening signs and symptoms of heart failure.

Upper Gastrointestinal Bleeding

In clinical studies, two patients treated with PARSABIV in 1253 patient-years of exposure had upper gastrointestinal (GI) bleeding noted at the time of death while no patient in the control groups in 384 patient-years of exposure had upper GI bleeding noted at the time of death. The exact cause of GI bleeding in these patients is unknown, and there were too few cases to determine whether these cases were related to PARSABIV.

Patients with risk factors for upper GI bleeding (such as known gastritis, esophagitis, ulcers, or severe vomiting) may be at increased risk for GI bleeding while receiving PARSABIV treatment. Monitor patients for worsening of common GI adverse reactions of nausea and vomiting associated with PARSABIV *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]* and for signs and symptoms of GI bleeding and ulcerations during PARSABIV therapy. Promptly evaluate and treat any suspected GI bleeding.

Adynamic Bone

Adynamic bone may develop if PTH levels are chronically suppressed. If PTH levels decrease below the recommended target range, the dose of vitamin D sterols and/or PARSABIV should be reduced or therapy discontinued. After discontinuation, resume therapy at a lower dose to maintain PTH levels in the target range *[see Dosage and Administration (2.1) in PARSABIV full prescribing information]*.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Hypocalcemia *[see Warnings and Precautions (5.1) in PARSABIV full prescribing information]*
- Worsening Heart Failure *[see Warnings and Precautions (5.2) in PARSABIV full prescribing information]*
- Upper Gastrointestinal Bleeding *[see Warnings and Precautions (5.3) in PARSABIV full prescribing information]*
- Adynamic Bone *[see Warnings and Precautions (5.4) in PARSABIV full prescribing information]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data in Table 2 are derived from two placebo-controlled clinical studies in patients with chronic kidney disease and secondary hyperparathyroidism on hemodialysis. The data reflect exposure of 503 patients to PARSABIV with a mean duration of exposure to PARSABIV of 23.6 weeks. The mean age of patients was approximately 58 years, and 60% of the patients were male. Of the total patients, 67% were Caucasian, 28% were Black or African American, 2.6% were Asian, 1.2% were Native Hawaiian or Other Pacific Islander, and 1.6% were categorized as Other.

Table 2 shows common adverse reactions associated with the use of PARSABIV in the pool of placebo-controlled studies. These adverse reactions occurred more commonly on PARSABIV than on placebo and were reported in at least 5% of patients treated with PARSABIV.

Table 2: Adverse Reactions Reported in ≥ 5% of PARSABIV-Treated Patients

Adverse Reaction*	Placebo (N = 513)	PARSABIV (N = 503)
Blood calcium decreased[a]	10%	64%
Muscle spasms	7%	12%
Diarrhea	9%	11%
Nausea	6%	11%
Vomiting	5%	9%
Headache	6%	8%
Hypocalcemia[b]	0.2%	7%
Paresthesia[c]	1%	6%

*Included adverse reactions reported with at least 1% greater incidence in the PARSABIV group compared to the placebo group

[a] Asymptomatic reductions in calcium below 7.5 mg/dL or clinically significant asymptomatic reductions in corrected serum calcium between 7.5 and < 8.3 mg/dL (that required medical management)

[b] Symptomatic reductions in corrected serum calcium < 8.3 mg/dL

[c] Paresthesia includes preferred terms of paresthesia and hypoesthesia

Other adverse reactions associated with the use of PARSABIV but reported in < 5% of patients in the PARSABIV group in the two placebo-controlled clinical studies were:

- Hyperkalemia: 3% and 4% for placebo and PARSABIV, respectively.
- Hospitalization for Heart Failure: 1% and 2% for placebo and PARSABIV, respectively.
- Myalgia: 0.2% and 2% for placebo and PARSABIV, respectively.
- Hypophosphatemia: 0.2% and 1% for placebo and PARSABIV, respectively.

Description of Selected Adverse Reactions

Hypocalcemia

In the combined placebo-controlled studies, a higher proportion of patients on PARSABIV developed at least one corrected serum calcium value below 7.0 mg/dL (7.6% PARSABIV, 3.1% placebo), below 7.5 mg/dL (27% PARSABIV, 5.5% placebo), and below 8.3 mg/dL (79% PARSABIV, 19% placebo). In the combined placebo-controlled studies, 1% of patients in the PARSABIV group and 0% of patients in the placebo group discontinued treatment due to an adverse reaction attributed to a low corrected serum calcium.

Hypophosphatemia

In the combined placebo-controlled studies, 18% of patients treated with PARSABIV and 8.2% of patients treated with placebo had at least one measured phosphorus level below the lower normal limit (i.e., 2.2 mg/dL).

QTc Interval Prolongation Secondary to Hypocalcemia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). The patient incidence of maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively.

Hypersensitivity

In the combined placebo-controlled studies, the subject incidence of adverse reactions potentially related to hypersensitivity was 4.4% in the PARSABIV group and 3.7% in the placebo group. Hypersensitivity reactions in the PARSABIV group were pruritic rash, urticaria, and face edema.

Immunogenicity

As with all peptide therapeutics, there is potential for immunogenicity. The detection of anti-drug binding antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to etelcalcetide with the incidence of antibodies to other products may be misleading.

In clinical studies, 7.1% (71 out of 995) of patients with secondary hyperparathyroidism treated with PARSABIV for up to 6 months tested positive for binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing anti-etelcalcetide antibodies.

No evidence of altered pharmacokinetic profile, clinical response, or safety profile was associated with pre-existing or developing anti-etelcalcetide antibodies.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no available data on the use of PARSABIV in pregnant women. In animal reproduction studies, effects were seen at doses associated with maternal toxicity that included hypocalcemia. In a pre- and post-natal study in rats administered etelcalcetide during organogenesis through delivery and weaning, there was a slight increase in perinatal pup mortality, delay in parturition, and transient effects on pup growth at exposures 1.8 times the human exposure for the clinical dose of 15 mg three times per week. There was no effect on sexual maturation, neurobehavioral, or reproductive function in the rat offspring. In embryo-fetal studies, when rats and rabbits were administered etelcalcetide during organogenesis, reduced fetal growth was observed at exposures 2.7 and 7 times exposures for the clinical dose, respectively.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

There were no effects on embryo-fetal development in Sprague-Dawley rats when etelcalcetide was dosed at 0.75, 1.5, and 3 mg/kg/day by the intravenous route during organogenesis (pre-mating to gestation day 17) at exposures up to 1.8 times human exposures at the clinical dose of 15 mg three times per week based on AUC. No effects on embryo-fetal development were observed in New Zealand White rabbits at doses of etelcalcetide of 0.375, 0.75, and 1.5 mg/kg by the intravenous route (gestation day 7 to 19), representing up to 4.3 times human exposures based on AUC. In separate studies at higher doses of 4.5 mg/kg in rats (gestation days 6 to 17) and 2.25 mg/kg in rabbits (gestation days 7 to 20), representing 2.7- and 7-fold clinical exposures, respectively, there was reduced fetal growth associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption.

In a pre- and post-natal development study in Sprague-Dawley rats administered etelcalcetide at 0.75, 1.5, and 3 mg/kg/day by the intravenous route (gestation day 7 to lactation day 20), there was a slight increase in perinatal pup mortality, delay in parturition, and transient reductions in post-natal growth at 3 mg/kg/day (representing 1.8-fold human exposures at the clinical dose of 15 mg three times per week based on AUC), associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption. There were no effects on sexual maturation, neurobehavioral, or reproductive function at up to 3 mg/kg/day, representing exposures up to 1.8-fold human exposure based on AUC.

Lactation

Risk Summary

There are no data regarding the presence of PARSABIV in human milk or effects on the breastfed infant or on milk production. Studies in rats showed [^{14}C]-etelcalcetide was present in the milk at concentrations similar to plasma. Because of the potential for PARSABIV to cause adverse effects in breastfed infants including hypocalcemia, advise women that use of PARSABIV is not recommended while breastfeeding.

Data

Presence in milk was assessed following a single intravenous dose of [^{14}C]-etelcalcetide in lactating rats at maternal exposures similar to the exposure at the human clinical dose of 15 mg three times per week. [^{14}C]-etelcalcetide-derived radioactivity was present in milk at levels similar to plasma.

Pediatric Use

The safety and efficacy of PARSABIV have not been established in pediatric patients.

Geriatric Use

Of the 503 patients in placebo-controlled studies who received PARSABIV, 177 patients (35.2%) were ≥ 65 years old and 72 patients (14%) were ≥ 75 years old.

No clinically significant differences in safety or efficacy were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old). No differences in plasma concentrations of etelcalcetide were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old).

OVERDOSAGE

There is no clinical experience with PARSABIV overdosage. Overdosage of PARSABIV may lead to hypocalcemia with or without clinical symptoms and may require treatment. Although PARSABIV is cleared by dialysis, hemodialysis has not been studied as a treatment for PARSABIV overdosage. In the event of overdosage, corrected serum calcium should be checked and patients should be monitored for symptoms of hypocalcemia, and appropriate measures should be taken *[see Warnings and Precautions (5.1) in PARSABIV full prescribing information]*.

AMGEN®

PARSABIV® (etelcalcetide)

Manufactured for:
KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

Patent: http://pat.amgen.com/Parsabiv/

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REFERENCES: 1. Savige J. Alport syndrome: its effects on the glomerular filtration barrier and implications for future treatment. *J Physiol*. 2014;592(14):4013-4023. **2.** Alport syndrome diagnosis. Alport Syndrome Foundation. Accessed September 29, 2019. https://www.alportsyndrome.org/what-is-alport-syndrome. **3.** Liapis H, Jain S. The interface of genetics with pathology in Alport nephritis. *J Am Soc Nephrol*. 2013;24(12):1925-1927. **4.** Savige J, Colville D, Rheault M, et al. Alport syndrome in women and girls. *Clin J Am Soc Nephrol*. 2016;11(9):1713-1720.

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