ASN American Society of Nephrology

KidneyNews

March 2021 | Vol. 13, Number 3

Cold, Power, and Water Outages Temporarily Upend Dialysis Care in Texas

By Bridget M. Kuehn

A massive mid-February winter storm and a week of freezing temperatures disrupted dialysis care for thousands of patients and temporarily shuttered many dialysis clinics across Texas.

Together, the cold and loss of water and power for millions of people in Texas created a "perfect storm" of crises for dialysis patients and providers, said Rajeev Raghavan, MD, FASN, associate professor of medicine at Baylor College of Medicine in Houston. Icy roads prevented dialysis patients and staff from getting to clinics or hospitals. The loss of power shut down many dialysis clinics, and as pipes froze and burst across the state, it led to a loss of water or water pressure at those clinics that still had power, making it "impossible to do treatments," he said.

Raghavan, who is also medical director for an outpatient dialysis unit, said he and his colleagues tried to prepare patients ahead of the storm by dialyzing those whose weekday appointments might be disrupted by the storm on Sunday, February 14, before freezing temperatures hit.

"The big issue . . . was that we expected things to improve by Tuesday," he said. "When they didn't improve by Tuesday or even by Friday, that's when we really had to scramble."

Patient surge

Dialysis centers across the state faced similar struggles. Six of the 16 clinics operated by American Renal Associates (ARA) in the Dallas area were closed at least temporarily because of a lack of water or power, affecting about 450 patients, said Geoffrey Walker, MD, a nephrologist with Dallas Nephrology Associates, whose patients are served by the clinics. About half of the Fresenius clinics in the Dallas area that serve his patients were also affected. DaVita Kidney Care faced similar outages across the state. Both companies brought in generators and water tankers to try to restore services and contacted patients to connect them with care.

Even these rescue efforts faced challenges. ARA faced a shortage of generators, and centers that had generators couldn't always get them to work because the diesel fuel froze. The additives used to prevent fuel from freezing in Northern states are not used in Texas where freezing temperatures are rare.

Home dialysis patients also faced hurdles, Raghavan said. Home hemodialysis patients could not dialyze without water and power, and home peritoneal dialysis patients who can dialyze without water and power struggled to find ways

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Findings: Physical Activity Linked to Reduced Mortality in Advanced CKD

Higher levels of physical activity were associated with a one-half reduction in risk of death among patients with advanced chronic kidney disease (CKD) in a recent study

The prospective study included 579 adults with stage 4 to 5 CKD treated at four Canadian multi-disciplinary kidney health clinics between 2012 and 2018. Patients were not receiving kidney replacement therapy at baseline. The study was published in the *American Journal of Kidney Diseases*.

Physical activity was assessed using the Physical Activity Scale for the Elderly (PASE) questionnaire, which addresses occupational, household, and leisure activities over the past week. Based on their PASE scores, patients were classified as having low, light, or moderate-to-high physical activity. Physical activity level was analyzed for associations with all-cause mortality, progression to kidney failure, and risk of falls. The researchers adjusted for age, sex, and other medical conditions or risk factors.

The median age of those studied was 72 years and 59% of patients were men. Physical activity was classified as low in 24.5% of patients, light in 34.2%, and moderate to high in 41.3%. Patients with moderate-to-high physical activity

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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.

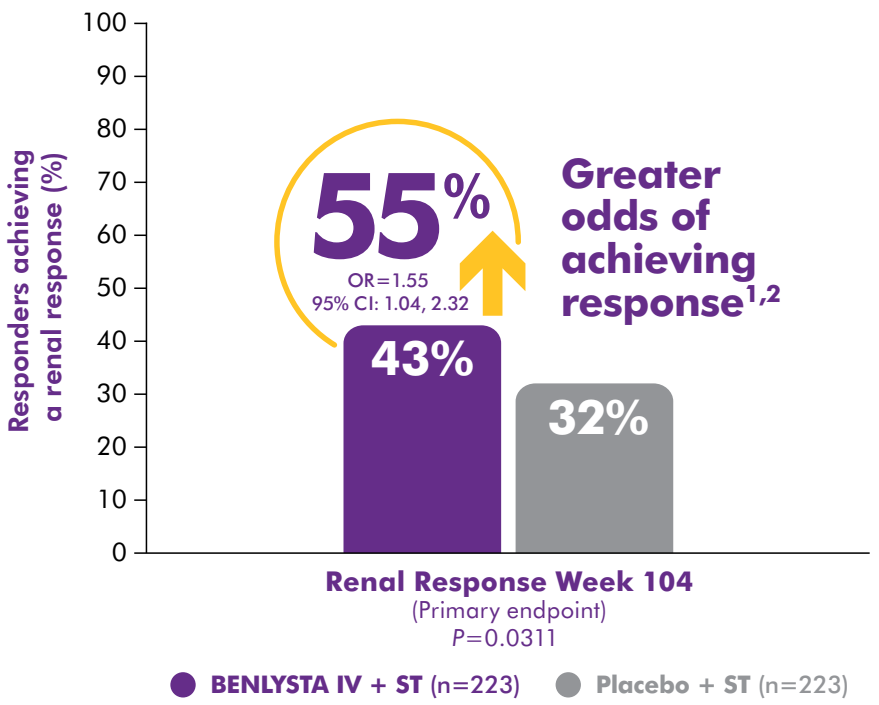
Malignancy: The impact of BENLYSTA on the development of malignancies is unknown; its mechanism of action could increase the risk for malignancies.

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)]*.

Manufactured by
Human Genome Sciences, Inc.
(a subsidiary of GlaxoSmithKline)
Rockville, Maryland 20850
U.S. License No. 1820

Marketed by

GlaxoSmithKline
Research Triangle Park, NC 27709

BNL:15BRS

BELJRNA200007 December 2020
Produced in USA.

Benlysta (belimumab)

ASN American Society of Nephrology

KidneyNews

ASN Kidney News is published by the American Society of Nephrology
1401 H Street, NW, Suite 900, Washington, DC 20005. Phone: 202-640-4660

www.asn-online.org

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Postmaster: Please send address changes to *ASN Kidney News*, c/o Customer Service, American Society of Nephrology 1401 H Street, NW, Suite 900, Washington, DC 20005.

Publications mail agreement No. 40624074. Return undeliverable Canadian addresses to PO Box 503, RPO West Beaver Creek, Richmond Hill ON L4B 4R6

ASN Kidney News (ISSN print 1943-8044 and online 1943-8052) is an official publication of the American Society of Nephrology, 1401 H Street, NW, Suite 900, Washington DC 20005, and is published monthly 11 times a year except November. Periodicals postage paid at Washington, DC and at additional mailing offices. Subscription rates: $12 per year. To order, please email bhenkel@asn-online.org. Subscription prices subject to change. Annual ASN membership dues include $12 for *ASN Kidney News* subscription.

Cold, Power, and Water Outages

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to safely warm their dialysis fluid in freezing homes.

As a result, hospitals already filled with patients owing to storm-related illnesses and injuries faced a surge of dialysis patients. A large county hospital in Houston that typically has 15 to 25 inpatient dialysis patients was up to 50 patients by Thursday, Raghavan said. Christopher Teofil Neagra, MD, a nephrology fellow at Baylor, covered the night float during the storm and saw about 25 patients, many of whom had been waiting for hours in the Emergency Department for dialysis. He worked to triage patients most in urgent need of dialysis and use medications to help manage patients until they could be dialyzed.

"As a nephrologist, all you have to do is be ready to help these people, because they are scared," Neagra said. "They haven't had their dialysis. They don't know where to go. You are their last hope."

Securing medications for patients also proved challenging. Tessa Novick, MD, assistant professor at the Dell Medical School at The University of Texas at Austin, said many pharmacies were closed, and patients had difficulties getting to those that were open.

Having enough machines and skilled nursing staff to dialyze patients was another challenge across the state. Some nurses stayed in the hospital for days. Schedules were created to dialyze patients 24–7, and some sessions were shortened to two hours to try to accommodate as many patients as possible.

With all three of The University of Texas Health San Antonio's (UHS) outpatient dialysis clinics temporarily closed by the outages, it took teamwork among all staff to find a way to provide inpatient dialysis for about 350 patients from the clinics and walk-ins from other clinics, said Kumar Sharma, MD, chief of the Division of Nephrology. Theresa De La Haya, RN, senior vice president of UHS Community Health and Clinical Prevention Programs, worked with nurses and managers to contact patients and arrange transport.

While nephrologists and staff around the state scrambled to meet patients' needs, they also faced a personal toll from the storm. Many went without electricity, heat, or water for days, and many had pipes burst in their own homes.

"We have never encountered a situation where our staff and our patients are going through the same unfortunate situation," De La Haya said.

Most dialysis centers were able to catch up patients and resume normal operations about a week after the storm, but the crisis highlighted the need for better emergency preparations. Novick noted that many dialysis centers in the Northeast prepare patients for potential weather-related emergencies in advance of winter. Some providers in areas of Texas with frequent hurricanes also do this. Novick and Raghavan suggested more dialysis centers have backup water and generators, as well as printouts of patient phone numbers, as a backup for power and internet outages. Sharma said he'd like to see nephrologists form an emergency preparedness network that could mobilize clinicians, equipment, or supplies from other states during a crisis.

"It has to be a big wake-up call that we need these backup measures in place even if it's rare," Novick said. "It's just devastating for the population. The dialysis population is so vulnerable." ■

Advanced CKD

Continued from page 1

were younger and had lower rates of comorbid conditions. Physical activity level was strongly related to physical functioning.

Over about 8 years of follow-up, approximately 20% of patients died, 35% progressed to dialysis, and 22% had a fall. On adjustment for age, sex, and comorbidity, moderate-to-high of physical activity was associated with substantially lower mortality, with a hazard ratio 0.48.

Physical activity was not associated with progression to kidney failure or to a risk of falls. Previous falls were the only significant risk factor for future falls.

CKD is characterized by declining physical function and physical activity. Low physical activity in CKD patients is associated with adverse outcomes, including poor quality of life and increased cardiovascular risk, and with worsening of CKD. There are few data on outcomes associated with physical activity in patients with advanced CKD who have not yet started dialysis.

The researchers found about a 50% reduction in all-cause mortality for advanced CKD patients with a moderate-to-high level of physical activity. Additionally, physical activity appeared to be unrelated to progression to kidney failure or to future falls. The risk of progressive CKD in this group of patients may be "relatively non-modifiable," the researchers suggest. "Interventional studies are now needed to investigate the effect of maintaining or increasing physical activity in the CKD population," they state. ■

Rampersad C, et al. Association of physical activity and poor health outcomes in patients with advanced CKD. *Am J Kidney Dis* [published online ahead of print February 10, 2021]. doi: 10.1053/j.ajkd.2020.12.018; https://www.ajkd.org/article/S0272-6386(21)00082-2/fulltext

Complement Inhibition in Kidney Disease. What's on the Horizon?

By Maria Jose Soler and Natalia Ramos

During the last decade, several therapeutics targeting the complement cascade have begun to enter the nephrology scene (Figure 1). Examples include the following diseases:

- Atypical hemolytic uremic syndrome (aHUS)
- C3 glomerulopathy
- Lupus nephritis
- Anti-neutrophil cytoplasmic antibody (ANCA) vasculitis
- Immunoglobulin A (IgA) nephropathy

The first agent to enter the stage was eculizumab, which showed impressive efficacy in patients with aHUS (1). Currently, most randomized clinical trials using complement inhibition therapy are in patients with aHUS and ANCA vasculitis. Data on use of complement inhibitors in other glomerular diseases are sparse and consist mostly of retrospective studies and case series (2, 3).

aHUS is a rare, life-threatening disease caused by complement dysregulation and characterized by thrombotic microangiopathy (TMA). Without appropriate medical treatment, mortality can be seen in up to 50% of patients with aHUS. Eculizumab is a monoclonal antibody (mAb) that binds to C5, inhibits the ability of C5 convertase to cleave C5 into C5a and C5b, and thus reduces membrane attack complex formation.

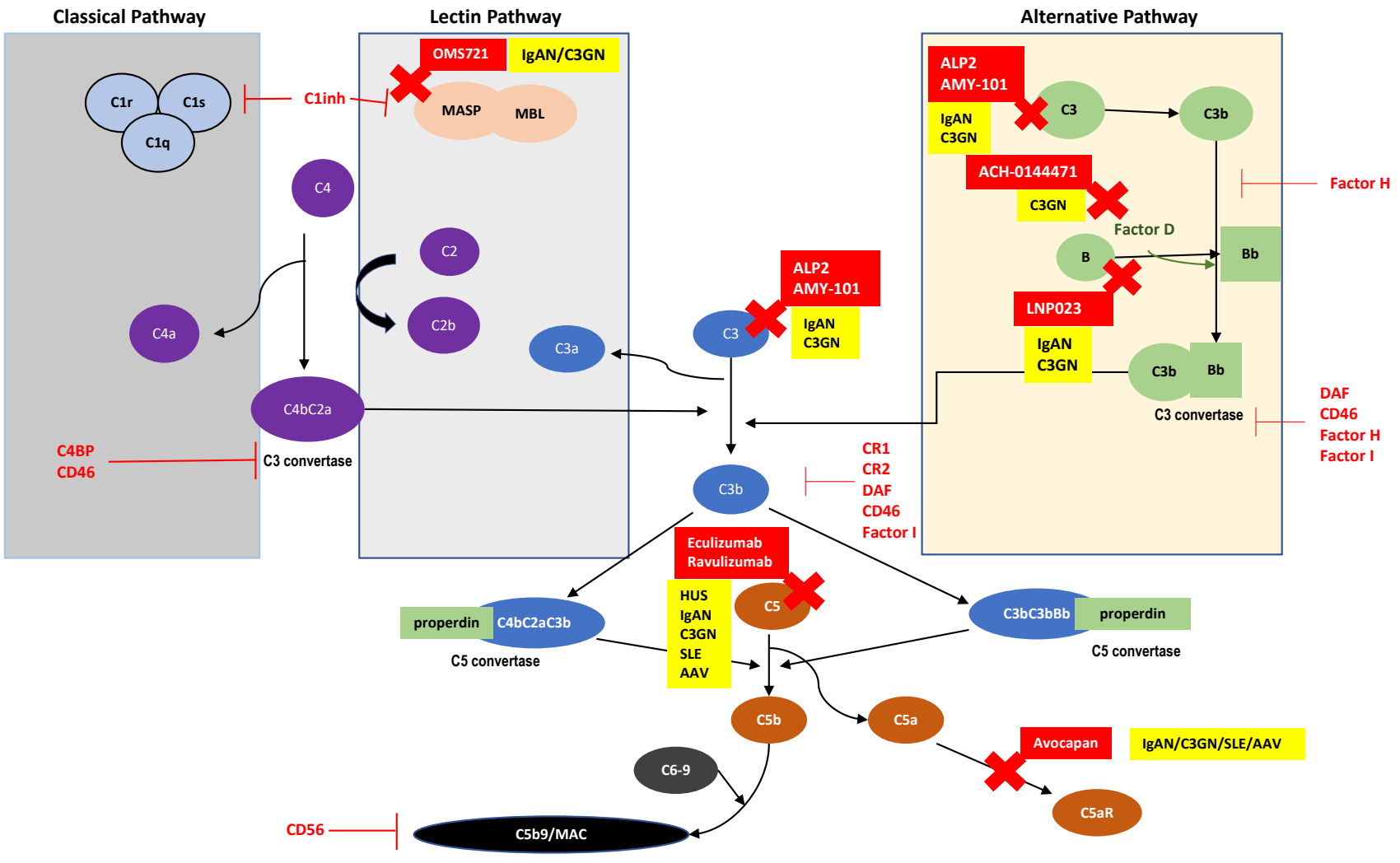
Eculizumab has been shown to be effective in children and adults with aHUS, dramatically improving patient survival and kidney prognosis. However, eculizumab needs to be administered intravenously every two weeks and is expensive. Moreover, the duration of eculizumab therapy is unclear in patients with aHUS, as only a few studies have been designed to answer this question. Thus, many questions are left unanswered about relapse rate and duration of therapy. Currently, there is an ongoing debate about whether eculizumab in aHUS is a lifelong therapy or can be safely discontinued (1). Recent studies suggest that serum from patients with aHUS may be useful to detect the risk for disease relapse. The in vitro capacity of serum from patients with aHUS to activate complement may be a future tool allowing for decisions to continue/discontinue complement inhibition therapy (4). As C3 glomerulopathy is related to complement activation, initial case series pointed out eculizumab as a therapeutic option; however, its beneficial effect has been shown to be highly heterogeneous without clear scientific evidence.

Ravulizumab is a mAb that was engineered to achieve an extended duration of complement inhibition while retaining the efficacy and safety of eculizumab. It differs from eculizumab by the substitution of 4 amino acids, which alter the pharmacokinetics and pharmacodynamics of the mAb, and resulted in a novel antibody against C5 with a terminal half-life 4 times longer than that of eculizumab. In October 2019, ravulizumab was approved by the US Food and Drug Administration (FDA) for treatment of aHUS in adults and children. The first prospective phase III, single-arm, multicenter study evaluating the efficacy and safety of ravulizumab (maintenance dosing every 4–8 weeks instead of every 2 weeks) in children with aHUS demonstrated complete and sustained terminal complement C5 inhibition, leading to hematologic remission and improvement of kidney function (5). The primary endpoint of complete TMA response (platelet count normalization, lactate dehydrogenase [LDH] normalization, and ≥25% improvement in serum creatinine at two separate assessments at least 28 days apart) was achieved in 77.8% of patients (n = 14). A clinical advantage of ravulizumab over eculizumab is the long-acting effect, allowing for fewer infusions, thus potentially leading to improved quality of life.

Avacopan is an oral C5a receptor inhibitor that has been studied in randomized clinical trials in aHUS, ANCA vasculitis, C3 glomerulopathy, and IgA nephropathy. The first study in ANCA vasculitis (CLEAR study) was promising and demonstrated an effective result in replacing high-dose glucocorticoids (6). The avacopan phase III study in the ANCA vasculitis ANCA-Associated Vasculitis (ADVOCATE) trial was first presented as an oral session during the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) Virtual Congress 2020 and was just published in the *New England Journal of Medicine* (7).

The study achieved both of its primary goals: disease remission at 26 weeks and sustained remission at 52 weeks, determined by changes in Birmingham vasculitis activity score (BVAS) from baseline to week 26 or 52. Seventy-two percent of patients in the avacopan group achieved remission at 26 weeks compared to 70.1% receiving standard care (control group). Sustained remission at 52 weeks occurred in 65.7% of patients in the avacopan group versus 54.9% in the control group, which was a significant improvement.

Figure 1. Summary of the drugs that target the complement cascade in glomerular disease



IgAN, IgA nephropathy; C3GN, C3 glomerulonephritis; HUS, hemolytic uremic syndrome; SLE, systemic lupus erythematosus; AAV, anti-neutrophil cytoplasmic autoantibodies; MBL, mannose-binding lectin; MASP, mannose-binding lectin-associated serine protease; CR1, complement receptor type 1; CR2, complement receptor type 2; DAF, decay-accelerating factor; ALP2, alkaline protease 2; ACH-0144471, danicopan; LNP023, iptacopan; MAC, membrane attack complex.

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Complement Inhibition in Kidney Disease

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However, the clear benefit of avacopan treatment at 26 weeks is the sparing of high doses of steroids and subsequently avoidance of glucocorticoid-related toxicity (8).

The exciting part of complement inhibition in glomerular diseases is ongoing, and new therapeutic strategies targeting other parts of the complement cascade, such as C3, factor B, factor D, and C1, are currently under various stages of basic and clinical development. ■

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Dr. Soler reports personal fees from Novo Nordisk, Janssen, AstraZeneca, Fresenius, Mundipharma, Pfizer, Bayer, Vifor, Esteve, Eli Lilly, and Boehringer and grants and nonfinancial support from Boehringer, outside of the submitted work. There are no conflicts of interest with the drugs mentioned in the paper. Dr. Ramos was a paid lecturer for Alexion in 2020 on the topic of eculizumab treatment.

References

1. Rodriguez E, et al. Should eculizumab be discontinued in patients with atypical hemolytic uremic syndrome? *Clin Kidney J* 2017; 10:320–322. doi: 10.1093/ckj/sfx024
2. Skoczynska M, et al. Thrombotic microangiopathy in the course of catastrophic antiphospholipid syndrome successfully treated with eculizumab: Case report and systematic review of the literature. *Lupus* 2020; 29:631–639. doi: 10.1177/0961203320917460
3. Nakamura H, et al. Atypical hemolytic uremic syndrome associated with complement factor H mutation and IgA nephropathy: A case report successfully treated with eculizumab. *Nephron* 2018; 138:324–327. doi: 10.1159/000485194
4. Palomo M, et al. Complement activation and thrombotic microangiopathies. *Clin J Am Soc Nephrol* 2019; 14:1719–1732. doi: 10.2215/CJN.05830519
5. Ariceta G, et al. The long-acting C5 inhibitor, ravulizumab, is effective and safe in pediatric patients with atypical hemolytic uremic syndrome naïve to complement inhibitor treatment. *Kidney Int* [published online ahead of print December 8, 2020]. doi: 10.1016/j.kint.2020.10.046; https://www.kidney-international.org/article/S0085-2538(20)31418-6/fulltext
6. Jayne DRW, et al. Randomized trial of C5a receptor inhibitor avacopan in ANCA-associated vasculitis. *J Am Soc Nephrol* 2017; 28:2756–2767. doi: 10.1681/ASN.2016111179
7. Jayne DRW, et al. ADVOCATE Study Group. Avacopan for the treatment of ANCA-associated vasculitis. *N Engl J Med* 2021; 384:599–609. doi: 10.1056/NEJMoa2023386
8. Merkel PA, et al. Evaluation of the safety and efficacy of avacopan, a C5a receptor inhibitor, in patients with antineutrophil cytoplasmic antibody-associated vasculitis treated concomitantly with rituximab or cyclophosphamide/azathioprine: Protocol for a randomized, double-blind, active-controlled, phase 3 trial. *JMIR Res Protoc* 2020; 9:e16664. doi: 10.2196/16664

Treatment of Uremic Pruritus

By Swetapadma Tripathy, and Jia Hwei Ng
Visual abstract by Jia Hwei Ng, MD

Uremic pruritus is a common, distressing condition that affects 60% of patients on hemodialysis (1, 2). Despite the high prevalence, this condition is under-recognized by physicians, and high-quality evidence on the treatment options is limited (3). Here, we summarize a recent narrative review on non-pharmacological and emerging pharmacological treatment options to treat uremic pruritus (4). We will highlight the therapies where randomized controlled trials (RCTs) were conducted (see visual abstract).

Optimization of dialysis and bone mineral disorder

Given that uremic toxins likely contribute to the symptoms of uremic pruritus, increasing dialysis dose (increased Kt/V) and using a high-flux dialyzer result in moderate improvement of symptoms (5). In addition to dialysis, optimization of the bone mineral disorder, along with parathyroidectomy, improves symptoms through the reduction of a calcium-phosphate product (6).

Topical agents

Patients with kidney failure commonly have dry skin, contributing to itchiness. Emollients are effective in reducing xerosis and reducing pruritus symptoms. Capsaicin and pramoxine have been used, but evidence on their efficacy is limited to a few RCTs with small sample sizes (5). Topical tacrolimus suppresses immune-mediated exacerbation of dry skin, inflammation, and pruritus. Despite its potential for treating uremic pruritus, an RCT showed its lack of efficacy in patients on hemodialysis (7). Additionally, there is a US Food and Drug Administration (FDA) warning on the risk of dermatological malignancies with the use of topical tacrolimus (8).

Systematic pharmacological interventions

Mast cell stabilizers block effects of histamine to reduce itch; however, evidence on their effectiveness has been conflicting (5). Gabapentin and pregabalin are the most widely studied medications for uremic pruritis, and both have been shown to be effective (5). They work by negatively modulating voltage-gated calcium channels and calcitonin gene-related peptide release. Some patients report dizziness and somnolence as side effects. Thus, extra caution has to be made to adjust the dose of gabapentin and pregabalin according to a patient's kidney function (9).

Opioid receptor modulators

More recently, clinical trials on opioid receptor modulators to treat uremic pruritus have been emerging. Based on current literature, the μ-antagonist promotes pruritus, whereas the κ-receptor inhibits pruritus. μ-Antagonists, such as naltrexone, have been found to be ineffective in RCTs; additionally, they come with adverse effects, such as sedation and gastro-intestinal complications (10, 11). κ-Receptor agonists are more favorable options than μ-antagonists, as κ-receptor agonists do not promote euphoria. Nalfurafine is the selective central activation of the κ-receptor, which contributes to anti-itch sensation; however, it is only approved for use in Japan (12, 13). Difelikefalin is a peripheral κ-receptor that does not penetrate the blood-brain barrier. In the recent phase 3 randomized clinical trial, difelikefalin showed increased effectiveness in reducing pruritus symptoms compared to placebo (14). Its adverse effects include diarrhea, dizziness, and vomiting. Difelikefalin is not yet approved by the FDA for use. Finally, nalbuphine, a dual κ-receptor agonist/μ-antagonist, has been studied in opioid-related pruritus but not widely studied in uremic pruritus. So far, one clinical trial showed that nalbuphine reduced the intensity of itchiness among patients on hemodialysis (15). Currently, nalbuphine is only approved by the FDA for use for analgesia, not for itching (16). ■

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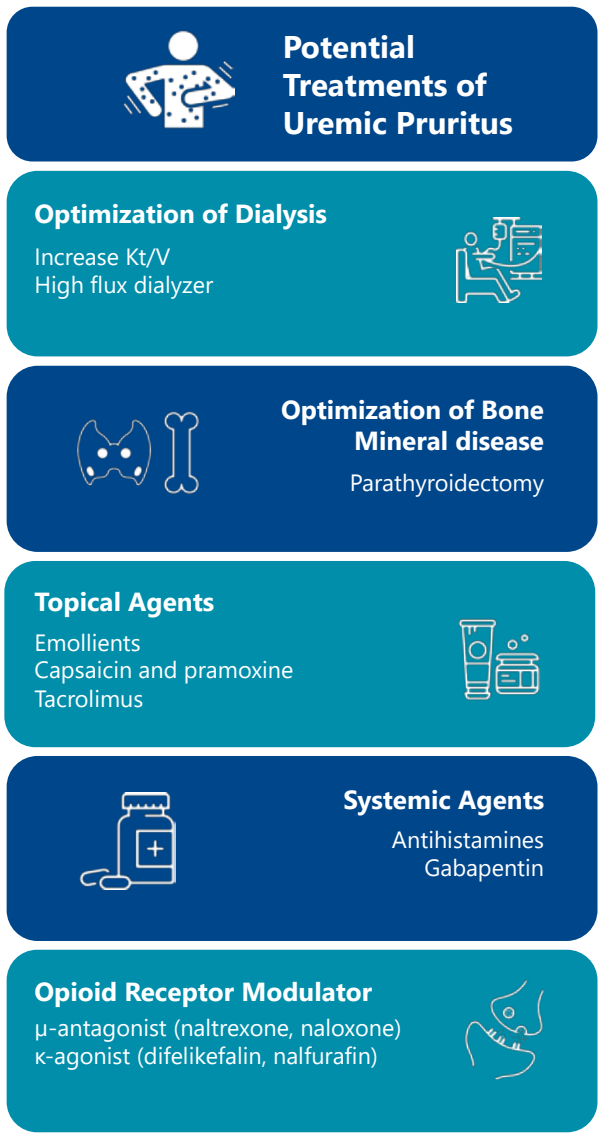
The authors report no conflict of interest.



References

1. Pisoni RL, et al. Pruritus in haemodialysis patients: International results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 2006; 21:3495–3505. doi: 10.1093/ndt/gfl461

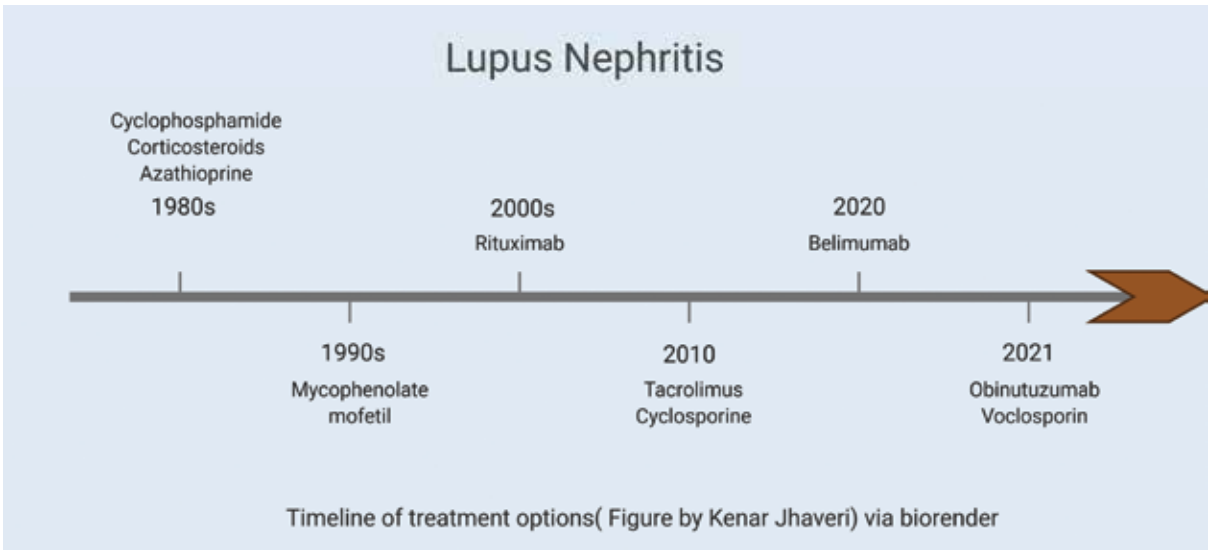
2. Zucker I, et al. Prevalence and characterization of uremic pruritus in patients undergoing hemodialysis: Uremic pruritus is still a major problem for patients with end-stage renal disease. *J Am Acad Dermatol* 2003; 49:842–846. doi: 10.1016/s0190-9622(03)02478-2
3. Rayner HC, et al. International comparisons of prevalence, awareness, and treatment of pruritus in people on hemodialysis. *Clin J Am Soc Nephrol* 2017; 12:2000–2007. doi: 10.2215/CJN.03280317
4. Martin CE, et al. Have we just scratched the surface? A narrative review of uremic pruritus in 2020. *Can J Kidney Health Dis* 2020; 7:2054358120954024. doi: 10.1177/2054358120954024
5. Simonsen E, et al. Treatment of uremic pruritus: A systematic review. *Am J Kidney Dis* 2017; 70:638–655. doi: 10.1053/j.ajkd.2017.05.018
6. Chou F-F, et al. A study on pruritus after parathyroidectomy for secondary hyperparathyroidism 1. *J Am Coll Surg* 2000; 190:65–70. doi: 10.1016/s1072-7515(99)00212-4
7. Duque MI, et al. Lack of efficacy of tacrolimus ointment 0.1% for treatment of hemodialysis-related pruritus: A randomized, double-blind, vehicle-controlled study. *J Am Acad Dermatol* 2005; 52 (3 Pt 1):519–521. doi: 10.1016/j.jaad.2004.08.050
8. US Food and Drug Administration. FDA Approves Updated Labeling with Boxed Warning and Medication Guide for Two Eczema Drugs, Elidel and Protopic. January 19, 2006. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-approves-updated-labeling-boxed-warning-and-medication-guide-two-eczema-drugs-elidel-and
9. Ishida JH, et al. Gabapentin and pregabalin use and association with adverse outcomes among hemodialysis patients. *J Am Soc Nephrol* 2018; 29:1970–1978. doi: 10.1681/ASN.2018010096
10. Pauli-Magnus C, et al. Naltrexone does not relieve uremic pruritus. Results of a randomized, double-blind, placebo-controlled crossover study. *J Am Soc Nephrol* 2000; 11:514–519. https://jasn.asnjournals.org/content/11/3/514
11. Legroux-Crespel E, et al. A comparative study on the effects of naltrexone and loratadine on uremic pruritus. *Dermatology* 2004; 208:326–330. doi: 10.1159/000077841
12. Inui S. Nalfurafine hydrochloride to treat pruritus: A review. *Clin Cosmet Investig Dermatol* 2015; 8:249–255. doi: 10.2147/CCID.S55942
13. Sumitomo Dainippon Pharma Co., Ltd. IR News: Toray's Pruritus Treatment REMITCH OD Tablets 2.5 μg to Be Introduced in Japan. May 31, 2017. https://www.ds-pharma.com/ir/news/2017/20170531.html
14. Fishbane S, et al. A phase 3 trial of difelikefalin in hemodialysis patients with pruritus. *N Engl J Med* 2020; 382:222–232. doi: 10.1056/NEJMoa1912770
15. Mathur VS, et al. A multicenter, randomized, double-blind, placebo-controlled trial of nalbuphine ER tablets for uremic pruritus. *Am J Nephrol* 2017; 46:450–458. doi: 10.1159/000484573
16. Endo Pharmaceuticals Inc. NUBAIN (Nalbuphine Hydrochloride). January 2005. https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/018024s040lbl.pdf

2021 and Beyond— Lupus Nephritis

By Marco Bonilla and Kenar D. Jhaveri

Figure by Kenar D. Jhaveri using biorender.com

Figure 1. Timeline for lupus nephritis treatment options



Lupus nephritis is a serious end organ manifestation of systemic lupus erythematosus (SLE). Regardless of the remarkable advances in the knowledge and understanding of lupus nephritis pathophysiology, it remains a weighty source of morbidity and mortality, and 10% to 30% of affected patients progress to end-stage kidney disease within 10 years of being diagnosed with SLE (1).

Therapy for lupus nephritis has continued to evolve, from the use of cyclophosphamide, azathioprine, and steroids developed in the 1970s–1980s to the use of mycophenolate, tacrolimus, cyclosporine, and rituximab in the 2000s (Figure 1). Given the significant adverse effects of some of the current agents, novel therapies are in the pipeline. The determination of an ideal management has been extremely challenging. Here, we highlight several potential treatments for lupus nephritis that we may see in 2021 and beyond.

Belimumab

Belimumab is a humanized monoclonal antibody (mAb) against a B cell–activating factor that has been studied in two prospective clinical trials: Efficacy and Safety of Belimumab in Patients With Active Lupus Nephritis (BLISS-LN) (2) and Rituximab and Belimumab for Lupus Nephritis (CALIBRATE) (3) studies.

The BLISS-LN study (2) was a phase 3, multi-center, international, randomized, double-blind, placebo-controlled trial, comparing belimumab (dose of 10 mg/kg of body weight) with matching placebo, in addition to standard therapy. The study showed that patients in the belimumab group had a higher complete kidney response than the placebo group (30% vs. 20%, respectively), and kidney adverse events were lower in the belimumab group compared to placebo. This has led to US Food and Drug Administration (FDA) approval of this agent in use of lupus nephritis. What is interesting is that the primary endpoint of the trial was changed 5 years after the commencement of the trial. The original endpoints categorized responses as complete, partial, or no response, according to the level of proteinuria and estimated glomerular filtration rate (eGFR) from 24 h urine collections, and microscopic examination of urinary sediment, although favoring belimumab, was not significantly different between the belimumab and placebo groups. Limitations of the study include the following: only two induction agents were permitted, the induction agent was not randomly assigned, and low enrollment of patients of Black race. The current trial still leaves us with a few uncertainties but leads the groundwork for ongoing trials using this novel agent. Could belimumab decrease the progression to end-stage kidney disease and subsequent flares in patients with severe lupus nephritis? It is yet to be seen.

The CALIBRATE study (3) was a phase 2, multi-center, randomized, controlled, open-label trial of cyclophosphamide plus rituximab, followed by belimumab, in patients with active lupus nephritis. The study showed at week 48, a complete or partial kidney response in the belimumab group compared to the control group (52% vs. 41%, respectively), and patients in the belimumab group did not have an increased frequency of adverse events. In the final conclusion, the addition of belimumab to a treatment regimen with rituximab and cyclophosphamide was safe in patients with refractory lupus nephritis. This regimen diminished maturation of transitional-to-naive B cells during B cell reconstitution and enhanced the negative selection of autoreactive B cells. Clinical efficacy was not improved with rituximab and cyclophosphamide in combination with belimumab when compared to a therapeutic strategy of B cell depletion alone in patients with lupus nephritis.

Obinutuzumab

Based on their mechanisms of action, CD20 mAbs are grouped into two types. Type I mAbs deplete B cells by inducing complement-dependent cytotoxicity (CDC), such as rituximab, and are referred to as antibody-dependent cell-mediated cytotoxic (ADCC). Alternatively, type II mAbs deplete B cells by initiating a combination of programmed cell death (PCD) and ADCC. Obinutuzumab and tositumomab are examples of type II agents.

Obinutuzumab, a type II anti-CD20 mAb that has been shown to be superior to rituximab (type I) in depleting B cells, was tested in the NOBILITY study (4). This was a phase 2, randomized, double-blind, placebo-controlled, multi-center study. The trial included patients with active class III/IV lupus nephritis who received obinutuzumab vs. placebo, combined with mycophenolate mofetil and steroids. The primary endpoint was complete kidney response at 52 weeks. The study showed that obinutuzumab had higher complete kidney response vs. placebo; serious adverse events and serious infections were not increased in the obinutuzumab group. The novel agent was not associated with increases in rates of serious adverse events or serious infections. Forthcoming data through week 104 will permit further assessment of the longer-term safety and efficacy of obinutuzumab in proliferative lupus nephritis. We again await the fully published results of yet another potential treatment for lupus nephritis. However, we should note that obinutuzumab was not compared directly to rituximab.

Voclosporin

The efficacy and safety of this novel calcineurin inhibitor were tested by the Aurinia Urinary Protein Reduction Active-Lupus with Voclosporin (AURA-LV) study. This was a phase 2, multi-center, randomized, placebo-controlled trial. This study showed a higher complete remission rate

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2021 and Beyond

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in the low-dose group, as well as the high-dose group, when compared to placebo at 48 weeks but a higher frequency of adverse events in the voclosporin group, with a higher mortality rate in the low-dose group when compared to the placebo group (5). In the abstract format presented at the European League Against Rheumatism (EULAR) meetings in 2020, the efficacy seen in Aurinia Renal Response in Active Lupus with Voclosporin (AURORA) was again demonstrated, as voclosporin improved the kidney response by 18.3% at 1 year (40.8% vs. 22.5%) (6). Voclosporin is now FDA-approved as of late January 2021 for use for lupus nephritis (7). At the time of this writing, the peer-reviewed publication of the AURORA trial had not yet been published.

Although the above three drugs may show promise this year, several clinical trials are either completed or recruiting for trials in lupus nephritis with other novel agents. **Pentoxifylline** is an oral phosphodiesterase inhibitor introduced 45 years ago for treatment of vascular insufficiency. It has also recently been found to reduce proteinuria in patients with diabetic nephropathy. The mechanism of this intriguing finding is not certain but may, in part, involve inhibition of the production of tumor necrosis factor (TNF)-α, an inflammatory cytokine known to be present in urine and kidneys of patients with lupus nephritis. Currently, a multicenter, double-blind, placebo-controlled, randomized trial of pentoxifylline or placebo, in addition to standard of care for treatment of proteinuria in patients with lupus nephritis, is ongoing (8).

Borrowing from the onconephrology world, **zanubrutinib** (a Bruton's tyrosine kinase inhibitor) is being studied in lupus nephritis as well. Currently, there is a phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of zanubrutinib in patients with active proliferative lupus nephritis (9). Finally, **guselkumab** is a mAb that binds to human interleukin (IL)-23 with high affinity and blocks binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23-specific intracellular signaling and subsequent activation and cytokine production. It is used in treatment of psoriatic arthritis, generalized pustular psoriasis, and erythrodermic psoriasis. There is an ongoing study (10) that will evaluate the safety and efficacy of guselkumab added to standard of care compared to placebo added to standard of care.

So as we enter 2021, the field of lupus nephritis is exploding with potential novel therapies on the horizon. ■

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The authors report no conflict of interest related to the article.

References

1. Parikh SV, et al. Update on lupus nephritis: Core curriculum 2020. *Am J Kidney Dis* 2020; 76:265–281. doi: 10.1053/j.ajkd.2019.10.017
2. Furie R, et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. *N Engl J Med* 2020; 383:1117–1128. doi: 0.1056/NEJMoa2001180
3. Atisha-Fregoso Y, et al. Phase II randomized trial of rituximab plus cyclophosphamide followed by belimumab for the treatment of lupus nephritis. *Arthritis Rheumatol* [published online ahead of print August 4, 2020]. doi: 10.1002/art.41466; https://onlinelibrary.wiley.com/doi/10.1002/art.41466
4. Furie R, et al. A phase II randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of obinutuzumab or placebo in combination with mycophenolate mofetil in patients with active class III or IV lupus nephritis (abstract). *Arthritis Rheumatol* 2019; 71 (Suppl 10):939. https://acrabstracts.org/abstract/a-phase-ii-randomized-double-blind-placebo-controlled-study-to-evaluate-the-efficacy-and-safety-of-obinutuzumab-or-placebo-in-combination-with-mycophenolate-mofetil-in-patients-with-active-class-iii/
5. Rovin BH, et al. A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis. *Kidney Int* 2019; 95:219–231. doi: 10.1016/j.kint.2018.08.025
6. Arriens C, et al. AURORA phase 3 study demonstrates voclosporin statistical superiority over standard of care in lupus nephritis. Aurinia. June 5, 2020. https://d1io3yog0oux5.cloudfront.net/_b9287cb2b9b32ac3fbb5d08113841567/auriniapharma/db/246/1327/pdf/EULAR+2020+AURORA_Presentation+Deck+05Jun2020.pdf
7. Aurinia. FDA Approves Aurinia Pharmaceuticals' LUPKYNIS™ (voclosporin) for Adult Patients with Active Lupus Nephritis. January 22, 2021. https://ir.auriniapharma.com/press-releases/detail/210
8. MetroHealth Medical Center. Pentoxifylline in Lupus Nephritis (Pentoxifylline). ClinicalTrials.gov: NCT03859570. https://clinicaltrials.gov/ct2/show/NCT03859570
9. BeiGene. Zanubrutinib in Participants with Active Proliferative Lupus Nephritis. ClinicalTrials.gov: NCT04643470. https://clinicaltrials.gov/ct2/show/NCT04643470
10. Janssen Research & Development, LLC. A Study of Guselkumab in Participants with Active Lupus Nephritis (ORCHID-LN). ClinicalTrials.gov: NCT04376827. https://clinicaltrials.gov/ct2/show/NCT04376827

Novel Anemia Treatment: HIF-PH Inhibitors

By Daniel W. Coyne

For more than 30 years, erythropoiesis-stimulating agents (ESAs) have reigned supreme as the treatment for chronic kidney disease (CKD)–related anemia. Can hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs) topple ESAs? HIF-PHIs are oral medications taken three times a week or daily and have been shown in trials to achieve and maintain goal hemoglobin to the same degree as ESAs. HIF-PHIs are small molecules that inhibit the prolyl hydroxylase enzyme that continually marks the HIF for degradation. Each dose transiently increases intracellular HIF2a, a transcription factor, leading to activation of a series of genes, including erythropoietin (EPO) and several iron transport genes. Consequently, endogenous EPO levels increase, and iron absorption and mobilization are enhanced (Table 1).

Phase 3 clinical trials of the HIF-PHI roxadustat show that it can replace ESAs in the dialysis population for anemia management and can reduce intravenous iron requirements. Roxadustat reduced major adverse cardiovascular event (MACE) rates compared to ESA in incident dialysis patients and had similar MACE rates to ESA in prevalent patients receiving dialysis. In CKD trials versus placebo, roxadustat achieved goal hemoglobin and did not significantly increase MACE.

It may not be clear sailing for HIF-PHIs, however. Recent phase 3 randomized clinical trials of vadadustat showed that it could replace ESA in managing anemia but raised serious safety issues. Two international trials in patients with CKD found that vadadustat significantly increased MACE rates compared to the ESA darbepoetin (hazard ratio [HR] 1.17, confidence interval [CI] 1.01–1.36). In those trials, the hemoglobin target was 10–11 g/dL in the United States, and 10–12 g/dL in all non-US sites.

An analysis showed MACE was not increased in the vadadustat arm versus the ESA arm in US patients (HR 1.01, CI 0.83–1.23) but was increased with vadadustat compared to ESA in the non-US patients (HR 1.29, CI 1.03–1.60). In contrast, two vadadustat vs. ESA trials in the dialysis population showed comparable anemia management, and no increase in MACE compared to ESA therapy.

Whether safety differences in trials to date reflect unique actions of particular HIF-PHI agents, differences in trial designs, or other factors remains to be answered. Phase 3 randomized clinical trials with daprodustat, another HIF-PHI, are completed in dialysis patients, and results will be released later in 2021. The daprodustat trial in CKD non-dialysis patients should be completed in April 2021. ■

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The author participated as a site investigator in trials of roxadustat and daprodustat and has been a consultant to the manufacturer of all three HIF-PHIs.

Table 1. Select HIF-PHIs and approval status

HIF-PHI Product	Half-Life	Phase 3 Trials' Status	US Approval Status	Approved for Use in
Roxadustat	14.7–19.4 h	All completed	Submitted for approval; FDA response required 3/20/21	Japan, China
Vadadustat	1.9–3.6 h	All completed	Anticipated FDA new drug submission early 2021	Japan
Daprodustat	0.9–2.3 h	Completed, except CKD-non-dialysis study (tentative closure April 2021)	Anticipated FDA new drug submission 2021	Japan

Urea for the Treatment of Hyponatremia: An Old Treatment Offers Fresh Hope

By Edgar V. Lerma and Helbert Rondon-Berrios

The conventional first-line therapy for any patient presenting with hypotonic hyponatremia due to SIAD (syndrome of inappropriate antidiuresis) is that of fluid restriction. However, we recognize that fluid restriction alone does not always work. The Expert Panel Recommendations on Diagnosis, Evaluation, and Treatment of Hyponatremia, published in 2013, identified certain criteria that are predictive of which patients are less likely to respond to fluid restriction alone (1). These include a urine-to-plasma electrolyte ratio ([urine Na + urine K]/plasma sodium [PNa]) >1 or a high urine osmolality (>500 mOsm/kg H_2O).

It has been suggested that those patients who are unlikely to respond to fluid restriction alone may be effectively treated with oral urea in combination with fluid restriction (2).

Historically, urea was first used as a diuretic in 1892 (3). Three decades later, Crawford et al. (4) reported on its use in advanced heart failure. With the recognition of its beneficial effects on brain swelling and water excretion, in 1982, Decaux et al. (5) published their paper, which highlighted the "use of urea for the treatment of symptomatic hyponatremia in SIAD."

For many decades, oral urea has been used for the treatment of SIAD. In fact, in 2014, the European Hyponatraemia Guideline Development Group published the clinical practice guideline on diagnosis and treatment of hyponatraemia, which stated that "In moderate or profound hyponatraemia, we suggest the following can be considered equal second line treatments: increasing solute intake with 0.25–0.50 g/kg per day of urea or a combination of low-dose loop diuretics and oral sodium chloride (2D)" (6).

Urea became commercially available in the United States in 2016. Unlike prescription drugs, it is regulated differently, as it does not require a prescription, and it is recommended to be used under the care of a healthcare provider. Current available formulations in the United States include ure-Na (https://www.ure-na.com/) and UreaAide (https://www.kidneyaide.com/about-ureaaide.html#/).

In 2018, a retrospective study was published, involving an inpatient population of 58 patients, whereby it compared the change in PNa between a subgroup of patients who included those with SIAD receiving urea as the "only" medication for hyponatremia, and a matched group of patients being treated for SIAD who did not receive urea (7). In the 12 patients who received "urea only," PNa increased from 125 to 131 ($p < 0.001$) with 33% achieving normal PNa (vs. 8%, $p = 0.08$). The study concluded that this formulation of oral urea appears to be safe and efficacious in the treatment of hyponatremia.

Other studies showed the efficacy of urea in the treatment of hyponatremia in the intensive care unit (ICU) setting (8), as well as in cancer-induced SIAD (9).

Another notable study showed that the efficacy of urea was similar to that of vasopressin antagonists for treatment of chronic SIAD, whereas tolerability was good for both agents (10).

Common side effects observed with urea include distaste, nausea, vomiting, diarrhea, and headaches (3, 9, 11). There is always a concern with rapid correction of PNa with any therapy used in hyponatremia, including fluid restriction. Two studies describe overly rapid correction associated with urea (8, 13); however, no cases of osmotic demyelination syndrome (ODS) have been reported, and there is experimental data suggesting that urea may be protective in ODS (12, 14). The main indication for urea is SIAD, and there is very limited data on its use in patients with hyponatremia associated with heart failure and cirrhosis.

With the consideration of all of the limitations of current studies on urea for treatment of chronic hyponatremia due to SIAD, are randomized controlled trials on the horizon?

Well, in fact, a pilot study (NCT04588207) at the University of Pittsburgh, led by Dr. Rondon-Berrios, is currently in the works (15). The study plans to recruit 30 ambulatory patients with chronic non-severe hyponatremia and randomize them to oral urea or no-drug treatment for a period of 42 days. Following a 10-day washout period, participants initially randomized to no-drug therapy will receive urea, and those initially treated with urea will receive no-drug therapy for another 42 days. In addition to measuring serum sodium at baseline and after urea therapy, participants will undergo neurocognitive and posture-stability measurements. This pilot study will inform the design of a large clinical trial that will assess the efficacy of urea for the prevention of serious clinical outcomes of chronic non-severe hyponatremia. ■

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Helbert Rondon-Berrios is funded by exploratory/developmental research grant R21DK122023 from the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.

References

1. Verbalis JG, et al. Diagnosis, evaluation, and treatment of hyponatremia: Expert panel recommendations. *Am J Med* 2013; 126 (10 Suppl 1):S1–S42. doi: 10.1016/j.amjmed.2013.07.006
2. Rondon-Berrios H. Urea for chronic hyponatremia. *Blood Purif* 2020; 49:212–218. doi: 10.1159/000503773

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3. Sterns RH, et al. Urea for hyponatremia? *Kidney Int* 2015; 87:268–270. doi: 10.1038/ki.2014.320
4. Crawford H, McIntosh JF. The use of urea as a diuretic in heart failure. *Arch Intern Med* (Chic) 1925; 36:530–541. doi:10.1001/archinte.1925.00120160088004
5. Decaux G, et al. Hyponatremia in the syndrome of inappropriate secretion of antidiuretic hormone. Rapid correction with urea, sodium chloride, and water restriction therapy. *JAMA* 1982; 247:471–474. doi: 10.1001/jama.1982.03320290017021
6. Spasovski G, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Intensive Care Med* 2014; 40:320–331. doi: 10.1007/s00134-014-3210-2
7. Rondon-Berrios H, et al. Urea for the treatment of hyponatremia. *Clin J Am Soc Nephrol* 2018; 13:1627–1632. doi: 10.2215/CJN.04020318
8. Decaux G, et al. Treatment of euvolemic hyponatremia in the intensive care unit by urea. *Crit Care* 2010; 14:R184. doi: 10.1186/cc9292
9. Nervo A, et al. Urea in cancer patients with chronic SIAD-induced hyponatremia: Old drug, new evidence. *Clin Endocrinol (Oxf)* 2019; 90:842–848. doi: 10.1111/cen.13966
10. Soupart A, et al. Efficacy and tolerance of urea compared with vaptans for long-term treatment of patients with SIADH. *Clin J Am Soc Nephrol* 2012; 7:742–747. doi: 10.2215/CJN.06990711
11. Lockett J, et al. Urea treatment in fluid restriction refractory hyponatremia. *Clin Endocrinol (Oxf)* 2019; 90:630–636. doi: 10.1111/cen.13930
12. Soupart A, et al. Azotemia (48 h) decreases the risk of brain damage in rats after correction of chronic hyponatremia. *Brain Res* 2000; 852:167–172. doi: 10.1016/s0006-8993(99)02259-3
13. Pierrakos C, et al. Urea for treatment of acute SIADH in patients with subarachnoid hemorrhage: A single-center experience. *Ann Intensive Care* 2012; 2:13. doi: 10.1186/2110-5820-2-13
14. Gankam Kengne F, et al. Urea minimizes brain complications following rapid correction of hyponatremia compared with vasopressin antagonist or hypertonic saline. *Kidney Int* 2015; 87:323–331. doi: 10.1038/ki.2014.273
15. Rondon-Berrios H. Urea for chronic hyponatremia. ClinicalTrials.gov: NCT04588207. https://clinicaltrials.gov/ct2/show/NCT04588207?cond=urea+hyponatremia&draw=2&rank=1

Light and Shadow in Oral Tolvaptan Treatment

By Yong Chul Kim and Hajeong Lee

Tolvaptan, an oral selective vasopressin V2 receptor antagonist, was approved by the US Food and Drug Administration (FDA) for the treatment of clinically significant hypervolemic or euvolemic hyponatremia and rapidly progressing autosomal dominant polycystic kidney disease (ADPKD). It antagonizes the effect of an arginine vasopressin (antidiuretic hormone), which has a key role in water and circulatory homeostasis in the collecting duct of the kidney. Tolvaptan leads to an increase in urine water excretion (aquaresis) that results in enhanced free-water clearance in states of relative vasopressin excess, increasing serum sodium concentrations. Additionally, tolvaptan induces a reduction in cyclic adenosine monophosphate (cAMP), a key second messenger in the pathogenesis of ADPKD, resulting in decreased kidney cyst proliferation and fluid secretion, diminishing ADPKD cyst growth.

Two randomized, double-blind, placebo-controlled trials (Study of Ascending Levels of Tolvaptan in Hyponatremia [SALT]-1, SALT-2) demonstrated both short-term and long-term efficacy of tolvaptan in patients with hyponatremia from various causes, such as syndrome of inappropriate antidiuretic (SIAD) hormone and heart failure (1, 2). In view of ADPKD, tolvaptan slowed kidney cyst growth and functional decline with reduced frequencies of ADPKD-related complications at both early and later stages of chronic kidney disease (CKD) in two large trials: Tolvaptan Efficacy and Safety in Management of ADPKD and Its Outcomes (TEMPO 3:4) (3) and Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) trials (4, 5).

Although the treatment of hyponatremia and ADPKD with tolvaptan is an important advance, there are several drawbacks. First, common adverse effects of tolvaptan should be considered, which include thirst, urination frequency, fatigue, polydipsia, and polyuria. All of these are the main causes of discontinuation during the treatment of ADPKD. Second, patients taking tolvaptan should monitor their liver function regularly due to possible drug-induced hepatotoxicity. Third, one should remain vigilant for osmotic demyelination syndrome, a rare but devastating complication arising from an overly rapid hyponatremia correction, especially if tolvaptan is used with diuretics or hypertonic saline solution concomitantly (6). Frequent monitoring of serum electrolyte and volume status is warranted, and physicians should consider using low doses at initiation because of the potential for overcorrection (7). Forth, tolvaptan is an expensive medication, and there is a huge difference in insurance coverage by the healthcare system among countries that approved tolvaptan. Currently, there are only a few studies looking at the cost-effectiveness of the treatment of ADPKD or SIAD with tolvaptan (8, 9). Last, although there is a recommendation for the timing of the initiation of tolvaptan in patients with ADPKD, it is unclear when to stop the medication. For example, do patients have to take it until dialysis? Do they quit around CKD stage 4?

Although these advances are certainly exciting and pave the way for continued investment of novel therapeutics in these areas, there are several concerns and questions about using tolvaptan in patients having either hyponatremia or ADPKD (10–12). Both require patient engagement to describe the risks and benefits before prescribing. The development of antagonists to vasopressin has ushered in a new era in clinical trials for hyponatremia and ADPKD and will hopefully only be the start of ushering in new therapies (13). ■

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The authors declare that they have no relevant financial interests.

References

1. Schrier RW, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med* 2006; 355:2099–2112. doi: 10.1056/NEJMoa065181
2. Berl T, et al. Oral tolvaptan is safe and effective in chronic hyponatremia. *J Am Soc Nephrol* 2010; 21:705–712. doi: 10.1681/ASN.2009080857. Erratum in: *J Am Soc Nephrol* 2010; 21:1407. https://jasn.asnjournals.org/content/21/8/1407.2
3. Torres VE, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2012; 367:2407–2418. doi: 10.1056/NEJMoa1205511
4. Torres VE, et al. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. *N Engl J Med* 2017; 377:1930–1942. doi: 10.1056/NEJMoa1710030
5. Edwards ME, et al. Long-term administration of tolvaptan in autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol* 2018; 13:1153–1161. doi: 10.2215/CJN.01520218
6. Malhotra I, et al. Unpredictable nature of tolvaptan in treatment of hypervolemic hyponatremia: Case review on role of vaptans. *Case Rep Endocrinol* 2014; 2014:807054. doi: 10.1155/2014/807054
7. Sterns RH. Tolvaptan for the syndrome of inappropriate secretion of antidiuretic hormone: Is the dose too high? *Am J Kidney Dis* 2018; 71:763–765. doi: 10.1053/j.ajkd.2018.02.355
8. Erickson KF, et al. Cost-effectiveness of tolvaptan in autosomal dominant polycystic kidney disease. *Ann Intern Med* 2013; 159:382–389. doi: 10.7326/L14-5001-7
9. Jamookeeah C, et al. Cost-effectiveness of tolvaptan for the treatment of hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion in Sweden. *BMC Endocr Disord* 2016; 16:22. doi: 10.1186/s12902-016-0104-z
10. Chebib FT, et al. A practical guide for treatment of rapidly progressive ADPKD with tolvaptan. *J Am Soc Nephrol* 2018; 29:2458–2470. doi: 10.1681/ASN.2018060590
11. Gross P, et al. Con: Tolvaptan for autosomal dominant polycystic kidney disease—do we know all the answers? *Nephrol Dial Transplant* 2019; 34:35–37. doi: 10.1093/ndt/gfy298
12. Meijer E, Gansevoort RT. Vasopressin V2 receptor antagonists in autosomal dominant polycystic kidney disease: Efficacy, safety, and tolerability. *Kidney Int* 2020; 98:289–293. doi: 10.1016/j.kint.2020.03.023
13. Gordon CE, Perrone RD. Tolvaptan or transplant: Why wait? *Kidney Int* 2020; 98:286–289. doi: 10.1016/j.kint.2020.03.022. Erratum in: *Kidney Int* 2020; 98:1622. doi: 10.1016/j.kint.2020.11.002

First of Its Kind Treatment for Primary Hyperoxaluria Wins Approval, Holds Promise

By Ray Bignall II

Figure created by Ray Bignall II and Matthew Sparks

In November 2020, the US Food and Drug Administration (FDA) approved lumasiran (brand name "Oxlumo"), the first medical therapy specifically for the management of primary hyperoxaluria type 1 (PH1), a rare and life-threatening disease that often progresses to kidney failure. This announcement may represent a breakthrough, not only in the treatment of PH1 but also in drug development for a host of rare kidney diseases.

PH1 is caused by a congenital defect in the hepatic enzyme alanine glyoxylate aminotransferase, resulting in a failure to metabolize glyoxylate to glycine and the toxic accumulation of oxalate. The buildup of unmetabolized oxalate leads to its increased urinary excretion and crystallization. With time, this excess oxalate damages the kidneys, further impairing excretion and resulting in systemic oxalosis, with deposition in the bones and other organs. Severe kidney disease from PH1 can be insidious: 30% of patients present with kidney failure at the time of diagnosis, and many develop kidney failure by adolescence or young adulthood (1).

Heretofore, the management of PH1 has been largely supportive. For many individuals living with PH1, treatment has included copious fluid intake, often requiring the placement of a gastrostomy tube; early and frequent daily hemodialysis; and combined liver and kidney transplantation, sometimes requiring hemodialysis posttransplant as well. The median age to start dialysis is between 1 and 2 years, and even with these interventions, patient survival rate 5 years after the start of kidney replacement therapy is 76%, compared with 92% among children with kidney failure from other causes (2).

Now enters lumasiran, a small interfering RNA drug produced by Alnylam Pharmaceuticals, which promises to radically change our approach to managing PH1. The drug was developed as part of a unique collaboration between the Oxalosis and Hyperoxaluria Foundation and the Kidney Health Initiative (KHI), ASN's public-private partnership with the FDA that aims to catalyze therapeutic innovations for people living with kidney diseases. With the use of RNA interference technology, lumasiran targets the messenger RNA for hydroxyacid oxidase 1 (HAO1) in the hepatocyte, which reduces levels of glycolate oxidase enzyme activity. Reduced glycolate oxidase enzyme activity means less substrate to catalyze the production of the toxic oxalate and thus less oxalosis overall (3) (Figure 1).

According to the FDA announcement, the top-line results of ILLUMINATE-A, the randomized multinational phase 3 study of lumasiran in participants 6 years of age and older, showed an average 65% reduction in 24-hour urinary oxalate excretion in the lumasiran cohort, compared with 12% in those who received placebo. In addition, one-half of patients in the lumasiran group achieved a normal 24-hour oxalate excretion level. No serious adverse events were reported, and among those treated with lumasiran, other adverse events were rare, including injection-site reactions like pain or redness and headache (4). In ILLUMINATE-B, the companion open-label multinational phase 3 study of lumasiran in children 5 years and younger, participants experienced a mean decrease in urinary oxalate of roughly 70% in the study's first 6 months. The endpoints reported in both the ILLUMINATE-A and -B trials suggest the drug's favorable impact on long-term PH1 sequelae, like kidney failure. This is welcome news to patients and families who had little therapeutic options prior to lumasiran's approval (5).

Could this drug's unique public-private industry-origin story signal a new trend in therapeutic developments for those living with relatively rare kidney diseases? Often, innovation to treat these diseases is stymied by financial impracticability. The FDA has worked to address this through rulemaking, and it awarded orphan drug and breakthrough therapy statuses to lumasiran, incentivizing the drug's production in an environment where market-based pressures often prevent the development of such tailored treatments (5). Ultimately, the people power of public-private collaborations, like the one led by ASN's KHI, which resulted in lumasiran's development, may signal the way of the future, leveraging emerging technologies to bring targeted therapies to treat rare diseases. ■

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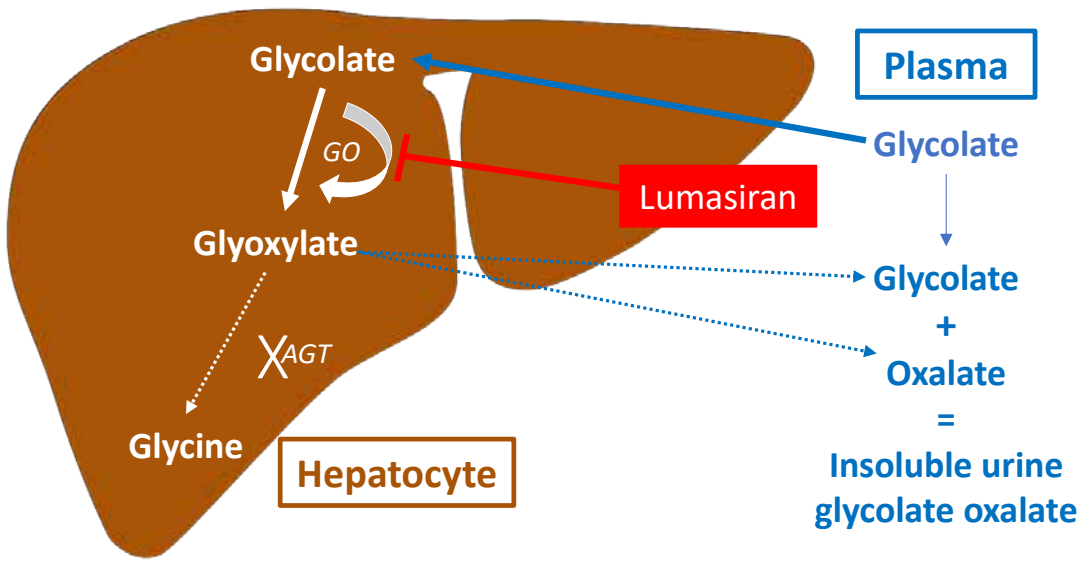
The author reports no conflict of interest.

References

1. Hoppe B. An update on primary hyperoxaluria. *Nat Rev Nephrol* 2010; 8:467–475. doi: 10.1038/nrneph.2012.113
2. Cochat P, Rumsby G. Primary hyperoxaluria. *N Engl J Med* 2013; 369:649–658. doi: 10.1056/NEJMra1301564
3. US National Library of Medicine. OXLUMO - lumasiran injection, solution. *DailyMed* (Alnylam Pharmaceuticals, Inc.). https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=16985a31-f5e4-4557-9266-fc78d4bc5055#section-8.1
4. Alnylam Pharmaceuticals. A Study to Evaluate Lumasiran in Children and Adults with Primary Hyperoxaluria Type 1 (ILLUMINATE-A). ClinicalTrials.gov: NCT03681184. https://clinicaltrials.gov/ct2/show/results/NCT03681184?view=results
5. US Food and Drug Administration. FDA Approves First Drug to Treat Rare Metabolic Disorder. November 23, 2020. https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-treat-rare-metabolic-disorder

Figure 1. Over-simplified cartoon depicting the aberrant hepatic glyoxylate metabolism in PH1 and the site of action of lumasiran, which inhibits glycolate oxidase (GO) activity, reducing downstream levels of glyoxylate and resulting in decreased excretion of insoluble urine GO



AGT = alanine glyoxylate aminotransferase

Fellows First

HIF Stabilizers Get in Sync: Are ESAs Bye Bye Bye?

By Gonzalo Matzumura

Anemia is a well-known complication of chronic kidney disease (CKD), and treatment of anemia with erythropoietin (EPO)-stimulating agents (ESAs) is associated with improved quality of life and less need for transfusions (1–3). Since the introduction of ESAs three decades ago, gone are the days when large numbers of patients on dialysis were transfusion dependent—well, nearly (4). Up to 10% of people still do not respond adequately to ESAs, and hyporesponsiveness has been associated with increased mortality (5, 6). For years, ESAs have been the mainstay of treatment for anemia of CKD, but ESA hyporesponsiveness, concerns regarding increased cardiovascular events and mortality, and the desire for an orally active therapy have pushed the development of alternative agents to the forefront of clinical research (3, 4, 7).

The development of novel therapeutics to manage anemia in CKD requires knowledge of the physiology of oxygen sensing and homeostasis in the kidney, as well as the pathophysiology of anemia in CKD (8). When oxygen levels in the kidney drop, peritubular fibroblast-like cells in the juxtamedullary cortex sense this and activate a large number of genes to adapt to the hypoxia, including those to increase synthesis of EPO, which increases red blood cell production with the goal of re-establishing oxygen delivery back to the kidney (9).

The predominant mechanism by which these cells sense and adapt to hypoxia is the hypoxia-inducible factor (HIF) pathway, first described by Drs. Gregg Semenza and G. L. Wang in 1992 (10). Dr. Semenza was awarded the Nobel Prize in Physiology or Medicine along with Dr. William Kaelin and Dr. Peter Ratcliffe (a nephrologist!) in 2019 for their work on oxygen sensing. HIF is a transcription factor that under normal oxygenation is hydroxylated on its HIF-α subunit by prolyl-hydroxylase domain (PHD)-containing proteins. Subsequently, HIF-α undergoes ubiquitination by the von Hippel-Lindau E3 complex and is finally degraded in proteasomes. Under conditions of hypoxia, inhibition of hydroxylation of HIF-α allows it to persist and translocate to the nucleus where it dimerizes with HIF-β. In the nucleus, this heterodimer binds to hypoxia response elements, leading to transcription of oxygen homeostasis target genes, like vascular endothelial growth factor 1 (VEGF-1), EPO, and over 200 other gene products that regulate cell proliferation, metabolism, iron homeostasis, and cell growth (Figure 1) (11).

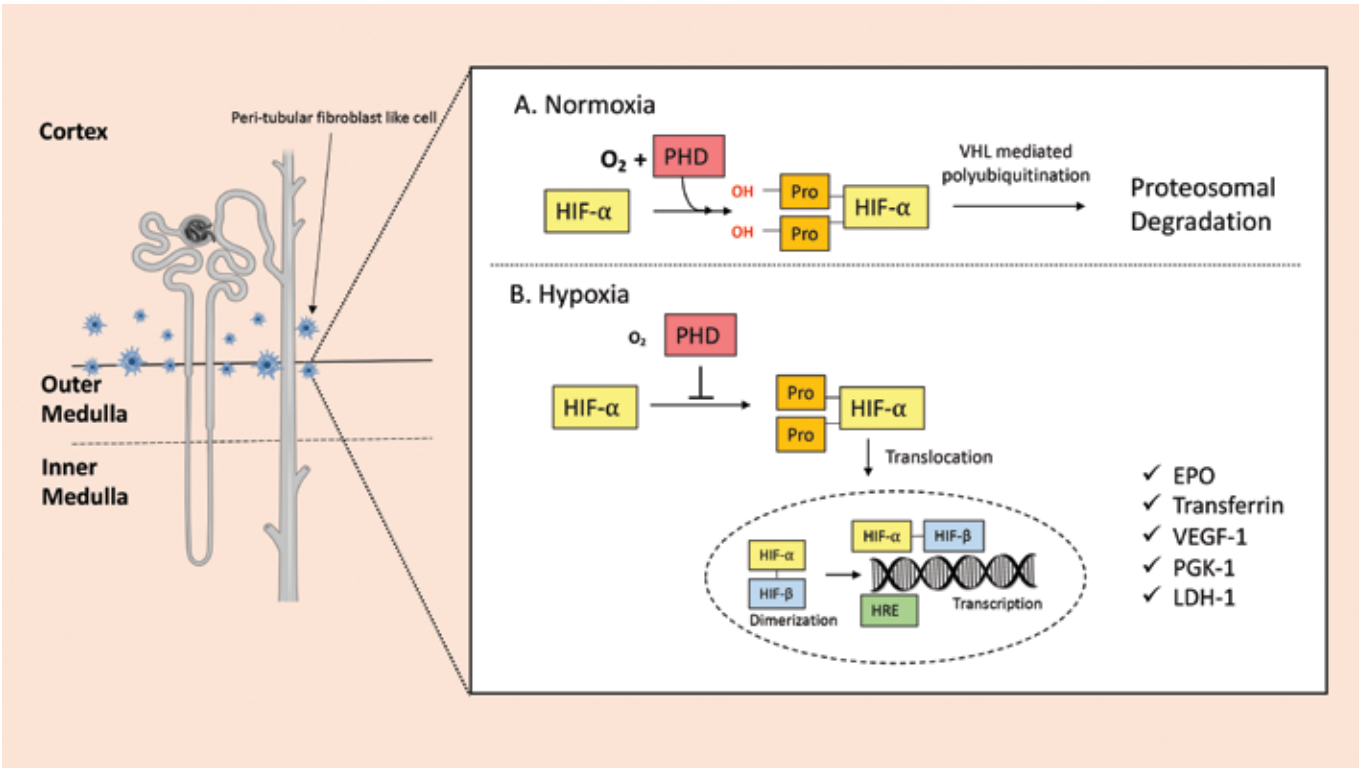
Over the past 15 years, HIF prolyl-hydroxylase inhibitors (HIF-PHIs), also known as HIF stabilizers, have been developed and studied for their efficacy and safety in patients with anemia in CKD (12). Stabilization of HIF by HIF-PHIs mimics a "pseudo-hypoxic" state, increasing endogenous EPO production in a fashion more closely resembling physiologic levels (as opposed to supraphysiologic peaks seen with exogenous ESA use) (13). One specific advantage of HIF-PHIs is their effect on iron homeostasis and iron store mobilization leading to a decrease in hepcidin, which improves anemia even in patients with elevated C-reactive protein (CRP) and ferritin who are traditionally thought to be hyporesponsive to ESAs (13).

Roxadustat is the first HIF-PHI to be approved for use anywhere globally and is currently undergoing US Food and Drug Administration (FDA) review in the United States. Data from a prior phase 3 clinical trial in China demonstrated it is non-inferior to darbepoetin alfa (DA) in patients with kidney failure receiving dialysis, and data from global phase 3 studies, including the Optimized Delivery of Mitomycin for Primary upper tract urothelial cancer (UTUC) Study (OLYMPUS), have found it is also effective in improving hemoglobin levels in patients with CKD not on dialysis when compared to placebo (14, 15). At ASN Kidney Week 2020 Reimagined, phase 3 clinical trials were presented on another HIF-PHI, vadadustat. Vadadustat was demonstrated to also be non-inferior to DA in achieving hemoglobin targets in patients with CKD not on dialysis (PRO2TECT [Efficacy and Safety Study to Evaluate Vadadustat for the Correction of Anemia in Subjects with Non-Dialysis-Dependent CKD (NDD-CKD)] trials) and in patients with kidney failure on dialysis (INNO2VATE [Efficacy and Safety Study to Evaluate Vadadustat for the Maintenance Treatment of Anemia in Subjects with Dialysis-Dependent CKD (DD-CKD)] trials) (16, 17). Other HIF-PHIs, including daprodustat, molidustat, and enarodustat, are in different stages of development, and a few have already been approved for use in other countries (13).

Due to the multiple downstream effects of HIF stabilization, concerns regarding nonspecific multiorgan effects beyond EPO production are being addressed during the development of HIF-PHIs (13). With regard to cardiovascular events, pooled safety data from trials of roxadustat showed that the risk of major adverse cardiovascular events (MACEs) was comparable to placebo in patients with CKD not on dialysis and non-inferior to epoetin alfa in patients with kidney failure receiving dialysis (18). This pooled study, recently published after first being presented at ASN Kidney Week 2019, showed a reduced risk of MACE in incident patients who had been on dialysis for less than 4 months (18, 19). Vadadustat, on the other hand, did not meet its primary safety endpoint of non-inferiority with regard to time to first MACE in patients with CKD not on dialysis (PRO2TECT trials) (16). However, in patients with kidney failure receiving dialysis, it was found to be non-inferior to DA in time to first MACE (INNO2VATE trials) (17). Regarding other adverse effects, increased VEGF-1 expression and other pro-angiogenic gene products by HIF-PHIs have led to concerns about the potential development of pulmonary hypertension, worsening retinopathy, and increased risk of malignancy (20). In a pooled analysis of roxadustat trials presented at ASN Kidney Week 2020 Reimagined, roxadustat, when compared to placebo and epoetin alfa, did not increase the risk of neoplasm-related adverse events during the treatment period; however, a relatively short follow-up limits the significance of this observation (21). We await the final peer-reviewed published data to decide on these effects.

Our progress in understanding oxygen homeostasis physiology and ongoing development of novel therapies, such as HIF-PHIs for anemia management in CKD, makes it an exciting time to start a career in nephrology. Whereas the prospect of "turning on" the HIF pathway master switch holds great promise for anemia and beyond, it will need to be carefully balanced with the ever-present risk of off-target effects. With the evidence accrued and different trials reaching completion with more efficacy and safety data to come, we just might be about to witness the rise to

Figure 1. Hypoxia inducible factor (HIF) pathway



HIF activity in peritubular fibroblast-like cells that produce erythropoietin under conditions of (A) normoxia and (B) hypoxia. HIF, hypoxia-inducible factor; PHD, prolyl-hydroxylase domain; VHL, von Hippel-Lindau; HRE, hypoxia response elements; EPO, erythropoietin; VEGF, vascular endothelial growth factor; PGK, phosphoglycerol kinase; LDH, lactate dehydrogenase.

stardom of HIF-PHIs. Will ESAs be bye bye bye? ■

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The author reports no conflict of interest.

References

1. Singh AK, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006; 355:2085–2098. doi: 10.1056/NEJMoa065485
2. Drüeke TB, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006; 355:2071–2084. doi: 10.1056/NEJMoa062276
3. Pfeffer MA, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009; 361:2019–2032. doi: 10.1056/NEJMoa0907845
4. Macdougall IC. Novel erythropoiesis-stimulating agents: A new era in anemia management. *Clin J Am Soc Nephrol* 2008; 3:200–207. doi: 10.2215/CJN.03840907
5. Macdougall IC. Poor response to erythropoietin: Practical guidelines on investigation and management. *Nephrol Dial Transplant* 1995; 10:607–614. https://doi.org/10.1093/ndt/10.5.607
6. Regidor DL, et al. Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients. *J Am Soc Nephrol* 2006; 17:1181–1191. doi: 10.1681/ASN.2005090997
7. Wyatt CM, Drüeke TB. HIF stabilization by prolyl hydroxylase inhibitors for the treatment of anemia in chronic kidney disease. *Kidney Int* 2016; 90:923–925. doi: 10.1016/j.kint.2016.08.016
8. Wenger RH, Hoogewijs D. Regulated oxygen sensing by protein hydroxylation in renal erythropoietin-producing cells. *Am J Physiol Renal Physiol* 2010; 298:F1287–F1296. doi: 10.1152/ajprenal.00736.2009
9. Haase VH. Oxygen sensors as therapeutic targets in kidney disease. *Nephrol Ther* 2017; 13 (Suppl 1):S29–S34. doi: 10.1016/j.nephro.2017.01.015
10. Semenza GL, Wang GL. A nuclear factor induced by hypoxia via de novo protein synthesis binds to the human erythropoietin gene enhancer at a site required for transcriptional activation. *Mol Cell Biol* 1992; 12:5447–5454. doi: 10.1128/MCB.12.12.5447
11. Sugahara M, et al. Hypoxia-inducible factor and oxygen biology in the kidney. *Kidney360* 2020; 1:1021–1031. doi: https://doi.org/10.34067/KID.0001302020
12. Li Z-L, et al. Treatment of renal anemia with roxadustat: Advantages and achievement. *Kidney Dis (Basel)* 2020; 6:65–73. doi: 10.1159/000504850
13. Locatelli F, et al. Targeting hypoxia-inducible factors for the treatment of anemia in chronic kidney disease patients. *Am J Nephrol* 2017; 45:187–199. doi: 10.1159/000455166
14. Fishbane S, et al. Roxadustat for treating anemia in patients with CKD not on dialysis: Results from a randomized phase 3 study. *J Am Soc Nephrol* [published online ahead of print February 10, 2021]. doi: 10.1681/ASN.2020081150; https://jasn.asnjournals.org/content/early/2021/02/09/ASN.2020081150
15. Chen N, et al. Roxadustat treatment for anemia in patients undergoing long-term dialysis. *N Engl J Med* 2019; 381:1011–1022. doi: 10.1056/NEJMoa1901713
16. Chertow GM. Global Phase 3 Clinical Trials of Vadadustat vs. Darbepoetin Alfa for Treatment of Anemia in Patients with Non-Dialysis-Dependent CKD. ASN Kidney Week 2020 Reimagined. 2020; FR-OR54. https://www.asn-online.org/education/kidneyweek/2020/program-abstract.aspx?controlId=3479290
17. Eckardt K-U. Global Phase 3 Clinical Trials of Vadadustat vs. Darbepoetin Alfa for Treatment of Anemia in Patients with Dialysis-Dependent CKD. ASN Kidney Week 2020 Reimagined. 2020; TH-OR01. https://www.asn-online.org/education/kidneyweek/2020/program-abstract.aspx?controlId=3441404
18. Provenzano R, et al. Pooled analysis of roxadustat for anemia in patients with kidney failure incident to dialysis. *Kidney Int Rep* [published online ahead of print December 24, 2020]. doi: 10.1016/j.ekir.2020.12.018; https://www.sciencedirect.com/science/article/pii/S2468024920318519
19. 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 2020 Reimagined. 2020; FR-OR131. https://www.asn-online.org/education/kidneyweek/2019/program-abstract.aspx?controlId=3275139
20. Kuriyama S, et al. A new insight into the treatment of renal anemia with HIF stabilizer. *Ren Replace Ther* 2020; 6:63. doi: https://doi.org/10.1186/s41100-020-00311-x
21. Coyne DW, et al. Roxadustat Is Not Associated with an Increased Risk of Neoplasm in Patients with CKD and Anemia. ASN Kidney Week 2020 Reimagined. 2020; TH-OR04. https://www.asn-online.org/education/kidneyweek/2020/program-abstract.aspx?controlId=3447031

Play NephMadness 2021 During March, National Kidney Month

By Joel Topf, Anna Burgner, Timothy Yau, Pascale Khairallah, Samira S. Farouk, and Matthew A. Sparks

The 9th annual NephMadness is a social media and medical education campaign focused on all things kidney. You can participate in NephMadness during the entire month of March, National Kidney Month. NephMadness adopts the single elimination brackets that are a hallmark of the popular March Madness (the college basketball tournament held yearly in the United States), but with a nephrology twist. Instead of basketball teams, the bracket is populated with 32 nephrology concepts from eight different regions. This year's regions are: Liquid Biopsy, the return of Animal House, COVID-19, ICU Nephrology, Workforce, Anemia, Primary Care, and Artificial Kidney. Each region has four concepts; the full bracket is shown in the figure.

The winners of each competition are selected by a blue ribbon panel of nine individuals including patients, scientists, clinicians, and educators. Read more about the teams and perhaps get insight on which way they'll vote by reading their bios at AJKDblog. Participants play by filling out their own brackets and try to predict the winners chosen by the blue ribbon panel. The best NephMadness parties, urine microscopy pictures, players with the highest scores, and much more will win NephMadness swag, awarded by the *American Journal of Kidney Diseases* and the National Kidney Foundation. ■

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NEWS FLASH

An Update on Novel Soluble ACE2 Therapeutics to Treat SARS-CoV-2: Insights from a Preclinical Study

By Andrew M. South and Matthew A. Sparks

Novel therapeutics remain urgently needed to treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 2019 (COVID-19), including associated acute kidney injury. Angiotensin-converting enzyme 2 (ACE2), the SARS-CoV-2 spike protein-binding site, is expressed in numerous tissues, including the lungs and kidneys. Soluble ACE2 is a potential *therapeutic* with dual roles: 1) binding SARS-CoV-2 to attenuate infection and replication and 2) shifting the renin-angiotensin system away from the pro-inflammatory angiotensin II and bradykinin pathways. There is precedent for using recombinant soluble ACE2 clinically. A pilot randomized clinical trial in 44 patients with acute respiratory distress syndrome (pre-COVID-19 pandemic) demonstrated that human recombinant ACE2 was well tolerated (1). A case report of compassionate use of human recombinant ACE2 in a patient with COVID-19 also demonstrated tolerability (2). However, major limitations to the soluble ACE2 therapeutic potential in humans remain, including short duration of action and susceptibility to degradation, unclear optimal dosing timing (e.g., early- vs. late-stage infection), and potentially limited viral affinity.

Emerging preclinical models using engineered human tissues have begun to shed light on mitigating these limitations. Monteil et al. (3) demonstrated that full-length (amino acids 1–740) soluble human recombinant ACE2 inhibited SARS-CoV-2 infection in human blood vessel and kidney organoids. In a recent *JASN* article, Wysocki et al. (4) investigated the effect of two short-length soluble ACE2 variants on SARS-CoV-2 infectivity using human kidney organoids and assessed their enzymatic activity in vitro and in vivo. They generated a human recombinant ACE2 of 618 amino acids (ACE2 1–618) and one fused to a small (5-kD) albumin-binding domain protein (ACE2 1–618-ABD) to improve stability. They generated human kidney organoids to create proximal tubules that expressed cell membrane ACE2 and transmembrane protease, serine 2 (TMPRSS2), to assess viral replication neutralization. Three days after infection, ACE2 1–618-ABD and ACE2 1–618 markedly reduced viral replication in the organoid cells to the same extent as native ACE2 1–740. They also found that ACE2 1–618-ABD had a greater peak and duration of enzymatic activity and ability to blunt the blood pressure response to angiotensin II compared to ACE2 1–618 and native ACE2 1–740 (Figure 1).

Soluble ACE2 1–618-ABD is an important step toward ACE2-based therapeutics, which include full-length ACE2 and ACE2 fused with a crystallizable fragment (1, 2, 5). However, several caveats remain. Similar studies in human lung organoids will be crucial to developing these therapies. It is unknown if soluble ACE2 penetrates into tissues (lung, kidney) to bind SARS-CoV-2 or if soluble ACE2 in circulation requires sufficient viremia to be efficacious. Although theoretically, soluble ACE2 should retain sufficient enzymatic activity upon binding the spike protein, this has not been determined in vivo. It remains to be seen if soluble ACE2-SARS-CoV-2 binding is transient or sustained and how and to what extent the ACE2-SARS-CoV-2 complex is cleared. Whereas short-fragment soluble ACE2 likely undergoes glomerular filtration to reach the proximal tubular lumen and thus may be beneficial in COVID-19–associated acute kidney injury, it is unclear if ACE2 1–618-ABD bound to albumin possesses this ability. Moreover, these preclinical studies must be appropriately translated into adequately designed and powered clinical trials. Several groups are currently working on various delivery approaches to enhance SARS-CoV-2 binding (6), and clinical trials treating patients with COVID-19 are ongoing (ClinicalTrials.gov: NCT04335136). Thus, further investigations to answer these questions are critical next steps. ■

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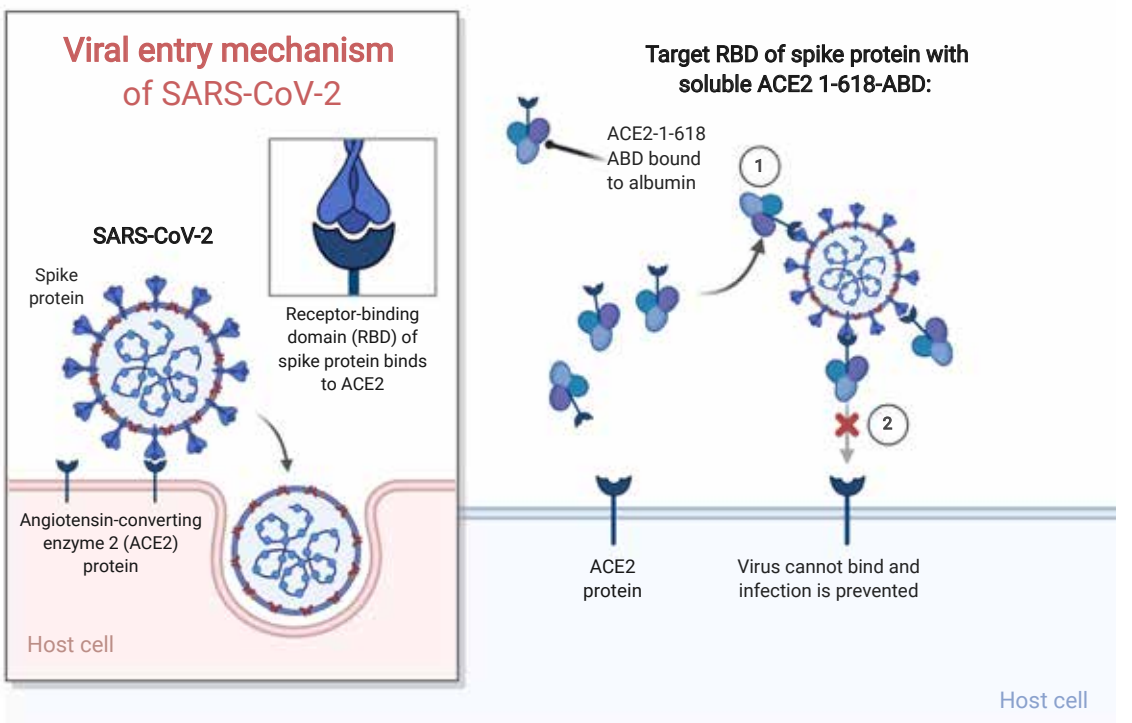
The authors have no conflict of interest.

References

1. Khan A, et al. A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. *Crit Care* 2017; 21:234. doi: 10.1186/s13054-017-1823-x
2. Zoufaly A, et al. Human recombinant soluble ACE2 in severe COVID-19. *Lancet Respir Med* 2020; 8:1154–1158. doi: 10.1016/S2213-2600(20)30418-5
3. Monteil V, et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. *Cell* 2020; 181:905–913.e7. doi: 10.1016/j.cell.2020.04.004
4. Wysocki J, et al. A novel soluble ACE2 variant with prolonged duration of action neutralizes SARS-CoV-2 infection in human kidney organoids. *J Am Soc Nephrol* [published online ahead of print February 1, 2021]. doi: 10.1681/asn.2020101537; https://jasn.asnjournals.org/content/early/2021/01/29/ASN.2020101537
5. Liu P, et al. Novel ACE2-Fc chimeric fusion provides long-lasting hypertension control and organ protection in mouse models of systemic renin angiotensin system activation. *Kidney Int* 2018; 94:114–125. doi: 10.1016/j.kint.2018.01.029
6. Chan KK, et al. Engineering human ACE2 to optimize binding to the spike protein of SARS coronavirus 2. *Science* 2020; 369:1261–1265. doi: 10.1126/science.abc0870

Figure 1. Mechanism for how soluble ACE2 1–618-ABD neutralizes SARS-CoV-2



(Left) Entry mechanisms for SARS-CoV-2 depend on the recognition and binding of the spike protein receptor-binding domain (RBD) to ACE2. (Right) 1. Amino acids 1–618 of ACE2 with the addition of ABD (a 5-kD albumin-binding domain) bind to albumin in the circulation and recognize the RBD of the SARS-CoV-2 spike protein, resulting in 2. the inability of SARS-CoV-2 to bind to ACE2, preventing infection. Made with BioRender.

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LUPKYNIS™ (voclosporin) in combination with MMF and low-dose steroids **increased complete renal response rates** and **decreased time to proteinuria reduction** compared to standard of care alone[1,a]

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[a]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 Week 44-52); and no administration of rescue medications. Proteinuria reduction was based on time to UPCR of ≤0.5 mg/mg.[1]

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.

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.

Aurinia™

eGFR=estimated glomerular filtration rate; FDA=Food and Drug Administration; MMF=mycophenolate mofetil; UPCR=urine protein/creatinine ratio.

Reference: 1. LUPKYNIS [package insert]. Rockville, MD: Aurinia Pharma U.S., Inc.

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), may 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: 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, 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.

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 may be 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 suggest 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 unless benefit outweighs risk. 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

No dose adjustment is recommended in patients with mild hepatic impairment. In patients with moderate hepatic impairment, reduce the LUPKYNIS dosage. Avoid LUPKYNIS in patients with severe hepatic impairment.

OVERDOSAGE

Experience with LUPKYNIS overdose is limited. Symptoms of accidental overdose with LUPKYNIS have included tremor, headache, nausea and vomiting, infections, urticaria, lethargy, and increases in blood urea nitrogen, serum creatinine, and alanine aminotransferase levels.

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.

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Additional information can be found at LUPKYNISpro.com.

Findings

Good Long-Term Outcomes after Metabolic Surgery in Diabetes

Ten-year follow-up data in patients with type 2 diabetes show better outcomes in those undergoing metabolic surgery, compared to conventional medical therapy, reports a study in *The Lancet*.

The researchers analyzed data from a previous open-label, single-center trial in which 60 obese patients with type 2 diabetes were randomly assigned to medical therapy, Roux-en-Y gastric bypass (RYGB), or biliopancreatic diversion (BPD). The main outcome of interest was diabetes remission, defined as glycated hemoglobin less than 6.5% with a fasting blood glucose level of less than 5.5 mmol and no diabetes medications for at least 1 year. Fifty-seven patients were available for long-term follow-up.

On intention-to-treat analysis, 10-year remission rates were 50.0% in the BPD group, 25.0% in the RYGB group, and 5.5% in the medical therapy group. One patient initially assigned to medical therapy achieved remission after crossing over to surgery. Overall, type 2 diabetes remained in remission throughout a 10-year follow-up in 37.5% of patients who had either form of metabolic surgery.

Of the 34 patients whose diabetes was in remission at 2 years, 20 had a relapse of hyperglycemia during follow-up. Relapse rates were 52.6% in the BPD group and 66.7% in the RYGB group. However, all patients with relapse had adequate glycemic control at 10 years. Risk of diabetes-related complications was substantially lower in the two metabolic surgery groups: relative risk 0.07. Compared to patients receiving medical therapy, serious adverse events were more frequent in the BPD group (odds ratio 2.7) and less frequent in the RYGB group (odds ratio 0.7).

Bariatric or metabolic surgery has become an established treatment for type 2 diabetes, with clinical trials showing prolonged remission and reductions in cardiometabolic and chronic kidney disease risks, among other benefits. The new report presents the first randomized trial data on outcomes of metabolic surgery for diabetes beyond a 5-year follow-up.

The results add further support to the effectiveness of metabolic surgery over conventional medical therapy for long-term control of type 2 diabetes. The investigators conclude, "Clinicians and policy makers should ensure that metabolic surgery is appropriately considered in the management of patients with obesity and type 2 diabetes" [Mingrone G, et al. Metabolic surgery versus conventional medical therapy in patients with type 2 diabetes: 10-year follow-up of an open-label, single-centre, randomised controlled trial. *Lancet* 2021; 397:293–304. doi: 10.1016/S0140-6736(20)32649-0; https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32649-0/fulltext].

Corticosteroid Withdrawal after Kidney Transplant: 15-Year Follow-Up

Long-term corticosteroid therapy may not be necessary in kidney transplant recipients receiving calcineurin-based immunosuppressive therapy, according to a clinical trial report in *JAMA Surgery*.

The researchers analyzed long-term follow-up data from a previous multi-center, randomized, double-blind trial including 385 adult patients undergoing living or deceased kidney transplantation between 1999 and 2002. All patients were classified at low-to-moderate immune risk and were free of delayed graft function or short-term rejection within the first week.

Patients were assigned to tacrolimus and mycophenolate mofetil, with or without corticosteroids, 7 days after transplantation. Outcomes were assessed via linkage to the national Organ Procurement and Transplantation Network (OPTN) registry up to 2018–2019; median follow-up was 15.8 years. The primary outcome was all-cause kidney allograft failure including death, accounting for the need for long-term dialysis or repeat transplantation.

On intention-to-treat analysis, there was no significant difference in time-to-allograft failure from any cause, or in allograft failure censored for death, for patients assigned to corticosteroid withdrawal versus continuation. Similar patterns were seen in subgroup analyses, as well as on per-protocol analysis of 223 patients who stayed on their assigned treatment for at least 5 years. Outcomes were also comparable to those of 3540 patients from the OPTN registry who met the study eligibility criteria and received the same immunosuppressive drugs.

To avoid adverse effects, several studies have evaluated the effects of eliminating corticosteroids from immunosuppressive regimens after kidney transplantation. Despite positive results of clinical trials, only 30% of recipients are managed with corticosteroid withdrawal.

The new analysis supports the long-term safety of corticosteroid withdrawal in low-to-moderate immune-risk transplant recipients receiving calcineurin-based immunosuppression. At 15 years' follow-up, patients assigned to corticosteroid withdrawal versus continuation show no significant difference in outcomes. The authors note that the original trial showed no increase in moderate-to-severe short-term rejection events in the corticosteroid withdrawal group [Woodle ES, et al. Early corticosteroid cessation vs. long-term corticosteroid therapy in kidney transplant recipients. Long-term outcomes of a randomized clinical trial. *JAMA Surg*, published online ahead of print February 3, 2021. doi: 10.1001/jamasurg.2020.6929; https://jamanetwork.com/journals/jamasurgery/article-abstract/2775940].

Antibiotics Don't Reduce UTI in Transplant Patients with Bacteriuria

For kidney transplant recipients with screening-detected asymptomatic bacteriuria (ASB), antibiotic treatment does not reduce the risk of developing urinary tract infection (UTI) and may lead to emergence of antibiotic-resistant bacteria, reports a study in *Clinical Microbiology and Infection*.

The pragmatic, open-label Bacteriuria in Renal Transplantation (BiRT) trial included 199 patients with ASB detected by screening at least 2 months after transplantation. Patients were randomly assigned to receive antibiotic treatment, using a drug active against the causative bacteria, or no treatment. The incidence of symptomatic UTI over routine 1-year follow-up was compared between groups.

Fluoroquinolones and second- or third-generation cephalosporins were the most commonly prescribed antibiotics in the treatment group. Incidence of symptomatic UTI during follow-up was 29.1% overall, with no significant difference between groups: 27% with antibiotics and 31% with no treatment. Per-protocol analysis of 87 patients in the antibiotic group and 92 in the no-treatment group showed similar results.

Secondary outcomes of pyelonephritis and kidney function were not significantly different between groups. On urine cultures performed 1 month after randomization, prevalence of ASB was 29% in the antibiotic group versus 66% in the no-treatment group. Throughout the follow-up year, antibiotic use was fivefold higher in the antibiotic group: 30 days per patient compared to 6 days per patient in the no-treatment group.

On continued screening, 78% of patients had at least one more episode of bacteriuria. Patients assigned to antibiotic treatment for initial ASB were more likely to have bacteriuria caused by bacteria resistant to clinically relevant antibiotics: 18% versus 4%.

Screening and treatment of ASB are often performed as part of routine surveillance after kidney transplantation. This practice can lead to increased antibiotic exposure, with the potential for selection of antibiotic-resistant bacteria. There are also questions as to whether ASB screening and treatment actually reduce the incidence of symptomatic UTI.

The BiRT study finds no significant reduction in symptomatic UTI with antibiotic treatment for screening-detected ASB more than 2 months after kidney transplantation. "By contrast, this strategy drastically increased antibiotic use and promoted the emergence of more resistant organisms in the urine," the researchers write. They note that their study supports recent recommendations against systematic antibiotic use in kidney transplant recipients with ASB [Coussement J, et al. Antibiotics versus no therapy in kidney transplant recipients with asymptomatic bacteriuria (BiRT): A pragmatic, multicentre, randomized, controlled trial. *Clin Microbiol Infect*, published online ahead of print September 10, 2020, doi: 10.1016/j.cmi.2020.09.005; https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(20)30534-6/fulltext].

SPONSORED NO-CHARGE GENETIC TESTING

DO YOU SUSPECT A GENETIC CAUSE OF LOW SERUM PHOSPHORUS IN YOUR PATIENT?

CERTAIN HYPOPHOSPHATEMIA DISORDERS HAVE AN UNDERLYING GENETIC CAUSE, WHICH MAY IMPACT CLINICAL MANAGEMENT OF THE CONDITION

Sponsored genetic testing may be available to your patients with hypophosphatemia. This program tests for 17 different hypophosphatemia conditions, including X-linked hypophosphatemia (XLH), the most common form of genetic hypophosphatemia.

Your patients may be eligible for no-charge sponsored genetic testing if they are 6 months of age or older and meet any of the following criteria:

- Have a previous diagnosis related to hypophosphatemia
- Have a family member with a confirmed XLH diagnosis
- Exhibit 2 or more clinical signs or symptoms of genetic hypophosphatemia, including short stature, gait abnormalities, and muscle pain and weakness

Learn more about a no-charge hypophosphatemia genetic testing program for your eligible patients at **invitae.com/hypophosphatemia**

MRCP-KRN23-00937 10/2020

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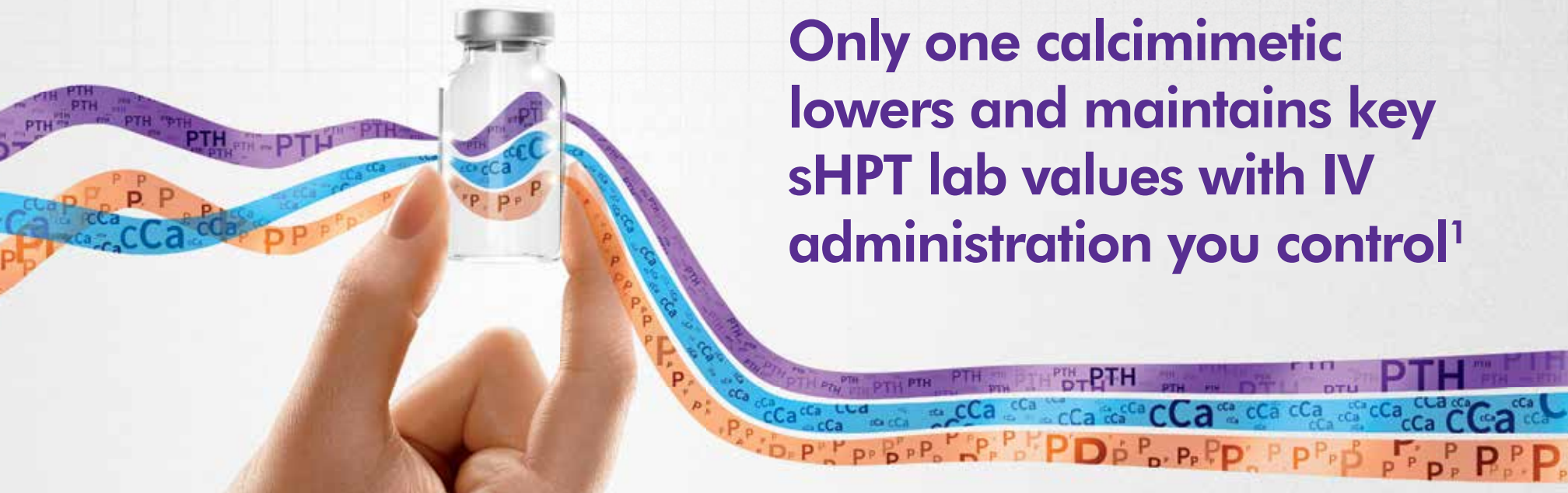

Only one calcimimetic lowers and maintains key sHPT lab values with IV administration you control[1]

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.

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 pruritic rash, urticaria, and face edema, 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.

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.

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 pruritic rash, urticaria, and face edema, have occurred with PARSABIV *[see Adverse Reactions (6.1) 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.

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.

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.

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. If formation of anti-etelcalcetide binding antibodies with a clinically significant effect is suspected, contact Amgen at 1-800-77-AMGEN (1-800-772-6436) to discuss antibody testing.

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]*.

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Don't Forget about the Other A in the RAAS; Primary Aldosteronism Is More Common Than You Think

By James Brian Byrd and Jordana B. Cohen

Visual Abstract by Sophia L. Ambruso

Recent data demonstrate that primary aldosteronism is much more common than previously believed (1). Despite common perceptions among many providers, most patients with primary aldosteronism do not have hypokalemia (2, 3). Importantly, patients with treatment-resistant hypertension have a particularly high prevalence of primary aldosteronism (~20%) (1, 4). Primary aldosteronism is associated with increased risk of development and progression of chronic kidney disease, heart disease, and mortality (5). Nonetheless, primary aldosteronism responds to treatment with a mineralocorticoid receptor antagonist and is curable with adrenalectomy in some patients (i.e., those with an aldosterone-secreting adrenal adenoma or who lateralize on adrenal vein sampling) (6).

Accordingly, clinical guidelines (7, 8) recommend testing for primary aldosteronism in patients with treatment-resistant hypertension. However, recent studies from local health systems suggest that <3% of individuals who meet guideline criteria are screened for primary aldosteronism (9–11). Similarly, clinical experience suggests that many overt cases of primary aldosteronism—with all the classical features and resulting cardiometabolic complications—go undiagnosed and without proper treatment for years (6).

In a national cohort of 269,010 veterans with new-onset, apparent treatment-resistant hypertension (i.e., elevated blood pressure on at least three antihypertensive agents or controlled blood pressure requiring at least four antihypertensive agents) from 2000 to 2017, we found that just 1.6% of veterans underwent testing for primary aldosteronism (with concomitant measurement of plasma aldosterone and renin on or after meeting criteria for resistant hypertension) (12) (Visual Abstract). Patients whose initial visit was with a nephrologist or an endocrinologist were about twice as likely to undergo testing as those seen by a primary care provider or cardiologist. Testing for primary aldosteronism, regardless of the results of testing, was associated with a fourfold higher likelihood of receiving a mineralocorticoid receptor antagonist compared with no testing. This observation argues against the possibility that clinicians usually bypass testing and simply prescribe a mineralocorticoid receptor antagonist for patients with resistant hypertension. In addition, we observed that blood pressure was better controlled over time in patients who underwent testing.

Our work is consistent with prior studies demonstrating low rates of testing for primary aldosteronism in smaller, local health systems (9). Together, the studies show a lack of appropriate testing for primary aldosteronism, which is currently neglected relative to its impact on patients.

Overall, we observed ample missed opportunities for appropriate testing and treatment of patients with resistant hypertension. Our findings suggests that there are critical gaps in provider knowledge of the importance of screening patients with resistant hypertension for primary aldosteronism and that there are likely barriers to implementing appropriate antihypertensive management in these patients. ■

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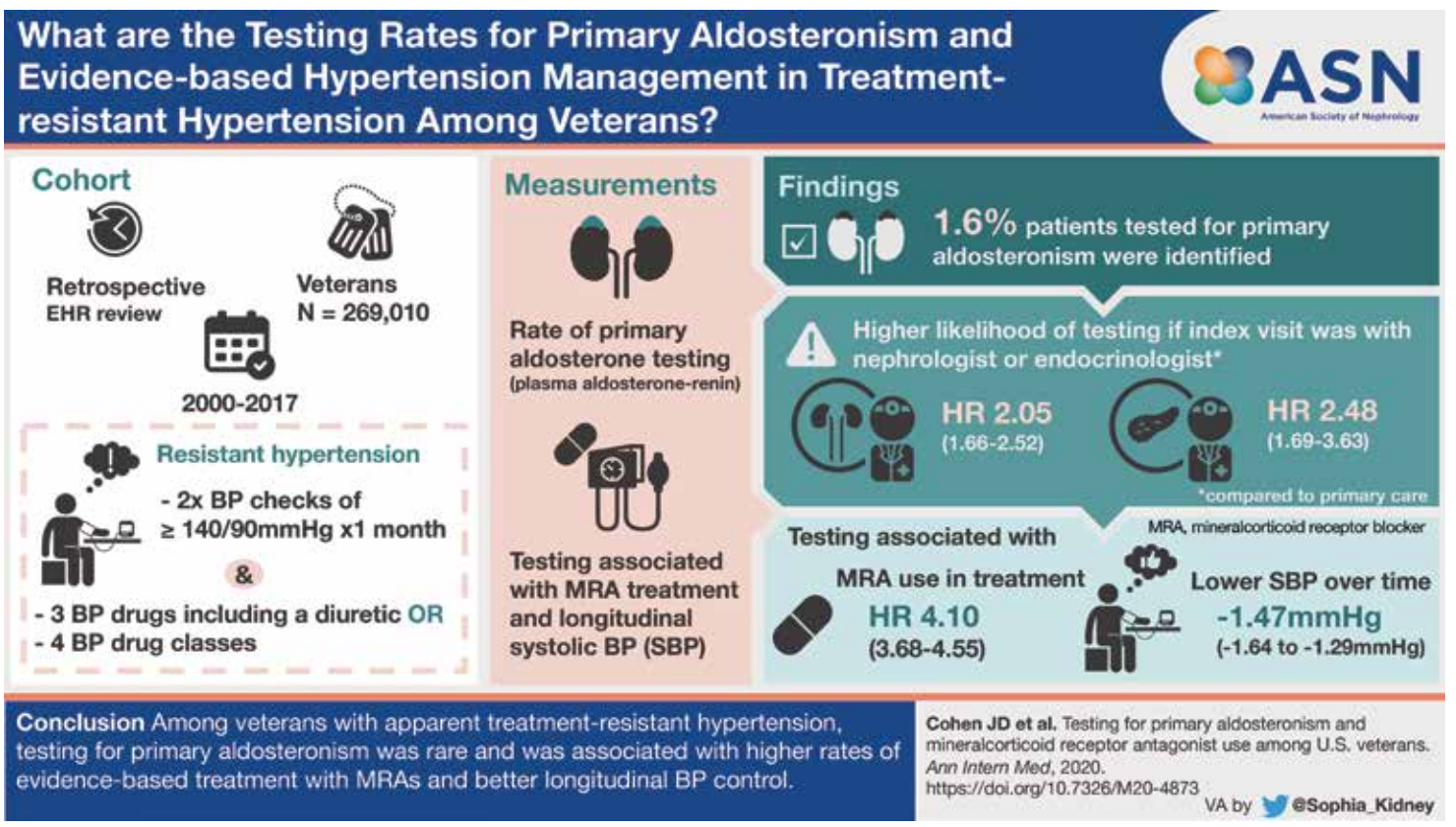
Conflicts of interest: Dr. Byrd holds an NIH grant investigating novel approaches to diagnosing excess mineralocorticoid receptor activation and is an inventor on a provisional patent for a novel diagnostic test related to primary aldosteronism. He has served on an advisory board for Phase Bio, which is developing an aldosterone synthase inhibitor. Dr. Cohen holds NIH grants investigating optimization of antihypertensive management in high-risk patient populations.

References

1. Vaidya A, et al. The unrecognized prevalence of primary aldosteronism. *Ann Intern Med* 2020; 173:683. doi: 10.7326/L20-1097
2. Monticone S, et al. Prevalence and clinical manifestations of primary aldosteronism encountered in primary care practice. *J Am Coll Cardiol* 2017; 69:1811–1820. doi: 10.1016/j.jacc.2017.01.052
3. Paolo Rossi G, et al. A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. *J Am Coll Cardiol* 2006; 48:2293–2300. doi: 10.1016/j.jacc.2006.07.059
4. Calhoun DA, et al. Hyperaldosteronism among black and white subjects with resistant hypertension. *Hypertension* 2002; 40:892–896. doi: 10.1161/01.hyp.0000040261.30455.b6
5. Hundemer GL, et al. Cardiometabolic outcomes and mortality in medically treated primary aldosteronism: A retrospective cohort study. *Lancet Diabetes Endocrinol* 2018; 6:51–59. doi: 10.1016/S2213-8587(17)30367-4
6. Byrd JB, et al. Primary aldosteronism: Practical approach to diagnosis and management. *Circulation* 2018; 138:823–835. doi: 10.1161/CIRCULATIONAHA.118.033597
7. Funder JW, et al. The management of primary aldosteronism: Case detection, diagnosis, and treatment: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2016; 101:1889–1916. doi: 10.1210/jc.2015-4061
8. Whelton PK, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018; 71:1269–1324. doi: 10.1161/HYP.0000000000000066
9. Jaffe G, et al. Screening rates for primary aldosteronism in resistant hypertension: A cohort study. *Hypertension* 2020; 75:650–659. doi: 10.1161/HYPERTENSIONAHA.119.14359
10. Ruhle BC, et al. Keeping primary aldosteronism in mind: Deficiencies in screening at-risk hypertensives. *Surgery* 2019; 165:221–227. doi: 10.1016/j.surg.2018.05.085
11. Sivarajah M, et al. Adherence to consensus guidelines for screening of primary aldosteronism in an urban healthcare system. *Surgery* 2020; 167:211–215. doi: 10.1016/j.surg.2019.05.087
12. Cohen JB, et al. Testing for primary aldosteronism and mineralocorticoid receptor antagonist use among U.S. veterans: A retrospective cohort study. *Ann Intern Med* [published online ahead of print December 29, 2020]. doi: 10.7326/M20-4873; https://www.acpjournals.org/doi/10.7326/M20-4873



Biden-Harris Administration Has Unique Opportunity to Advance Kidney Health Policies

By Ryan Murray

On January 20, 2021, Joseph R. Biden Jr. and Kamala D. Harris were sworn in as President and Vice President of the United States. Their ascension to the White House, amid the twin public health crises posed by the COVID-19 pandemic and system racism, provides new opportunities for the kidney community to collaborate and advance polices that will benefit people with kidney diseases and their families.

The Biden-Harris ticket campaigned on the need for the country to build back better, and the nation owes it to the 37 million Americans living with kidney diseases, especially those from communities of color who are disproportionately burdened, to focus on improving kidney health in America as it moves out of COVID-19.

ASN is encouraging the new administration to recognize, in all COVID-19–related decision-making, that Americans living with kidney disease are at unique risk for COVID-19 owing to their vulnerable condition, weakened immune systems, and the settings in which they receive care. In particular, kidney patients must be prioritized for access to COVID-19 vaccines and rapid post-market analysis to determine the safety of COVID-19 vaccines in transplant recipients.

The COVID-19 pandemic is exacerbating the public health epidemic of systemic racism, laying bare the deadly consequences of inaction, and making the need to address systemic racism through policy all the more urgent. ASN is emphasizing the clear opportunities to ensure that new and revised policies enacted by the Biden-Harris administration increase kidney health equity within the research and innovation ecosystem, across the entire kidney care continuum, and throughout the nation's kidney health workforce. Read ASN's complete recommendations to the Biden-Harris administration to address COVID-19 and increase health equity in the First 100 Days at www.asn-online.org/policy.

Federal investment in kidney research and innovation has long lagged behind the $130 billion annual Medicare kidney health expenditure. President Biden and Vice President Harris must halt this trend by supporting policies and programs aimed at reversing decades of stagnation in kidney care and fostering a robust research and innovation ecosystem. By investing in patient-directed and investigator-initiated research through visionary federal programs like the Kidney Precision Medicine Project and KidneyX, the new administration can catalyze scientific discovery and the development of—and patient access to—new kidney diagnostics, therapeutics, and devices.

Addressing the significant racial and ethnic disparities in therapy access and patient outcomes is at the center of ASN's advocacy agenda. By placing the patient's voice at the center of policy-making, the Biden-Harris administration can significantly improve the lives of patients

with kidney diseases and increase patient choice in kidney care therapies and environments, such as increased access to telehealth, home dialysis, self-care dialysis, in-center dialysis, conservative care, and, crucially, transplant.

But while working to address the needs of people living with kidney diseases, policymakers cannot afford to forget the tens of thousands of kidney health care professionals who are dually tasked with treating their patients and battling COVID-19. It is crucial that the nation's kidney health workforce accurately reflect the diversity of the population it serves in order to increase the likelihood that patients will have a higher-quality care experience. That is why ASN is advocating for policies that support a robust and diverse trainee pipeline and recognize the value that international medical graduates—who constitute half of America's kidney health professionals—bring to Americans with kidney diseases.

ASN is leading the kidney community to assist the Biden-Harris administration in confronting both COVID-19 and systemic racism. ASN is collaborating with stakeholders from patient, professional, and provider organizations to improve the kidney health of all Americans by advancing patient-centered and evidence-based kidney health policies. Read further about these efforts in a community-wide letter supported by 22 organizations, accessible at www.asn-online.org/policy. Together, the kidney community can work with the Biden-Harris administration to build a better, more equitable future for kidney health.

President Biden's Executive Orders on Healthcare and COVID-19

By Killian Gause

The Biden administration has taken the following executive actions that address healthcare and COVID-19 relevant to the kidney community in its first few days in office:

- The Executive Order (EO) on Organizing and Mobilizing the United States Government to Provide a Unified and Effective Response to Combat COVID-19 and to Provide United States Leadership on Global Health and Security accelerates manufacturing and delivery of supplies for vaccination, testing, and personal protective equipment, which has been a top policy priority of ASN's since the beginning of the public health emergency. This EO, along with the EO on the Sustainable Public Health Supply Chain initiative, will ensure that these vital supplies remain available as the country continues through the public health emergency.
- President Biden reopened enrollment on HealthCare.gov through May 15, 2021, and has directed federal agencies to reexamine policies that may reduce or undermine access to the Affordable Care Act under the Strengthening Medicaid and the Affordable Care Act order.
- To limit the transmission of COVID-19 and its variants, President Biden signed the EO on Promoting COVID-19 Safety in Domestic and International Travel to require masks in airports and on certain modes of transportation, and certain international travelers must provide proof of a negative COVID-19 test prior to coming to the United States.
- President Biden also stopped the United States' withdrawal from the World Health Organization (WHO), and designated Anthony Fauci, MD, to serve as the head of the delegation to the WHO.

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

World Kidney Day 2021 Calls for Patient and Care Partner Empowerment, Focus on Living Well

By Karen Blum

After promoting the prevention of kidney diseases for several years, steering committee members for World Kidney Day now are taking a different approach. This year's celebration, on Thursday, March 11, will instead focus on living well for patients already diagnosed with kidney diseases and for these patients' families and care partners.

Chronic kidney disease (CKD) and its associated symptoms and treatments can disrupt and constrain daily living and impair overall quality of life for patients and their family members, steering committee members wrote in an editorial in the journal *Kidney International* (1). Yet despite their level of disease or treatment stage, the authors said, patients want to be able to live well, maintain their role in society and social functioning, protect some semblance of normality, and have a sense of control over their health and well-being.

Health professionals and patients with kidney disease may have different priorities, explained Philip Kam-Tao Li, MD, FRCP, a senior consultant physician and honorary professor at Prince of Wales Hospital, The Chinese University of Hong Kong, and a co-chair of the steering committee, on behalf of the International Society of Nephrology (ISN).

Physicians, for example, may focus on metrics, like hospitalizations, lengths of stay, and mortality rates, Li said: "We are not saying patients do not care about these, but they may care more about their well-being, including pain, itchiness, and being able to eat and sleep well. This year's theme is trying to engage more patients and caregivers."

Healthcare professionals and patients should focus on "life participation"—patients' ability to engage in meaningful activities, such as work, study, travel, sports, and other social and recreational activities—Li said. The editorial calls for the development and implementation of validated patient-reported outcome measures, which could be used during routine care to assess and address areas of life participation.

About 10%–15% of adults in most nations have kidney diseases, Kamyar Kalantar-Zadeh, MD, PhD, the other steering committee co-chair, said on behalf of the International Federation of Kidney Foundations–World Kidney Alliance. He is chief of nephrology and professor of medicine at the University of California, Irvine.

"We need to make sure that we think of these individuals and that their contributions to society remain important," he said. "They need to live long and prosper with kidney disease, and therefore, the 2021 celebration is dedicated to all of them and to their care partners."

Nephrologists are at the frontier for making this process happen, Kalantar-Zadeh said.

"We spend a lot of time providing care to them in our CKD clinics, the hospital, and in dialysis and kidney transplant centers," he said. "We sometimes write orders for dialysis or transplant medications and move on. We forget that they may be suffering—they may have pain, cramps, nausea/vomiting, mental health issues, or other symptoms. . . . If I talk to my patients for 10 minutes, at least one minute should be inquiring how they are doing at home, if life has meaning for them, and how we can direct them to resources to support them and their families."

The editorial authors said they want to promote to policymakers an increased focus on both drug and non-drug programs to improve patient wellness, including multidisciplinary approaches for effective symptom management and funding for erythropoiesis-stimulating and anti-pruritic agents to manage anemia and itching. Additionally, care guidelines should be adapted for vulnerable and disadvantaged populations with kidney disease and their care partners

World Kidney Day is a joint initiative of ISN and the International Federation of Kidney Foundations. See https://worldkidneyday.org/.

Reference

1. Kalantar-Zadeh K, et al. Living well with kidney disease by patient and care-partner empowerment: Kidney health for everyone everywhere. *Kidney Int* 2021; 99:278–284. doi: 10.1016/j.kint.2020.11.004

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