Plasma Pheresis for Thrombotic Thrombocytopenic Purpura (TTP)

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The diagnosis of thrombotic microangiopathy (TMA) can be divided into primary (typical; diarrhea positive) hemolytic uremic syndrome (HUS) and atypical (diarrhea negative) HUS as well as primary (autoimmune) thrombotic thrombocytopenic purpura (TTP) and secondary TTP (1-3). The diagnosis of TTP is based upon the clinical findings of coombs negative microangiopathic hemolytic anemia, thrombocytopenia, neurologic involvement (more common in TTP then HUS), acute kidney injury (less common in TTP then HUS) and fever (4-5). Whereas one would make the diagnosis of TTP based upon clinical findings, in primary/autoimmune TTP, measurement of ADAMTS13 shows activity of < 10% whereas in secondary TTP and in HUS, ADAMTS13 activity is approaching normal (5-6). Within the diagnosis of TTP one needs to delineate between congenital ADMATS13 deficiency (as seen in Upshaw-Schulman Syndrome) and autoimmune TTP that is due to either a circulating ADMATS13 inhibitor or an IgG antibody directed to ADMATS13 (6).

Mortality rates of typical HUS are less than 3%, while atypical HUS has mortality rates that approach 22%. The mortality rate of untreated primary/autoimmune TTP may exceed 90%, but since 1991 and the institution of plasma exchange with plasmapheresis (PP), the mortality rate has decreased to an average of 15% (7).

Understanding the involvement of ADMATS13 in TTP explains why plasma exchange is superior to plasma infusion. Plasma infusion offers a donor source of ADMATS13 activity but if antibodies are present the benefit of plasma infusion becomes rapidly ineffective due to antibody binding. Plasmapheresis removes large von Willebrand factor (vWF) proteins along with anti-ADMATS13 IgG antibodies then replenishes the plasma ADMATS13 levels with fresh plasma (6).

Plasmapheresis can be performed as centrifugation using standard PP machinery or by plasmafiltration using devices designed for CRRT. Only centrifugation has been used in clinical studies of TTP, for plasmafiltration filters are presently not designed to remove large vWF multimers with sizes as large as 12,000 kD (8).

Review of literature and Cochrane Collaboration analysis identifies 6 prospective randomized controlled studies demonstrating the benefit of PP over all other therapies (7).

Rock et al randomized 102 adults with clinical TTP to either plasma exchange by PP vs. plasma infusions (PI). Each arm received aspirin and dipyridamole. Response was defined by normalization of the platelet count. At day 9, 24/51 in the PP vs. 13/51 in the PI had responded. At 6 months 40/51 had responded while only 25/51 had responded in the PP vs. PI arms. Deaths were greater in the PI arm, with 8 and 19 at day 9 and 6 months vs. 2 and 11 at the same time intervals in the PP arm. A criticism of this study was that the PP arm received 3 times greater plasma as compared to the PI arm (9).

Henon et al looked at PP vs. PI in TTP keeping constant the amount of plasma infusion in each arm to 15 mls/kg; additionally both arms received antiplatelet therapy. Survival and remission was 85% and 80% respectively in the PP arm while it was less at 57% and 52% in the PI arm. Further, they noted that early intervention with PP is superior to late intervention with PP in TTP (10).

Bobbio-Pallavicini et al evaluated the risk benefit of antiplatelet therapy in TTP. Adults with TTP in both arms were treated with PP and steroids but one arm received additionally aspirin and dipyridamole. At day 15 of acute TTP, response was 91% in the group receiving the antiplatelet therapy while it was only 76% in the arm without. Deaths (did not reach statistical significance) was less in the antiplatelet arm of 1 vs. 5 deaths. They noted no increase bleeding risk in the antiplatelet arm (11).

Three studies were each done looking at the use of PP with fresh frozen plasma vs. cryoprecipitate as the replacement fluid. A total of 116 patients were treated within these 3 trials. Outcome as measured by failure to achieve remission at 2 weeks and at 4 weeks, overall mortality and rates of relapse. None showed any difference between these 2 replacement fluids (12-14).

Response rates of TTP treated with PP is high with low mortality rates, yet rates of relapse may be as great as 40%. Immunosuppressive therapies added to PP have included steroids, azathioprine, cyclosporine and more recently rituximab (5).

Jasti et al reported patients treated with rituximab who had failed PP. Ten of eleven initially treated patients responded at an average of 10 days after one dose of rituximab with 9 patients remaining relapse free for 57 months. There were 2 deaths in this report (15).

Presently, Foley et al is conducting a prospective use of rituximab in adults with TTP that is either relapsed or refractory to PP. No preliminary data is available and study completion is hoped within the next 18 months (16).

Finally a recent study by Balduini and collogues compared solumedrol as “standard dose” (1 mg/kg/day) vs. “high dose” (10 mg/kg/day for 3 days then taper) in adults with TTP treated with PP. At day 23, 14/40 “standard dose” obtained remission while 23/30 of “high dose” obtained remission (17).

In summary, the diagnosis of TTP is based upon clinical criteria with the exclusion of secondary forms or TTP. Measurement of ADMATS13 is important as a retrospective confirmation of TTP. Daily or every other day 1-1.5 volume exchange PP is recommended until platelet counts are > 150000. The use of aspirin or antiplatelet medications has been shown to be additively effective to PP. Immunosuppressive agents are commonly used, yet no control study has been done to support or refute their use. Relapse rates are high and may be predicted by initial ADMATS13 levels.

In conclusion, TTP treated with PP has resulted in significant improvement in remission and patient survival. The choice of FFP or cryoprecipitate as a replacement fluid does not impact upon effectiveness of PP. The use of antiplatelet therapies appears to be beneficial but may place the patient at an increase risk of bleeding. The uses of immunosuppressive agents are considered standard of care, yet they are not without risk. Preliminary data with the use of anti B cell therapies are encouraging and prospective studies are ongoing in refractory patients.

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