ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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Technology Assessment (TA) Program
Agency for Healthcare Research and Quality (AHRQ)
tareview@ahrq.hhs.gov

Re: Draft Report: The Impact of Pre-Transplant Red Blood Cell Transfusions in Renal Allograft Rejection - Project ID: RENT0610

To whom it may concern:

On behalf of the American Society of Nephrology (ASN), a not-for-profit organization of 11,000 physicians and scientists dedicated to promoting excellence in the care of patients with kidney disease, thank you for the opportunity to provide comment to the Technology Assessment (TA) Program at the Agency for Healthcare Research and Quality (AHRQ) regarding the Technology Assessment "The Impact of Pre-Transplant Red Blood Cell Transfusions in Renal Allograft Rejection." Foremost among ASN's concerns is the preservation of access to optimal quality of chronic kidney disease (CKD) and transplant care for patients with renal disease.

The society recognizes that questions have been raised regarding the use of ESAs in patients with CKD, including those with end-stage renal disease (ESRD) who may be candidates for renal transplantation. ASN supports CMS and AHRQ's commitment to protecting patient safety and access to the most appropriate treatments through the TA prepared for the Centers for Medicare and Medicaid Services (CMS) Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) meeting convened on January 19, 2011, as well as through the CMS National Coverage Analysis (NCA) for Erythropoiesis Stimulating Agents (ESAs) for Treatment of Anemia in Adults with CKD Including Patients on Dialysis and Patients not on Dialysis. As AHRQ and CMS examine the relationship between ESAs and renal transplant graft outcomes, ASN encourages that they bear in mind the following considerations.

- **Donor-Specific Transfusions have not been utilized for more than two decades.**

Due to the development of modern immunosuppressive therapies donor-specific transfusion (DST) protocols have not been utilized for more than twenty years. The improvement in graft survival made possible by modern immunosuppressive therapies overtook the apparent benefit offered by DST protocols in terms of improved in graft survival.

- **The true effect of Donor-Specific Transfusions remains unclear**

It is unclear whether DSTs actually had an active tolerance-inducing effect that helped patients maintain grafts or whether the transfusions merely led to a selection bias, identifying patients who would develop antibodies to the donor in advance and transplanting only those patients who were not sensitized by the transfusions. Importantly, the experience with DSTs provided clear evidence that pre-transplant blood transfusions can sensitize a recipient to HLA antigens and limit the availability of donors for that individual. Thirty percent of recipients of DSTs became sensitized to the blood donor and were unable to receive a subsequent kidney transplant from that donor. Regardless of whether the benefit shown in DST studies was the result of tolerance-inducing effect or selection bias, improvement in graft survival through the implementation of modern immunosuppressants overtook that effect. More recent evidence about DST protocols

does not exist because the protocols were replaced by more effective practices, nullifying the need for research in this area.

- **Modern single-antigen antibody tests have supplanted classic PRA analyses and are used to improve the efficiency of organ allocation**

Classic Panel Reactive Antibody (PRA) is a blood test that measures the anti- human antibodies that are present in a transplant candidate's blood. The PRA is represented as a percentage represents the percentage of the country's population that the anti-human antibodies react with. The PRA test has been largely replaced by more accurate and more specific single-antigen antibody assays in the past 5 years. By combining information about a transplant candidate's specific HLA antibodies and the information about the relative incidence of these antibodies in a donor population, this new method describes a candidate's transplant potential more accurately than ever before.

Importantly, it can pre-identify donors with whom the candidate should not be matched. Anti-human antibodies develop after exposure to human antigens, chiefly through blood transfusions, prior organ transplants or pregnancy. Candidates with high levels of anti-human antibodies are considered sensitized. Sensitized candidates have a smaller pool of possible organ donors and must wait longer until a compatible donor is identified. In addition, sensitized candidates who do receive transplants are frequently considered high-risk because their transplant outcomes are inferior. The primary utility of these antibody tests, however, is to allocate organs for transplantation, not to predict outcomes after transplantation. Calculated PRAs are used to characterize individual transplant candidates for purposes of prioritization and single-antigen antibody tests now permit virtual cross matches which are used to avoid donors to which a candidate has a specific antibody.

- **ESAs are indicated to treat anemia; administration of ESAs prevents patients from risk of sensitization due to transfusions that would otherwise be necessary**

Because the TA was commissioned before the key questions considered at the MEDCAC meeting were finalized, the TA did not examine several issues later discussed by MEDCAC, including questions regarding the relationship between ESAs and renal transplant graft survival. No prospective randomized clinical trial has examined whether ESAs directly contribute to improved renal transplant graft survival. However, ESAs are specifically indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis.

The FDA label states that ESAs dosing should be "individualized to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL." ESAs enable nephrologists to treat their patients' anemia without transfusions, which can lead to sensitization due to exposure to foreign human antigens. Sensitization is associated with a longer time on the wait list, higher rates of hyper-acute rejection, accelerated acute rejection, delayed graft function, and longer-term complications. The balance of modern data suggests that it is most appropriate to avoid sensitization prior to kidney transplantation. Currently the most successful method of avoiding sensitization is to avoid exposure to foreign human antigens, which in the vast majority of patients with severe chronic kidney disease or end-stage renal disease is possible only through the administration of ESAs.

- **Changes to current CMS policies regarding ESA use are not warranted at this time**

Overall, ASN believes that no changes to the current CMS policies regarding ESAs are called for at this time. ESAs are a cornerstone of CKD care—specifically for anemia management—and have been proven effective for that purpose. Maintaining reasonable latitude for patients and their physicians to make individualized decisions about these medications, within FDA guidelines, is crucial.

Because ESAs are not indicated for the purpose of improving renal transplant graft survival, ASN suggests that it would be inappropriate for CMS to issue a National Coverage Determination (NCD), or make any other changes to existing policies, based on considerations of the evidence of effect of ESAs on renal transplant graft survival.

ASN members are committed to providing the best possible care and want to ensure that nephrologists have the necessary flexibility to treat patients safely and effectively to preserve their quality of life. We believe that our recommendations in this letter will prove helpful in CMS' considerations of ESA-related regulations. ASN would be pleased to discuss these comments with the CMS if it would be helpful.

Again, thank you for your time and consideration. To discuss ASN's comments, please contact ASN Director of Policy and Public Affairs, Paul C. Smedberg, at (202) 416-0640 or at psmedberg@asn-online.org.

Sincerely,

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