

## Treatment Options for Refractory Lupus Nephritis

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Lupus nephritis, one of several organ manifestations of SLE, affects mostly young women and imposes a risk to develop ESKD and premature cardiovascular disease. Every episode or flare of lupus nephritis implies irreversible nephron loss and therefore, shortens kidney lifespan (1). Only immediate and rigorous control of intrarenal inflammation as well as systemic disease activity can minimize nephron loss and hence, maximize kidney lifespan (1). Current induction therapy protocols seem to achieve this aim in the majority of but not all patients as judged from the current lupus nephritis response criteria (*i.e.*, proteinuria, serum creatinine levels, and urinary sediment abnormalities). Here, the misery begins. First, it is unclear when to assess these parameters, because many patients do not complete response criteria before 1–2 years after initiation of therapy. Second, it has become clear that reaching clinical response does not necessarily mirror immunologic response (absence of activity criteria at protocol biopsy), and not reaching clinical response does not necessarily imply persistent lupus nephritis. Third, protocol biopsy, the only diagnostic tool to reliably inform about ongoing immune complex nephritis, is not yet broadly implemented. Thus, the term refractory lupus nephritis is largely undefined, inconsistently used in the literature and clinical practice, and unlikely to depict a homogenous patient entity (2). Indeed, patients with refractory lupus nephritis may have unrecognized drug nonadherence, especially because oral medications prevail; also, individuals may have unrelated genetic factors promoting persistence of proteinuria or CKD progression (3). Nevertheless, in a certain number of patients, the underlying immunopathogenesis remains unresponsive to a decent exposure of immunosuppressive drugs, namely a course of steroids plus cyclophosphamide and a course of steroids plus mycophenolate mofetil. There is a paucity of randomized, controlled evidence on patients with active lupus nephritis despite these treatments, whereas a plethora of patient studies or small patient series suggest efficacy of this or the other immunosuppressive regimen. Among the sparse evidence, there have been reports of treatment of patients with severe autoimmune diseases, including those patients with SLE, with hematopoietic stem cell transplantation. In principle, the concept is intriguing, because only bone marrow ablation can ultimately remove the long-lived plasma cell and memory cell clones accounting

for disease persistence beyond other immunosuppressive therapy. Indeed, only such a reset of the entire adaptive immune system currently allows for an ultimate cure of SLE, but also, it involves the risk for fatal infections during the aplastic phase as a tradeoff (4,5). For the latter reason, only a few centers offer hematopoietic stem cell transplantation to patients with lupus, and the approach has remained at an experimental status level (6).

In this issue of *CJASN*, Huang *et al.* (7) from the National Clinical Research Center of Kidney Diseases in Nanjing, China report the clinical history and outcomes of 22 patients undergoing hematopoietic stem cell transplantation for the treatment of refractory lupus nephritis. In this study, refractory lupus nephritis was defined as no response to at least one type of immunosuppressant therapy (corticosteroids, cyclophosphamide, tacrolimus, mycophenolate mofetil, or cyclosporin) for >6 months or relapse during maintenance therapy as defined by kidney remodeling or persistently positive antibodies (7). Patients were not considered for hematopoietic stem cell transplantation if younger than 14 years old or older than 45 years old or if they had a serum creatinine  $\geq 2$  mg/dl, elevated liver enzymes, a left ventricular ejection fraction of  $\leq 50\%$ , or active infections. All patients underwent another kidney biopsy before hematopoietic stem cell collection. Hematopoietic stem cells were mobilized with cyclophosphamide (2.0 g/m<sup>2</sup>) and granulocyte colony-stimulating factor. Patients were conditioned with intravenous cyclophosphamide (40 mg/kg per day for 4 days) and rabbit antithymocyte globulin (2.5 mg/kg per day for 3 days) before transplantation. Methylprednisolone was given along with infusions. After hematopoietic stem cell transplantation, patients were monitored clinically for SLE and lupus nephritis disease activity at regular intervals for 2 years, but protocol biopsy was not performed after hematopoietic stem cell transplantation. Complete remission of lupus nephritis was defined as proteinuria <0.4 g/24 h, urinary red blood cells less than three per high-power field, serum albumin >3.5 g/dl, and serum creatinine <1.24 mg/dl. Partial remission of lupus nephritis was defined as 50% proteinuria decline compared with baseline, serum albumin >30 g/L, and serum creatinine <1.24 mg/dl.

Altogether, the authors treated 22 patients, of whom 13 (59%) were women. Eighteen presented with a relapse

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of lupus nephritis, and four had not responded to standard therapy. All patients showed active lupus nephritis in the pretransplant biopsy, with an average activity index of 8 (7–11) and a chronicity index of 2 (1–3). All of the patients were successfully transplanted without grade 4 or 5 complications (7). Fever, gastrointestinal symptoms, and mucositis were the most common complications. Nineteen (86%) patients achieved complete remission of lupus nephritis within a median time of 3 months (1–8.5). This was associated with a drop in the levels of antinuclear antibodies and normalization of serum complement C3. Altogether, the SLE activity index decreased greatly right after hematopoietic stem cell transplantation and remained low during follow-up. The overall 5-year kidney survival was 86%. However, SLE and lupus nephritis did not generally disappear, because kidney flares occurred in five patients, requiring reinitiation of immunosuppressive drugs. One patient required kidney replacement therapy at month 12. Nonkidney manifestations of SLE disappeared in all but one patient, in whom arthralgia could be controlled with low-dose prednisone.

Toxicity and infections are a major concern in this setting; 2 of 22 (9%) patients died during follow-up, both from infections within the first 6 months after hematopoietic stem cell transplantation (7). Procedure-related complications were infections, aplastic anemia, leukopenia, thrombopenia, and diabetes.

This study is the first to focus on patients with lupus nephritis. Previous reports were either single-center studies or summary reports of multinational registries that included patients with a range of severe autoimmune diseases or kidney and nonkidney SLE (4,5). This report is consistent with others in terms of procedure-related mortality and complications, with a mixed bag of outcomes. Consistent with previous reports, complete remission or persistent cure occurs in some patients, many experience a considerable improvement of clinical manifestations and serum parameters, and some relapse and keep requiring persistent immunosuppression as before. The follow-up interval was certainly too short to make reliable predictions about long-term kidney outcomes, but assessing GFR slopes before and after hematopoietic stem cell transplantation could have been a way to monitor hematopoietic stem cell transplantation–related effects on CKD progression.

A painful limitation of this study, like in the ones before it, is the lack of a control group treated with standard of care. Only such a control group would allow for comparison and balancing of efficacy versus safety for this elaborate and costly procedure. Another concern is the lack of a rigorous exclusion of drug nonadherence, an explanation for nonresponders that can be addressed by social interventions or switching to parenteral treatments. Also debatable is the definition of refractory lupus nephritis used here. All patients had active lupus nephritis as documented by the prehematopoietic stem cell transplantation kidney biopsy, but the criteria for defining refractory were rather soft and were not consistent with current treatment recommendations published by the American College of Rheumatology and the European League against Rheumatism together with the European Renal Association (8,9). These entities recommend an antimalarial drug for all

patients, which was not followed here. In addition, induction therapy should be started with either steroids plus cyclophosphamide or steroids plus mycophenolate mofetil and switched to the other regimen when response cannot be achieved. Only after that are rescue therapies recommended. Certainly, such recommendation may not necessarily apply to Chinese or other Asian Pacific populations, but considering patients with no response to at least one of corticosteroids, cyclophosphamide, tacrolimus, mycophenolate mofetil, or cyclosporin for >6 months or relapse after hematopoietic stem cell transplantation will certainly include too many patients who could easily be controlled in a conventional manner (*e.g.*, with reinduction using the alternative regimen, the use of mycophenolate plus tacrolimus [multitargeted therapy], or B cell–targeted therapies). Indeed, uncontrolled data are in favor of anti-CD20 for refractory lupus nephritis (10). The anti-double-stranded (ds) DNA autoantibody titers, which often correlate with active lupus nephritis and persist in patients with refractory SLE, were maximum 1:16. On the basis of our experience, we would expect higher anti-dsDNA titers in patients who belong to a refractory population, especially because there are no data presented on the proportion of patients who are anti-dsDNA negative. The rather insufficient immunologic characterization of the patients, which included autoantibody profile and immune reconstitution before hematopoietic stem cell transplantation and during follow-up, is another weakness of this study. This information would help us to understand why some patients relapsed.

In summary, the study by Huang *et al.* (7) provides the first single-center cohort study on efficacy and safety of hematopoietic stem cell transplantation in patients with refractory lupus nephritis. Importantly, active lupus nephritis was verified by prehematopoietic stem cell transplantation kidney biopsy. Efficacy and safety results were in the range of what has been reported before for hematopoietic stem cell transplantation for other autoimmune indications, including SLE. Future studies on this topic should consider protocol biopsies to validate lupus nephritis activity and chronicity after hematopoietic stem cell transplantation. In general, a consensus definition is needed to diagnose “refractory lupus nephritis” among the many other causes of clinical nonresponding and developing flares, because this does not always imply that the patients’ immune systems are not responsive to the drugs prescribed. Maybe hematopoietic stem cell transplantation is an acceptable rescue therapy only for a subset of patients referred to as those with “refractory lupus nephritis” as defined by resistance to standard of care by international recommendations.

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See related article, “Autologous Hematopoietic Stem Cell Transplantation for Refractory Lupus Nephritis,” on pages 719–727.