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Editorial

Lupus Nephritis Treatment Strategies

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Lupus nephritis (LN) is present in approximately 25% to 50% of patients at the time of systemic lupus erythematosus diagnosis and eventually develops in up to 60% of adults and 80% of children.[1] Over the past 5 decades, major advances in immunosuppressive medications for patients with severe LN (classes III, IV, and V alone or in combination) have resulted in significant improvements in patient survival.[2] These advances are due in part to the specificity of these medications in blocking targets of the adaptive immune response, greatly sparing the innate immune response and thus lowering the risk of severe infections that can be fatal. However, the risk of endstage kidney disease (ESKD) has remained unchanged, with a rate as high as 22%,[3] due to incomplete blockage of the adaptive immunity, with persistent residual LN activity clinically manifesting as relapsing LN and/or progressive chronic kidney disease (CKD) leading to ESKD.

The most common approach for the treatment of severe LN is the use of sequential therapies, with an initial induction phase of an intensive immunosuppressive regimen aiming to achieve complete renal remission (CRR). This is followed by the maintenance phase, which uses an immunosuppressive regimen aiming to consolidate remission and reduce the risk of relapse, without increasing the risk of serious adverse events (SAEs). CRR is an important clinical predictor associated with low risk of both relapse and CKD during the induction phase.[4] Relapse is an important clinical predictor associated with high risk of CKD during the maintenance phase.[5] A high rate of CRR and low rate of relapse indicate greater control of the adaptive immune response. Currently, for the initial induction phase, the Kidney Disease: Improving Global Outcomes (KDIGO)[6] recommends glucocorticoids (GCs) plus one of the following regimens: (1) mycophenolic acid (MPA) analog; (2) low-dose intravenous (IV) cyclophosphamide (CYC); (3) belimumab and either MPA analog or low-dose IV CYC; or (4) MPA analog and a calcineurin inhibitor (CNI). In clinical trials, triple-therapy regimens of either (1) GCs plus belimumab and MPA analog, or (2) GCs plus MPA analog and a CNI achieved the highest CRR rates (34-46%) without excessive risk of SAEs (7.2-26%) and mortality (0-3%),[7-9] resulting in net benefit. KDIGO also recommends for the maintenance phase that patients should be placed on an MPA analog as the first choice,[6] because mycophenolate mofetil (MMF) was associated with the lowest risk of relapse (13-19%) without excessive risk of SAEs (15-24%) and mortality (0-4%) compared to azathioprine (AZA) in recently completed clinical trials in patients with severe LN treated and followed for 3 to 4 years.[10,11] KDIGO recommends maintenance with AZA as an alternative to MPA analogs in patients considering pregnancy or in those with intolerance or lack of access to MPA analogs.[6]

In this issue of *The Journal of Rheumatology*, Takeuchi et al published the results of "Long-term safety and effectiveness of tacrolimus in patients with LN in Japan: 10-year analysis of real-world TRUST study."[12] The main goal of the study was to assess the long-term safety and effectiveness of tacrolimus, a CNI, as maintenance therapy. This was an observational, prospective, noncomparative study that included a large cohort of 1395 patients with LN. Safety data were available for 1355 patients, of whom only 49% of patients remained on tacrolimus for the 10 years of follow-up. Effectiveness data of kidney prognosis were available for 1140 patients. The investigators' conclusion was that tacrolimus was effective and well tolerated as maintenance therapy for patients with LN.

Investigators of the TRUST study also argued that tacrolimus maintenance was as effective and safe as MMF or AZA maintenance,[12] and they compared their data to that of patients enrolled in the MAINTAIN trial.[13] The 2 studies[12,13] reported similar 10-year rates of relapse (45% with tacrolimus, 45% with MMF, and 49% with AZA), CKD (12% with tacrolimus,

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11% with MMF, and 19% with AZA), ESKD (5% with tacrolimus, 7% with MMF, and 2% with AZA), and mortality (4% with tacrolimus, 7% with MMF, 4% with AZA). The reported rate of SAEs was lowest with tacrolimus maintenance (23%) compared to MMF (36%) or AZA (42%) maintenance. More patients remained in the tacrolimus maintenance therapy (49%) compared to MMF (35%) or AZA (33%) maintenance therapy by 10 years of follow-up.

How should we interpret the conclusions of the investigators of the TRUST study that tacrolimus is safe and effective for maintenance in patients with LN? We must evaluate if their claims are supported by internal data provided by their research, and if comparisons to the MAINTAIN trial address the differences between the 2 studies. First, only 591 patients had biopsy-proven LN using the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification,[14] and 309 patients had other renal findings in the biopsy before initiation of tacrolimus maintenance in the TRUST study (Supplementary Table S1[12]). If we used only the cohort of 591 patients with biopsy-proven LN, rates of adverse events and adverse outcomes are likely to be higher than those reported in the Takeuchi study.[12] Second, the evaluation of long-term CNI nephrotoxicity was poorly done and mostly limited to the reported decline in estimated glomerular filtration rate, without histological data of follow-up kidney biopsies, which were performed only in 72 patients in the TRUST study.[12] CNI nephrotoxicity can only be assessed with accuracy when performing kidney biopsies during follow-up, wherein the peculiar new development and progression of striped cortical fibrosis and arteriolar hyalinosis are demonstrated.[15-17] CNI nephrotoxicity is a well-established adverse event in kidney transplantation[15,17,18] and transplantation of other solid organs,[16,19] occurring as early as 1 year after transplantation.[15,16] By 10 years after kidney transplantation, histological finding of CNI nephrotoxicity becomes universal, leading to progressive CKD.[15,17,18] Finally, the TRUST study[12] and MAINTAIN trial[10,13] are different in several aspects, including study design, population ancestry, severity of renal involvement, and definition of outcomes. The TRUST study had an observational prospective uncontrolled design, whereas the MAINTAIN trial had a design with a randomized controlled period followed by a long-term observational prospective controlled period. The population of the TRUST study was universally Japanese, compared to the primarily European population of the MAINTAIN study. Both studies did not include enough numbers of high-risk patients of African, Middle Eastern, and Hispanic ancestries. Only 57% (513 of 900 patients with biopsy at baseline) of patients in the TRUST study had severe LN defined as ISN/RPS classes III, IV, and V compared to 100% of patients with severe biopsy-proven LN enrolled in the MAINTAIN trial.[10,13] Definitions of relapse, CKD, and SAEs were also different in both studies.

The study by Takeuchi et al provides important data of the long-term maintenance therapy with CNI in patients with LN; however, their results should be taken as informative rather than conclusive.[12] Future studies of the long-term use of maintenance immunosuppressive medications are still needed. These studies must use high-quality study designs and include high-risk patients, histological confirmatory outcomes, and interventions exploring the optimal time of withdrawal of immunosuppressive medications to reduce the still-outstanding risk of SAEs (23-42%), without increasing the risk of both relapse and progressive CKD leading to ESKD.

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