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See related article, “*TCF7L2* Variants Associate with CKD Progression and Renal Function in Population-Based Cohorts,” on pages 1989–1999.

Multitarget Therapy of Lupus Nephritis: Base Hit or Home Run?

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In the Fall of each year, the attention of many Americans is diverted to their national pastime—baseball—and to base hits and home runs. The former often lack any definitive impact on the outcome of the game, but the latter usually have a decided effect, noted immediately. This analogy has its parallel in therapeutic trials: Some must await more conclusive observations, whereas others have an immediate and lasting effect on the treatment approaches to a disease. The article describing the benefits of multitarget therapy (mycophenolate mofetil and tacrolimus) on class V + IV lupus nephritis by Bao *et al.*¹ from the Research Institute of Nephrology in Nanjing, China, that appears in this issue of *JASN* falls into the base hit category, at least in my opinion.

Lupus nephritis is an extremely heterogeneous disorder, in terms of pathogenesis, morphology, clinical features, prognosis, and responsiveness to therapy.^{2,3} This heterogeneity, coupled with unpredictable clinical behavior, makes the execution of definitive clinical trials in lupus nephritis difficult and problematic.

Variations in the morphology of lupus nephritis are central to the understanding of the trial by Bao *et al.* The morphologic pattern of class V + IV lupus nephritis, according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification schema,⁴ is the subject of interest in this trial. This pattern is widely known to have a much worse prognosis than either class V (membranous lupus nephritis) or class IV (diffuse lupus nephritis) alone.⁵ A new safe and effective therapy for class V + IV lupus nephritis would be most welcome. The results of this trial should be compared with the results of previous studies in roughly comparable conditions. Using a regimen consisting of short-term oral cyclophosphamide and steroids and a World Health Organization (WHO) classification schema, Najafi *et al.*⁵ found a remission rate (serum creatinine ≤ 1.4 mg/dl and proteinuria ≤ 0.33 g/d) of only 27% after 6 yr of follow-up in the WHO class Vc/Vd lupus nephritis category. Heterogeneity in outcome (remissions or renal survival) in the WHO class Vc/Vd group was found de-

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pending on the nature and distribution of the proliferative lesions. In the WHO classification schema, class V lupus nephritis (membranous lupus nephritis) consists of four subclasses: Va, Vb, Vc, and Vd. Lupus nephritis class Vc includes severe class III focal and segmental proliferative lupus nephritis (>50% of glomeruli affected) superimposed on class V lupus nephritis. Class Vd represents severe class IV diffuse proliferative lupus nephritis superimposed on class V lupus nephritis.⁶ In the trial by Bao *et al.*,¹ the severe focal and segmental and diffuse proliferative (>50%) forms of class IV lupus nephritis were not segregated. As Schwartz *et al.*⁶ pointed out, the ISN/RPS classification incorporates severe WHO class III (>50%) lupus nephritis into the IV(s) subcategory, whereas the WHO classification keeps these categories separate. Thus, Schwartz *et al.*⁶ suggested that the informational content of the ISN/RPS classification system is reduced compared with that of the WHO classification system, causing a “blurring” of the effect of pathologic classification on prognosis. In the study by Najafi *et al.*,⁵ the category including severe focal and segmental proliferate involvement superimposed on membranous lupus nephritis (class Vc) displayed a long-term prognosis that was far worse than the category with diffuse proliferative lesions superimposed on membranous lupus nephritis (class Vd). Renal survival at 10 yr was only 40% in Vc compared with 75% in Vd. Very important, the 10-yr renal survival was not different for “pure” class IV (75%) and class Vd (75%) lupus nephritis. Thus, the interpretation of the trial by Bao *et al.* is complicated by its use of the ISN/RPS classification schema that condenses both the severe focal and proliferative lesions (>50%) and the diffuse nephritic lesion into a single category (IV).

Although subtle, these distinctions may be important because severe focal and segmental (>50%) forms of lupus nephritis may have distinct underlying pathogenetic mechanisms that are different from the diffuse proliferative forms of lupus nephritis.^{6–8} It is quite possible that the effects of tacrolimus on T cells may be a critical component of the observed benefits in the class V + IV lupus nephritis, as a result of an effect on the severe focal and segmental forms of lupus nephritis that might have a dominant T cell–dependent pathogenesis.^{9–11} Future studies of the therapeutic effectiveness of tacrolimus and other calcineurin inhibitors should take cognizance of possible differences in the pathogenesis and outcomes for the severe focal and segmental and proliferative (>50%) forms of lupus nephritis, obscured by the ISN/RPS classification schema.^{4–6}

Even with these caveats in mind, the results of the multitarget therapy in the trial by Bao *et al.* was very impressive compared with what many regard as “standard” therapy for this severe disease. A 50% initial complete remission rate at 6 mo for multitarget therapy compared with only 5% for intravenous cyclophosphamide + steroids is quite remarkable indeed. The trial by Bao *et al.* was of necessity open label but conformed closely to recommendations for randomized clinical trials. The relevant primary outcome (complete remission) was assessed at between 6 and 9 mo, so this can correctly be

called an induction trial. Although the number of patients randomly assigned to the two treatment groups was small (only 20 in each group), the statistical power of trial to detect a clinically significant difference was adequate as determined by previous pilot uncontrolled observations. The criteria for efficacy were very stringent, much more so than in the study by Najafi *et al.*⁵ Complete remission was defined as proteinuria <0.4 g/d, a serum albumin of ≤ 3.5 g/dl, normal urinary sediment (no abnormal hematuria), and a normal level of serum creatinine (or a value no greater than 15% above baseline values). These strict criteria undoubtedly contributed to the low remission rate observed after induction therapy in the intravenous cyclophosphamide arm of the trial. When complete and partial remissions are combined, the difference between the two groups persists (90% with multitarget compared with 45% with intravenous cyclophosphamide therapy). Partial remission rates were no different between the two groups. This may be important because the longer term outcome of treatment of lupus nephritis, measured as patient or renal survival, is significantly affected by the extent of the initial remission.¹² Partial as well as complete remissions have a salutary effect on long-term outcome of lupus nephritis.¹²

The most consequential aspect of the trial by Bao *et al.* is the short-term nature of the observations. Although the extent of the initial remission induced by multitarget induction therapy is very impressive, one needs to be cautious in interpreting these results in light of long-term outcomes, as appropriately discussed by the authors. We still do not know the frequency of renal relapses (flares) with postinduction therapy or the possible cumulative nephrotoxic effects of tacrolimus on renal function. The extent and frequency of relapses are a major determinant of the long-term outcome of lupus nephritis,¹³ and these can likely be influenced by the choice of maintenance therapy. Prolonged use of calcineurin inhibitors can produce chronic kidney disease when it is used for nontransplantation indications.¹⁴ This adverse effect can be mitigated, at least to some extent, by using a minimally effective maintenance dosage of tacrolimus or conversion to a less nephrotoxic maintenance therapy regimen.

Finally, the design of the trial by Bao *et al.* does not permit an evaluation of the relative effects of individual components of the multitarget therapy, at least for lupus nephritis considered as a whole. The preliminary results of the large Aspreva Lupus Management Study (ALMS)¹⁵ seem to indicate that a mycophenolate mofetil + steroid induction regimen is probably equivalent to induction therapy with intermittent intravenous cyclophosphamide + steroids for lupus nephritis; however, prospective comparisons of the efficacy and safety of these two regimens in the subgroups of patients with class V + IV lupus nephritis was not a part of the ALMS trial. As has been commented on before in the context of other trials of therapy for lupus nephritis emanating from China, the lack of patients of black or Hispanic ancestry makes generalization of this study to other populations uncertain.¹⁶

In summary, the results of the trial by Bao *et al.* undoubtedly represent a major contribution to our understanding of the treat-

ment of class V + IV lupus nephritis. The trial was designed and executed in an impeccable manner. The limitations of the study lay in the vagaries of classification systems of morphology in lupus nephritis (WHO *versus* ISN/RPS), in the lack of long-term follow-up for relapses and renal function changes, in the unavoidable variations in ancestry between the Asian population in this study and the Euro–African-American populations of lupus nephritis as whole, and in the uncertainties regarding the independent effects of the two main components of multitarget therapy (mycophenolate mofetil and tacrolimus). For these reasons, I would categorize the trial as a base hit (probably a “double”) rather than a home run, but it may yet have a tangible effect on the final outcome of the game.

DISCLOSURES

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