

Trials and Tribulations in Systemic Lupus Erythematosus

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Abstract

The pace of clinical trials activity in systemic lupus erythematosus (SLE) continues to accelerate. After decades of reliance on largely empiric approaches, a solid evidence-based foundation to guide our use of traditional agents, such as cyclophosphamide and azathioprine, is finally developing. In addition, we are learning how to integrate relatively new immunosuppressive agents, such as mycophenolate mofetil, into the treatment of SLE. These advances provide an important backdrop for recent trials designed to determine the potential value of several promising biologic therapies for SLE.

At the close of the 20th century, the best data we had to guide treatment decisions for patients with systemic lupus erythematosus (SLE) came from a handful of relatively small but nonetheless very important trials of conventional immunosuppressive therapy for lupus nephritis.¹ For other manifestations of lupus, we relied heavily on clinical judgments about the risk-benefit ratio of various agents, and on the principle that careful attention to overall physical and mental health is critically important for people with lupus (e.g., blood pressure control, prevention of osteoporosis, appropriate vaccination, psychosocial support, etc.). Even for those agents that had been subject to trials, simple questions about dose and duration of therapy had not been answered. Promising biologic therapies had

not yet been tested. During the past decade, all of that has changed (Table 1).

Cyclophosphamide

Pulse cyclophosphamide (CTX) defined the standard of care for lupus nephritis for many years, even though the optimal dosing regimen had not been determined. Recent studies conducted in Europe have taken important steps toward establishing a new approach to the use of CTX that might improve the risk-benefit ratio. Houssiau and colleagues² compared so-called “mini-pulse” CTX with conventional pulse CTX therapy, as defined by the original National Institutes of Health (NIH) trials. The mini-pulse regimen consists of six biweekly infusions of 0.5 gm of CTX, followed after 12 weeks by maintenance therapy with azathioprine (AZA). After 10 years of follow-up, there was no difference in efficacy between the groups, as defined by frequency of renal deterioration or death, mean serum creatinine, amount of proteinuria, or overall lupus damage score.

Many investigators in North America have been hesitant to extrapolate the European findings to other populations. They cite the increased frequency and severity of SLE in minority populations, as well as the relative resistance of some of these populations to CTX, as cause for caution in interpreting the European outcomes. Further trials will be needed to address these concerns.

Mycophenolate Mofetil

There has been mounting enthusiasm in recent years for the use of mycophenolate mofetil (MMF) in the treatment of SLE. In an open-label study, Ginzler and coworkers³ compared MMF and pulse CTX as induction therapy for lupus nephritis. The goal of this trial was to demonstrate equivalent efficacy and superior safety for MMF; however, surprisingly, the results actually demonstrated an efficacy advantage for MMF. At roughly the same time, Contreras

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and associates⁴ showed that MMF was at least as effective as pulse CTX in maintaining renal response and that it caused fewer serious adverse events.

Based on these findings, a large multinational trial was initiated, with the intent of examining in one cohort the efficacy of MMF as induction as well as maintenance therapy. During the 6-month induction phase, MMF was compared with intravenous CTX; subsequently, patients who had fulfilled response criteria in the induction phase were re-randomized to receive either MMF or AZA for 36 months as maintenance therapy. Both components of this trial are now complete. The induction phase failed to replicate prior positive results.⁵ After 6 months of treatment, the response rates were virtually identical in the MMF and CTX groups. Moreover, no safety advantage was shown for MMF during the induction phase. In contrast to this disappointing result, the maintenance phase demonstrated a clear advantage for MMF over AZA.⁶ After 36 months of follow-up, 32% of subjects in the AZA group had experienced progression or relapse of renal disease, or both, compared to a failure rate of 16% in the MMF group ($p < 0.003$). This result differs from a smaller recent trial among European patients, in which MMF and AZA appeared to be comparable as maintenance therapies.⁷ It remains to be determined how these differing results can be reconciled.

Rituximab

Among potential biologic therapies for SLE, rituximab generated the greatest initial excitement, based largely on uncontrolled case series^{8,9} and numerous anecdotal reports in the literature and throughout the lupus community. Rituximab is a chimeric mouse-human monoclonal antibody that binds the CD20 antigen that is present on the surface of most B cells, but not on B-cell precursors or plasma cells. As B cells appear to play an important role in the pathogenesis of SLE, there was a strong mechanistic rationale for expecting that depletion of B cells by rituximab might have beneficial effects in SLE.

To date, the results of controlled clinical trials have not supported this expectation. Two year-long trials, one in 257 patients with active non-renal manifestations of SLE¹⁰ and one in 144 patients with active lupus nephritis,¹¹ both failed to demonstrate efficacy. At this time, it is not clear how to interpret these results in the light of so much uncontrolled experience to the contrary. It is possible that these studies chose the wrong background medication (MMF) and that other combinations (e.g., rituximab plus CTX) might have provided a different result. It is also possible that these studies were underpowered or that their duration was inadequate to demonstrate benefit that would have become apparent later. In this regard, it may be noteworthy that prior trials in lupus nephritis required many years to distinguish among various approaches to therapy.¹ However, the most

straightforward interpretation may prove to be the correct one: the impression that rituximab would be effective for the majority of patients with SLE may just be wrong.

Belimumab

Belimumab offers an alternative approach to B-cell therapy that is not predicated on profound B-cell depletion. Belimumab is a fully human monoclonal antibody that targets B-lymphocyte stimulator (BLyS), a cytokine that promotes B-cell proliferation and differentiation. Two phase III multinational trials of belimumab, designated BLISS-52 and BLISS-76, have now been completed. These trials were similar in design. Both enrolled more than 800 patients with active lupus; both involved three treatment groups (placebo, belimumab 1 mg/kg/mo, or belimumab 10 mg/kg/mo) superimposed on standard of care; both focused on patients with moderate disease activity but excluded patients with serious life-threatening organ involvement; and both used the same primary outcome measure. The duration of treatment was 52 weeks in BLISS-52 and 76 weeks in BLISS-76, but the primary outcome was still assessed at 52 weeks in both trials. The outcome measure consisted of a novel SLE responder index that incorporated components of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), the British Isles Lupus Assessment Group (BILAG) disease activity instrument, and physician's global assessment. The studies differed slightly from one another in that they were conducted in different regions of the world.

BLISS-52 and BLISS-76 each achieved the goal of demonstrating a statistically significant advantage for belimumab, compared to placebo at 52 weeks. In BLISS-52, 57.6% of the high dose belimumab group achieved the primary end point at week 52, compared to 43.6% of the placebo group ($p = 0.0006$).¹² In BLISS-76, the belimumab advantage in the high-dose group was 43.2%, compared to 33.8% ($p = 0.02$). However, the initial excitement that greeted these first-ever reports of successful treatment of lupus with a biologic agent has been tempered somewhat by the relatively small magnitude of the difference among groups and by the subsequent announcement that, in BLISS-76, the statistically significant difference was no longer demonstrable after 24 additional weeks of treatment.

We are still in the early stages of determining the role of belimumab in the treatment of lupus. The demonstration of a positive clinical effect constitutes a landmark moment in the search for effective biologic therapy for SLE. However, many hard questions lie ahead. Can we identify a subpopulation of lupus patients who will benefit most from belimumab? Where in the course of the disease will it best fit (e.g., treatment of active disease or maintenance of remission)? What is the optimal dose and regimen? Can the benefit be sustained over time? Will it

Table 1 Recent Controlled Clinical Trials in SLE

Study Drug	Number of Patients	SLE Manifestation	Result
Cyclophosphamide (mini-pulse vs conventional Rx)	90	Lupus nephritis	No difference after 10 years
MMF vs CTX (induction Rx)	370	Lupus nephritis	No difference at 6 months
MMF vs AZA (maintenance Rx)	105	Lupus nephritis	No difference at 5 years
MMF vs AZA (maintenance Rx)	227	Lupus nephritis	MMF superior to AZA after 36 months (failure rate 16% vs 32%)
Belimumab (BLISS-52)	865	Active non-renal SLE	At 52 weeks, 43% of the belimumab (10 mg/kg) group vs 34% of the placebo group achieved a clinical response
Belimumab (BLISS-76)	819	Active non-renal SLE	Statistically significant benefit over placebo at 52 weeks, but benefit not sustained at 76 weeks
Rituximab	257	Active non-renal SLE	No difference at 52 weeks between the rituximab and placebo groups (by BILAG)
Rituximab	144	Active lupus nephritis	No difference in renal response rate at 52 weeks between rituximab plus MMF vs. MMF alone
Abatacept	175	Active non-renal SLE (arthritis, serositis, or rash)	No difference in flare rate at 52 weeks between the abatacept and placebo groups (by BILAG)

be helpful in people with the most severe manifestations of lupus? All of these questions remain to be answered.

Abatacept

Unlike rituximab and belimumab, which target B cells, abatacept (CTLA4-Ig) inhibits T-cell costimulation. Abatacept is a soluble fusion protein, composed of the extracellular domain of CTLA4 bound to the constant region of an IgG molecule. Abatacept blocks T-cell costimulation by binding to the B-7 family of molecules on antigen-presenting cells, thereby preventing them from signaling T cells via CD28.

Three trials of abatacept have been initiated in lupus patients, but only one has been completed. In that study, abatacept was compared to placebo in a randomized, phase II trial of patients with active SLE characterized by arthritis, serositis, or rash.¹³ The primary end point was flare rate following initial control of disease activity with corticosteroids; the result was negative. There was no difference in the percentage of patients who experienced flare, as defined by BILAG, over the course of 52 weeks. However, this trial contained hints of possible activity that have fueled interest in further investigation. At each visit during the trial, investigators were asked to declare whether, in their judgment, the patient was experiencing a disease flare. By this measure, there was a difference in flare rates between the abatacept group (64%) and placebo group (83%). This difference was especially pronounced in the subgroup of patients with arthritis. This observation may be helpful in the design of subsequent trials. In the meantime, abatacept is being studied in two ongoing trials involving patients with

lupus nephritis. Results from the first of these trials will be available next year.

Conclusion

We have entered an era of unprecedented activity in the quest to improve therapy for people with SLE. Recent trials suggest that mini-pulse CTX therapy may be the treatment of choice, at least for some patients with lupus nephritis, and that MMF may emerge as an attractive evidence-based choice for maintenance of response. Trials of biologic agents are beginning to provide hope for more selective therapy. That being said, for now it should also be noted that these trials have raised many more questions than they have answered.

Disclosure Statement

The author was a member of the steering committee that participated in the design and eventual interpretation of the Aspreva Lupus Management Study (ALMS), which examined the efficacy of mycophenolate mofetil as induction or maintenance therapy for lupus nephritis; he declined compensation for serving in this role. The author has served as a paid consultant for Genentech and Bristol-Myers Squibb, manufacturers of rituximab and abatacept, respectively. He is also principal investigator of an ongoing NIH-sponsored trial to examine the efficacy of abatacept superimposed on mini-pulse CTX therapy in patients with lupus nephritis.

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