Treatment of Systemic Lupus Erythematosus
A 2012 Update

Joan T. Merrill, M.D.

Treatment for lupus is evolving. This review summarizes some of the major recommendations for care from the time of the EULAR Task Force Guidelines for SLE Treatment in 2008 through the more recent ACR guidelines for lupus nephritis which was published within the last year. Some newer papers and some reports still in abstract form are also cited, covering less conventional treatments that are available to physicians in practice. Treatments in trials which are not available to the general clinic will not be discussed here.

The European League Against Rheumatism Recommendations for SLE
The EULAR Task Force on SLE published guidelines for lupus treatment several years ago, which was based on an extensive literature review and expert consensus.1 This effort was helpful in providing a framework for practical treatment decisions and in recognizing the limits to the evidence base and the many unanswered questions that remain. For this set of recommendations, the complexity of lupus was addressed efficiently, segmenting the approach to patients by whether they did or did not have major organ involvement. When a physician considers therapy for those without major organ manifestations, antimalarial or steroid treatment were recommended as well as the selective consideration of nonsteroidal anti-inflammatory agents for limited periods. Of course in most lupus practices, antimalarials and steroids are not restricted to patients who are less ill. Hydroxychloroquine is usually maintained along with additional therapy when patients develop worsening disease, and the steroid doses are usually raised.

For patients with more severe disease or in any patients when steroids could not be reduced to acceptable levels, immunosuppressive agents such as azathioprine, mycophenolate mofetil, and methotrexate were recommended.1 For renal disease, cyclophosphamide (with better proof of long term efficacy) and mycophenolate mofetil (with a better side effect profile) were recommended to be given along with steroid therapy.1 These recommendations reflected reasonable, worldwide standards of care, boiled down to a rational set of guidelines, but patients with lupus were nevertheless left with a limited set of choices between treatments which for the most part are known to have imperfect efficacy and potentially toxic consequences.

Steroids: Less is More but Only if Possible
Corticosteroids are the friend and the enemy to a patient with lupus. At the right individualized dose, they are rapid in onset and nearly universally effective, regardless of the organ activity that has manifested. The myriad side effects are well known, including severe toxicities and damage to the metabolic balance, cardiovascular system, eyes, bones, and (not in the least underestimated by our patients) the body habitus and general appearance. Even though all of these things are well known to physicians, the actual percentages of lupus patients who develop serious sequelae from corticosteroids can be surprising2 and are reflective of the chronic use and difficulty in tapering these highly effective and seriously detrimental treatments. In fact, steroids are responsible for many of the most severe comorbidities that threaten patients with lupus, and may be a key factor in one of the most

Joan T. Merrill, M.D., is in the Clinical Pharmacology Research Program at Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma.
Correspondence: Joan T. Merrill, M.D., Clinical Pharmacology Research Program, Oklahoma Medical Research Foundation, 2929 NW 19th Street, Oklahoma City, Oklahoma 73107; JTM-mail@aol.com.

common causes of complications and death for lupus patients: infection.3,4

Is There a Science Behind Our Immune Suppressants?

Azathioprine is still widely used for moderate to severe lupus in 2012. It is a pro-drug that is metabolized after ingestion to 6-mercaptopurine (the active form which is marketed as such in many parts of the world) and 6-thioguanine. A genetic deficiency in an enzyme which converts 6-mercaptopurine (Thiopurine S-Methyltransferase) as well as polymorphisms in genes for several other components of the same metabolic pathway can lead to hematologic and liver toxicities.5,6 Although increasingly used when other immune suppressants fail, evidence base for its use is not extensive.7 Its site effect profile is similar to those of azathioprine or methotrexate, but dosing is usually per algorithm with a loading dose followed by a conventional fixed dose.

Methotrexate is well known as an inhibitor of dihydrofolate reductase MTX, but it also acts on a number of other enzymes, leading to interference with both purine and pyrimidine pathways and DNA methylation.9 Methotrexate is eliminated by the kidney and can become rapidly toxic, again necessitating more frequent monitoring early in the dosing period and cautious use in patients with renal impairment.10 Leflunomide inhibits an enzyme in the pyrimidine pathway, dihydroorotate dehydrogenase. Although increasingly used when other immune suppressants fail, the evidence base for its use is not extensive.11 Its side effect profile is similar to those of azathioprine or methotrexate, but dosing is usually per algorithm with a loading dose followed by a conventional fixed dose.

Belimumab: The First Biologic Approved for Lupus

Belimumab has now been available to general rheumatology practices for more than a year. The results of the Phase III trials were modest, but since there is a natural ceiling on the percentage of heterogenous lupus patients that could possibly respond to any targeted therapy, an argument can be made that the effect size was small because the trial design mandated aggressive standard of care treatments of all patients, including placebo patients. Since the approval of Belimumab, several exploratory and long-term follow up datasets have been released, showing in one exploratory analysis that the difference between placebo and belimumab was greater in subsets of what are arguably more active patients (positive anti-dsDNA, low complement, treatment with mycophenolate with or without steroids, patients with renal involvement, and patients with higher SLEDAI scores) underscoring the hypothesis that this drug could be more effective than the Phase III trial design was able to demonstrate. An additional new publication provides more data on the long-term safety of this treatment over a 4 year period.15 Unfortunately, both the United Kingdom and Germany payers have refused to cover belimumab, and this may have repercussions on access of this treatment to patients worldwide.

Treatment of Nephritis

In the last year, ACR guidelines specifically for the treatment of nephritis have been published.16 Similar to the EULAR approach an extensive literature search was performed, evidence was weighted, and a panel of experts was asked to consider a number of case scenarios. Level A evidence was given to a recommendation for treatment of proliferative nephritis with steroids plus either cyclophosphamide or mycophenolate mofetil, and these regimens were considered equivalent for induction therapy, although there is better long term efficacy evidence for cyclophosphamide at this time. Mycophenolate might be the preferred treatment, however, for patients of African or Hispanic descent16 based on some evidence that these groups respond less well to cyclophosphamide. For crescentic nephritis, the same regimen choice was recommended along with both IV pulse and high dose oral steroids. For Class V, nephritis mycophenolate and lower dose (0.5 mg/kg/day) prednisone were recommended.16

A recent meta-analysis of studies comparing mycophenolate to cyclophosphamide in lupus nephritis suggests possible superiority of mycophenolate in overall efficacy, and when comparing side effects, there is (not surprising in either case) more diarrhea and less amenorrhea with the mycophenolate regimen.17 However, not every study confirms this as the best induction therapy, and there is no treatment optimal for every individual. In looking at results of any treatment studies a certain degree of skepticism is always in order, since if one treatment is effective 40% of the time and another 30% of the time, it remains unclear whether that 30% includes some patients who would not have responded to the first treatment. A better connection between pathology, immune markers, and treatment selection remains elusive in 2012. When selecting a treatment for a patient with active nephritis, there are other factors to take into account as well, such as the patient’s history, age, renal chronicity, tolerance of different forms of treat-
ment, ability to comply with an IV versus oral regimen, all of which could have a significant impact on individual efficacy.

Cyclosporine A and tacrolimus have been used for nephritis for many years based on a few open label and prospective trials. These are cited as a choice for refractory patients by the ACR Guideline committee. Two more small series have been published from Asia in the past year, and these treatments may provide options for individual patients when needed. Rituximab is used for severe lupus and refractory lupus nephritis and was also cited by the ACR nephritis committee as a choice. Preliminary anecdotes support the use of other biologics, including TNF inhibitors for nephritis and other severe lupus activity when alternative options are no longer possible. IVIG or plasma exchange is also used in very ill patients or those with hematologic or vascular complications, especially microangiopathy, which can occur in the context of nephritis or without renal involvement. This option was also discussed by the ACR Guideline Committee.

Maintenance regimens usually involve mycophenolate or, as a viable second choice, azathioprine, both of which can be effective in the right setting and prevent progressive chronic kidney disease to some extent. The ACR task force cited these regimens as equivalent choices based on level A evidence.

**Stem Cell Transplantation**

This draconian measure, in which there is an attempt to rebalance a fundamentally disturbed immune system with new stem cells, is predicated on the assumption that known downstream factors which affect developing immune cells and are known to contribute to lupus may never reoccur or might at least be delayed for many years. The pioneering of SCT procedures for lupus was heralded, a decade ago, by equal degrees of adulation from the committed and horror from the skeptics. Reports of complete remission in some individuals continue to filter in. However, the mortality risk coupled to continued uncertainty about the permanence of the improvement or comparative efficacy to less expensive and less dangerous therapies relegate current consideration of stem cell procedures to those patients with the most severe disease and limited alternatives.

**Treatment of Comorbidities**

Adjunctive therapies and treatment of comorbidities were not overlooked by the EULAR experts who cited healthy lifestyle modifications, such as weight control, exercise, and smoking cessation; and supplementary treatments, such as aspirin, cholesterol lowering treatment, and antihypertensives, as being important to consider. It was suggested that the pros and cons of estrogen be considered and used with caution while it was acknowledged that they would be appropriate for some individuals.

Patients with lupus are known to be at increased risk for cardiovascular complications, and the EULAR group stressed that physicians should consider the probability that these patients are at high risk. Indeed, a recent report from the 30 center Systemic Lupus International Collaborating Clinics found that metabolic syndrome could already be identified in 16% of lupus patients near the time of diagnosis (mean age 35), and this was associated with a number of factors, notably and not surprisingly with steroids and renal disease. Particular caution about the risk for arterial disease in the lupus population should specifically include the aggressive treatment of conventional cardiac risk factors and maintaining a high index of suspicion when events occur that could be suggestive of cardiovascular complications. Whether or not improving the control of longstanding, low-grade autoimmunity would change the long-term

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**Table 1  Current Treatment Options for SLE in Clinical Practice: 2012**

<table>
<thead>
<tr>
<th>Treatment/Indication</th>
<th>Not Organ Threatening</th>
<th>Organ Threatening</th>
<th>Nephritis Induction</th>
<th>Nephritis Maintenance</th>
<th>Refractory Disease</th>
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<tr>
<td>Antimalarials</td>
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<td>Mycophenolate</td>
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<td>Azathioprine</td>
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<td>Methotrexate</td>
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<td>Leflunomide</td>
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<tr>
<td>Cyclophosphamide</td>
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<tr>
<td>Cyclosporine/tacrolimus</td>
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<tr>
<td>Belimumab</td>
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<tr>
<td>Rituximab/other biologics</td>
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<tr>
<td>IVIG/plasma exchange</td>
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<tr>
<td>Stem cell transplant</td>
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prognosis for atherosclerotic complications in our patients is a compelling question which remains unknown, and must be weighed against the potential toxicities of the treatments we have at hand to achieve this.

Osteoporosis is another comorbidity exacerbated by chronic use of steroid therapies that the physician can help to prevent. The EULAR recommendations include consideration of calcium and vitamin D in women who might become pregnant and bisphosphonates in postmenopausal patients.\(^1\) Since risk for this disorder is so strongly affected by steroid therapy, there is more reason to continue doing all that is possible to minimize the use of corticosteroids. Finally, sun avoidance is an important lifestyle change that most physicians recommend, as did the EULAR guidelines,\(^1\) but this should be counseled in the context of the impact it has on vitamin D\(_3\), and underscores the potential importance of vitamin D supplementation.

**Summary and Conclusions**

Table 1 lists most of the treatments available to clinicians in 2012 for the treatment of lupus. In milder, non-organ threatening disease, antimalarials, lower dose steroids, and transient use of NSAIDs is usually effective. For organ threatening disease or illness that is not responding to acceptable doses of steroids, immune suppressants are initiated. Mycophenolate mofetil or cyclophosphamide are usually used as the first line treatment for nephritis, and in either case, corticosteroids are added. For maintenance therapy, either mycophenolate mofetil or azathioprine is preferred. For refractory disease, any treatments on the list might be tried and combined including biologics and antibody inhibiting strategies, such as IVIG or plasma exchange. Stem cell transplant should be reserved for the most refractory cases with the most limited options.

**Disclosure Statement**

The author has no financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

**References**

21. Mascarenhas S, Avalos B, Ardoyn SP. An Update on Stem Cell