Abstract

This 2013 update on the treatment of systemic lupus erythematosus provides rationale for universal use of antimalarials even absent skin or joint manifestations, but chiefly focuses on the management options for refractory cutaneous, articular, and renal disease and current status of biologics; both FDA approved belimumab and off-label infliximab, rituximab, abatacept, and tocilizumab. A discussion of antiphospholipid syndrome secondary to lupus, specifically use of aspirin for asymptomatic patients, suggestions for catastrophic antibody syndrome, and potential roles for rituximab and eculizumab are provided. This review is a companion to an article published in this journal last year and in combination provides recommendations for standard care in routine cases of lupus as well as for the problematic, intractable patient.

An article published last year in this journal provided a comprehensive review summarizing the major recommendations for care based on the EULAR Task Force Guidelines for SLE Treatment in 2008 through the ACR guidelines for lupus nephritis reported in 2012. Therefore, rather than discuss what was so well addressed last year, the standard management of routine aspects of lupus, this report will focus on areas not covered in that publication, namely the role of antimalarials, management of refractory lupus, status of the one FDA approved biological, belimumab, as well as the currently available biologics for off label use in SLE, including TNF antagonists, rituximab (RTX), abatacept, and tocilizumab, and conclude with a brief update on aspects of antiphospholipid syndrome secondary to SLE.

The update begins with a justification for universal use of antimalarials in SLE. The investigator trained in an era where hydroxychloroquine was touted for relief of constitutional, musculoskeletal, and mucocutaneous manifestations of SLE or DLE. However, a 2013 update would be remiss without presenting evidence supporting the view that all patients with lupus are candidates for antimalarials with the following caveat: patients that experience allergic drug induced hypersensitivity rash should be excluded. Similarly, medication needs to be discontinued for patients who experience drug toxicity associated maculopathy, but this is rare, especially in patients that receive less than 6.5 mg/kg/day, as well as before total exposure exceeds 1,000 grams, which at a dose of 400 mg per day is not reached until 6.8 years. Table 1 reviews the purported mechanisms of action and evidence based clinical benefits of hydroxychloroquine in treatment of lupus. Some of the data that supports prescribing antimalarials even in patients without joint or skin activity include disease modifying benefit suggested by increased flare rate with discontinuation, improved renal response rate as an adjuvant therapy with mycophenolate mofetil, reduction in thrombotic events, and improved mortality.

Current therapeutic options for intractable cutaneous, musculoskeletal, and renal lupus are shown in Table 2.

Cutaneous Lupus

Standard of care currently includes sun avoidance, topical as well as intralesional steroids, antimalarials, including combining hydroxychloroquine or chloroquine with quinacrine, monitoring with cutaneous lupus disease area and severity index (CLASI) to allow for standardized assessment of skins disease activity and damage, low dose oral steroids, as well as MTX, AZA, MMF and belimumab. Patients with refractory skin disease can be candidates for cyclo-
Musculoskeletal Lupus

The vast majority of SLE patients experience arthralgia and myalgia, and it is important to recognize the high incidence of secondary fibromyalgia that often is the etiology of chronic musculoskeletal pain in patients. Anti-inflammatory or immunomodulatory medication should be reserved for that subset of patients at risk for nonerosive but deforming arthritis (i.e., Jaccouds arthropathy) or the even rarer patient with erosive inflammatory changes otherwise indistinguishable from rheumatoid arthritis (i.e., rhupus). Standard of care spans the spectrum of limited courses of non-selective as well as Cox-2 selective NSAIDS, antimalarials, antimitabolites, including MTX, AZA, MMF, and leflunomide, and belimumab. Novel options in 2013 include TNF antagonists, rituximab (i.e., French registry of 136 patients 73% demonstrated complete or partial response), abatacept, and tocilizumab. Since anti-TNF treatment may induce formation of antibodies, including ANA and anti-dsDNA in more than a third of patients and rarely cases of drug induced lupus, including with nephritis, surveillance for internal organ involvement is required.

Renal Lupus

Published ACR guidelines on the management of lupus nephritis provide recommendations that are similar for proliferative and mixed proliferative with membranous class disease but distinct from pure membranous alone and emphasize the need for induction and maintenance treatment. However, even with state of the art care, this approach is effective in at most 80% of patients leaving 20% of patients at risk for glomerulosclerosis, ESRD, and for renal replacement either as dialysis or, if patient qualifies, renal transplant. Options for patients who do not achieve complete or even partial response at induction with either CYT or MMF (i.e., patients should cross over from one to alternative drug if no response to first), relapse early or frequently or experience inadequate response during maintenance therapy with either MMF or AZA, include calcineurin inhibitors (e.g., cyclosporine 3 to 5 mg per kg divided BID daily or tacrolimus 0.15 mg per kg divided BID daily for induction and 0.06 mg per kg divided BID daily for maintenance), multi-targeted treatment with MMF plus tacrolimus, rituximab, and abatacept. Despite negative results of the single, large randomized control study of rituximab in lupus nephritis, the LUNAR Trial, multiple open labeled observational studies reported renal responses with the B cell depletion that accompanies use of this anti-CD20 chimeric monoclonal antibody. Explanations for the contradictory results between the RCT and case report studies include the following:

1. Open label observational studies may falsely attribute pharmacologic benefit where there is none especially since series where patients experience a poor response maybe underreported. However, there is no a priori reason to expect that has been the case with RTX and SLE.

2. Demographics in the open labeled studies vary from the LUNAR Trial. Specifically more nonwhites (e.g., Asians and Latinos) were enrolled in the LUNAR Trial as compared to observational studies which disproportionately entered patients from European medical centers with Caucasian race. Moreover, nonwhite patients have more aggressive nephritis (independent of socioeconomic and access to care factors), and it is theoretically possible that RTX like CYT is more

Table 1

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Clinical Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toll-like receptor activation antagonism</td>
<td>Effectively treats constitutional, cutaneous, and musculoskeletal activity</td>
</tr>
<tr>
<td>Inhibition of interferon-alpha expression and IFN-alpha mediated pathways</td>
<td>Synergy with MMF in achieving complete renal response</td>
</tr>
<tr>
<td>Inhibits auto-antigen presentation</td>
<td>Prevents flares</td>
</tr>
<tr>
<td>Anti-platelet effect</td>
<td>Reduced organ damage accrual</td>
</tr>
<tr>
<td>Cholesterol lowering effect</td>
<td>Prevents thrombotic events</td>
</tr>
<tr>
<td>Clinical Benefits</td>
<td>Improves survival</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Skin</th>
<th>Joint</th>
<th>Renal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>TNF antagonists</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Rituximab</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Abatacept</td>
<td>Multitarget- tacrolimus + MMF</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Tocilizumab</td>
<td>Rituximab</td>
</tr>
<tr>
<td>Dapsone</td>
<td></td>
<td>Abatacept</td>
</tr>
<tr>
<td>Retinoids</td>
<td></td>
<td>ACTH gel</td>
</tr>
</tbody>
</table>

phosphamide (CYT), rituximab, thalidomide (i.e., 100 mg daily), lenalidomide (i.e., 5 to 10 mg daily), dapsone (e.g., especially patients with bullous skin lesions characterized by antibodies targeting type VII collagen), and retinoids (e.g., isotretinoin and acitretin).
effective in whites than, for example, African Americans. However, the observational studies from USA and the experience at an inner city municipal facility, Bellevue Hospital, demonstrate benefits of RTX in minority populations.

3. The LUNAR Trial exclusively combined RTX with MMF, whereas many of the observational studies used combination with CYT. The notion of the importance of combination is supported by the BELONG study that used ocrelizumab, a non-FDA approved fully humanized anti-CD20 monoclonal antibody, which demonstrated superior response compared to placebo when used in combination with fixed low-dose European lupus nephritis (ELNT) CYT but not in those receiving background MMF. Primary outcome may influence apparent efficacy of biological medications. For example, recent post hoc use of a slightly different definition of complete response primary outcome for RCT with abatacept changed study from negative to positive, as described in greater detail below. Additionally, the negative findings of the LUNAR Trial may be explained by the short period of follow-up of one year, especially because of the trend toward lower dsDNA and higher C3 and C4 with RTX at study conclusion and at 78 weeks RTX response rate superior to standard of care (e.g., placebo plus MMF).

4. Finally, the majority of patients enrolled in LUNAR Trial were treated for the initial renal flare (54%) where most of the patients in the open observational studies with RTX had intractable nephritis, refractory to treatment that often included prior MMF and course of CYT, or both. This explains the current view that RTX is a rescue or salvage therapy and consistent with the possibility that prior “priming” of B cells by an anti-metabolite or alkylating agent renders them more susceptible to the beneficial effects of B cell depleting therapy that is achieved by RTX. This scenario is reminiscent of a prior treatment regimen that “synchronized” plasmapheresis with CYT and was based on a notion of “stimulation depletion.” This approach relied on a hypothesis that plasmapheresis induces a compensatory “rebound” proliferation of pathogenic B cells such that CTX administered immediately after plasmapheresis should inhibit these activated clones when they are most vulnerable. Admittedly, the initial benefits of this combination could not be replicated, and the purported scientific rationale never validated, but it is possible a similar effect, although without need for close temporal association of treatments, contributes to the distinction between the LUNAR data and the use of RTX in patients who have failed prior therapy.

Another interesting opportunity with regard to RTX treatment in lupus nephritis is the desire to be steroid sparing in the management of disease activity even a step further as the ritixilup cohort in London, UK, experienced high response rates using RTX with methylprednisone 500 mg day 1 and 15 for induction followed by MMF for maintenance without any daily oral steroids in effort to achieve “steroid avoidance.”

This cohort consisted of neither exclusively new onset nor refractory disease, but if results are replicated, it provides an option, especially later in disease course, to provide immunomodulatory treatment while avoiding steroid toxicity.

Although the Abatacept and Cyclophosphamide Combination: Efficacy and Safety Study (ACCESS Trial), which compared abatacept combined with MMF and corticosteroids to standard of care with MMF and steroids, did not meet the predetermined defined complete response (CR) primary outcome, if the definition for CR that was employed in the LUNAR Trial is applied, then the rate was 6% in the control group compared to 22% and 24% in the two different dose regimens of abatacept. Based on studies from the 1950s, ACTH as H.P. Acthar®, a timed release formulation produced in an expensive process from porcine pituitary glands, has FDA approval for several indications including use in “rheumatic disorders and collagen diseases,” as well as “inducing a remission of proteinuria in the nephrotic syndrome without uremia due to idiopathic type or lupus erythematosus.” There is renewed interest in this drug based in part on a newly proposed mechanism of action. It had long been assumed the efficacy of ACTH was a consequence of the peptide’s ability to increase endogenous corticosteroid production, but evidence including those from adrenalectomized animals supports the view that steroidogenesis may only partly account for ACTH effect and that its influence is explained by binding to melanocortin receptors, which are generally expressed, for example, in renal podocytes. ACTH has affinity for all five of the melanocortin receptors, and these interactions are associated with anti-inflammatory and immune-modulating actions. Small open label series have recently reported on improvement in nephrotic syndrome associated with lupus membranous nephropathy and Questcor sponsored as well

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Biologics in Systemic Lupus Erythematosus</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Approved</td>
<td>Belimumab</td>
</tr>
<tr>
<td>Off-label*</td>
<td>TNF antagonists</td>
</tr>
<tr>
<td></td>
<td>Rituximab</td>
</tr>
<tr>
<td></td>
<td>Abatacept</td>
</tr>
<tr>
<td></td>
<td>Tocilizumab</td>
</tr>
<tr>
<td></td>
<td>Eculizumab</td>
</tr>
</tbody>
</table>

*Off-label use justfied only after all standard of care drugs failed, defined by toxicity or definite lack of response, as these medications are not approved for lupus and efficacy based only on theoretic benefits, open label case reports, and preliminary Phase I trial data or Phase II or III trials where primary outcomes not statistically significant and only post hoc analysis demonstrates improvement. Additionally, prescriber needs to be fully familiar with side-effects as reported in package insert.
as investigator-initiated studies are underway to determine if ACTH gel provides a more beneficial efficacy and safety profile than traditional corticosteroids in lupus nephritis.\textsuperscript{13}

Biologic therapy for SLE is shown in Table 3.

**Belimumab**

Belimumab was approved for treatment of SLE by the U.S. Food and Drug Administration in March, 2011, based on two definitive Phase III trials demonstrating superiority to the standard of care but which excluded patients with active nephritis or CNS disease. Current studies with this biologic include RCT combining anti-BLyS treatment versus placebo for nephritis in combination with either MMF or ELNT fixed low dose CYT, trial to demonstrate efficacy in African Americans as they were underrepresented (e.g., 13%) in original multinational and multicenter reports and post hoc analysis could not prove statistical benefit, pediatric patients, and subcutaneous formulation. Even though the magnitude of the benefit compared to the standard of care was modest in the BLISS 52 and BLISS 76 week trials, subset analysis suggests that belimumab has greater therapeutic benefit than standard therapy alone in patients with higher disease activity as well as greater serologic activity (e.g., anti-DNA positivity and hypocomplementemia).\textsuperscript{14,15} Finally, although the RCT that led to approval of belimumab excluded patients with active nephritis at 52 weeks, rates of renal flare, renal remission, renal organ disease improvement, and proteinuria reduction all favored belimumab, while differences in most renal outcomes did not reach statistical significance. Among the 267 patients documented with renal involvement at baseline, those also receiving MMF had greater renal organ disease improvement with belimumab than with placebo.\textsuperscript{16}

**TNF Antagonists**

TNF is an important mediator of inflammation with data demonstrating increased levels in serum, skin, and kidney samples of SLE patients, while at the same time it can control autoimmunity as demonstrated by appearance of ANA and dsDNA antibodies, as well as occasionally drug induced lupus during TNF blockade. Despite the double-edged sword concern regarding this treatment, TNF antagonism has been tried for several years in single case and open label studies, most often with infliximab. Clinical flares of lupus have not been reported. Efficacy has been demonstrated in SLE patients with arthritis, nephritis, hemophagocytic syndrome and interstitial lung disease, infections have been reported, and an increase in antiphospholipid antibodies with theoretic risk of thrombosis has also been noted. These findings support use of TNF inhibitor as infliximab for induction treatment but not for maintenance given the concern for drug-induced toxicity over time.\textsuperscript{17}

**Rituximab**

Since the initial case reports in 2000, literature now includes numerous series and meta-analysis in support of B cell depleting therapy, including a systematic review of 188 patients with severe, refractory disease showing 91% had significant improvement in at least one lupus manifestation.\textsuperscript{18} The French Autoimmunity and Rituximab Registry reported on improvements in articular, cutaneous, renal, and hematological manifestations with satisfactory safety profile. A meta-analysis of 611 patients with intractable renal and non-renal lupus revealed overall improvement after induction with RTX in disease activity, reduction in steroid use, and benefit after retreatment.\textsuperscript{9} Despite the negative EXPLORER and LUNAR studies, RTX is currently the option as rescue therapy for lupus nephritis and a reasonable choice for non-renal lupus if standard care has failed.

**Abatacept**

As a selective T cell co-stimulation modulator that inhibits T cell activation and subsequent antibody production B cells, it was unexpected that a RCT did not reveal benefit of abatacept in non-renal or renal lupus. However, here again trial design and specifically selection of primary efficacy endpoints may explain the negative results as post hoc analysis of studies reveal benefit from abatacept for polyarthritis, constitutional symptoms, and nephritis.\textsuperscript{18}

**Tocilizumab**

IL-6 receptor blockade has been shown to reduce immunoglobulin levels and produce small decreases in anti-dsDNA levels, as well as improvement in disease activity scores during a Phase I dose escalation study reported in 2010 of renal and non-renal lupus patients.\textsuperscript{19} Subsequently, there have been a handful of case reports describing benefits in lupus including for intractable serositis with pericardial effusion, autoimmune hemolytic anemia, and cutaneous lupus.\textsuperscript{20-22}

**APS Secondary to SLE**

A randomized controlled trial, the Antiphospholipid Antibody Acetylsalicylic Acid (APLASA) study, failed to demonstrate reduction in thrombotic events with aspirin (ASA) compared to placebo, but likely is not generalizable to all lupus populations.\textsuperscript{23} For example, this report included asymptomatic, persistently aPL-positive individuals with or without coexisting connective tissue disease, and the included lupus patients tended to have mild disease. Moreover, the total number of enrolled patients as well as number of observed events in both arms of the study were low consistent with risk of Type II statistical error and insufficient power to demonstrate benefit. Additionally, animal studies of APS as well as theoretic models of mechanism of action of antibody mediated thrombosis in APS establish that antibodies to negatively charged phospholipid protein complexes are adequate but not sufficient (e.g., patients experience long periods of time with measurable, even high titer, anti-phospholipid antibodies [APAbs] without events) to generate thrombosis. Therefore, a second signal is necessary for thrombosis to occur. SLE patients experience disease flares characterized...
by circulating cytokines, generation of complement activation products, and endothelial cell stimulation with increased expression of adhesion molecules and tissue factor that can conspire to create “perfect storm” for thrombotic events. Therefore, SLE patients with asymptomatic APAbs that have frequent flares, high titer anti-dsDNA, and persistent or episodic hypocomplementemia are candidates for low dose ASA as primary prevention. In fact, a Markov analysis weighing theoretic event reduction with ASA versus risk of toxicity recommended use of ASA for primary prophylaxis. A second report argues similarly for ASA as primary prophylaxis in patients with SLE. In conclusion, the current recommendation is to use ASA and hydroxychloroquine for primary prevention of thrombotic events in patients with SLE and secondary anti-phospholipid antibodies. Warfarin remains the drug of choice, once a patient has experienced an event, as there is too little data to recommend routine use of direct thrombin or Factor Xa inhibitors, but since these newer anticoagulants offer convenience, future trials should explore their safety and efficacy.

As far as SLE and catastrophic antiphospholipid syndrome (CAPS) current recommendations include initial management with continuous heparin drip, pulse Solu-Medrol followed by divided dose intravenous steroids and plasmapheresis. Uncertainty relates to the need for cyclophosphamide since in one large study of 250 patients concomitant treatment with cyclophosphamide did not demonstrate additional benefit, role for IVIG or rituximab and appropriate replacement fluid (e.g., albumin versus FFP).26,27 Again there may be a distinction between the recommended treatment and efficacy for primary CAPS compared to CAPS in the setting of SLE with the view that chemotherapy and IVIG is appropriate in patients with a systemic immune mediated inflammatory disorder (e.g., lupus) as the illness is accompanied by B cell autoantibody production. The routine use of rituximab cannot be recommended as the single series published to date interestingly reported no reduction in antiphospholipid antibody titer and only improvement in some but not all non-criteria manifestations of APS.28 In contrast, a single recent case report showed a response to RTX treatment in a patient with resistant APS, complicated by recurrent PEs, and was accompanied by reduction in aPL titers.29 Many studies report a benefit with the use of albumin as replacement fluid while FFP has to be blood type specific and is associated, albeit infrequently, with risk of blood borne pathogens as well theoretic infusion of prothrombotic products.30 On the other hand, one concern with the use of albumin is depletion, by concurrent plasmapheresis of anti-thrombin Factor III, thereby potentially reducing efficacy of heparin drip. A reasonable approach is to start with albumin as replacement fluid and consider switching to FFP if there is a poor clinical response or difficulty achieving anticoagulation. The latter issue raises a point that determining the appropriate titrated dose of heparin may require measuring anti-factor Xa levels rather than aPTT if the latter is prolonged due to the presence of lupus anticoagulant. Finally, as discussed previously, a role for complement activation in CAPS including stimulation of endothelial cells and formed elements of blood such as platelets and neutrophils is supported by case reports of benefits associated with the use of the monoclonal inhibitor of C5, eculizumab, which prevents generation of C5a and C5b-9.31,32

Patients with SLE in 2013 are fortunate that our understanding of the etiology and pathogenesis of disease activity continues to improve and informs our treatment. Most patients have disease that can be well controlled with standard therapy, but this update discusses options for more recalcitrant cases. There is reason for further optimism as ongoing trials of newer biological therapies (e.g., novel B and T cell modulation, IL-6 antagonists, inhibition of Type 1 interferon pathway, etc.) will in time provide additional options for both routine and refractory patients and by virtue of more targeted mechanisms of action offer greater benefits with less risk of toxicities than the current standard of care.

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

11. Condon MB, Ashby D, Pepper RJ, et al. Prospective observa-


