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Treatment of Mild, Moderate, and Severe Lupus Erythematosus: Focus on New therapies

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Abstract

Despite large-scale efforts devoted to the conduct of clinical trials in systemic lupus erythematosus (SLE), there has been no new therapy approved for this disease in over fifty years. Increased understanding of the immunologic mechanisms underlying SLE has led to the development of a variety of biologic agents that target specific aspects of the adaptive and innate arms of the immune system including B cells, T cells, dendritic cells, and various cytokines. One of these agents, belimumab, was the subject of two positive phase III trials in non-renal lupus that have given us hope that a new therapy for SLE is finally within our grasp. In addition to these newer therapies, recent studies of traditional medications such as mycophenolate mofetil and hydroxychloroquine have better defined the efficacy and safety of these agents for the treatment of lupus nephritis and non-renal lupus. This article will provide a discussion of several novel biologic agents at different stages of development for the treatment of SLE as well as an analysis of newer data on more traditional agents that have been used in the treatment of SLE for many years.

Keywords

systemic lupus erythematosus; lupus nephritis; therapy; clinical trials; atacicept; rituximab; belimumab; epratuzimab; mycophenolate mofetil; interferon alpha; abatacept; hydroxychloroquine

Introduction

As we are all too aware, few medications have FDA approval for the treatment of systemic lupus erythematosus (SLE): aspirin, prednisone, and antimalarials. Thus, the majority of treatments commonly used for SLE are off-label indication use of medications developed and studied primarily for different indications including cancer, organ transplantation, rheumatoid arthritis, and other autoimmune conditions. Many therapeutic strategies frequently employed do not have rigorous randomized, placebo-controlled trials to support their use. Fortunately, the era of largely hit-or-miss treatments for SLE is closing and this new century is bringing with it new paradigms of therapeutics targeting specific immune

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defects in SLE as well as improved design of randomized controlled trials (RCT) to better quantify efficacy and safety of new (and old) therapies. In this review, we aim to summarize the available data on several promising new therapies for SLE in addition to new data supporting the use of therapies already considered efficacious in SLE.

Modulating B cells

One hallmark feature of SLE is the presence of autoantibodies. As B cells are principle components of the adaptive immune system that lead to the production of antibodies, they become a natural target of therapeutic modulation. Of all new therapeutic approaches for SLE, targeting B cells has the most experience and the largest number of products in clinical development. Two distinct mechanisms of modulating B cells have emerged: peripheral B-cell depletion versus the targeting of B cell survival factors such as BAFF and APRIL. B-cell depletion is achieved using monoclonal antibodies against cell surface receptors present on B cells during different periods of differentiation. The BAFF pathway can be modulated using monoclonal antibodies directed against the ligand BAFF (also known as B-lymphocyte stimulator, BLyS), or by blocking BAFF receptors on B-cells (BAFFR, TACI, BCMA) [1].

Rituximab

Since its approval in 1997 for the treatment of non-Hodgkin's lymphoma, there has been considerable interest in the therapeutic potential of B-cell depletion using rituximab, a chimeric monoclonal anti-CD20 antibody for the treatment of SLE. Following numerous case reports and case series describing clinical improvements in active renal and non-renal SLE among patients with refractory disease following treatment with rituximab [2], two multi-center, blinded, placebo-controlled trials were undertaken to better understand the safety and efficacy of rituximab when added to background immunosuppressants and corticosteroids for the treatment of lupus nephritis and for moderately-to-severely active non-renal SLE. Results of the phase II/III study of rituximab or placebo on background immunosuppressive medications and initial steroid taper for the treatment of moderate to severely active non-renal SLE were published this year. All 257 subjects received at least 0.5 mg/kg daily prednisone at study entry with a defined taper over 10 weeks [3]. Major clinical response was defined as a reduction of all BILAG scores to C or better in all organs by week 24 then maintenance of that response without BILAG A or B flare through week 52. At the conclusion of the study, no statistically significant differences between the rituximab and placebo groups achieving a major clinical response or partial clinical response were detected: approximately 70% of subjects in each group failed to achieve any clinical response. Although clinical outcomes did not appear to differ between groups, there was a significant normalization of anti-double stranded DNA antibodies, C3, and C4 levels in subjects receiving rituximab compared to placebo. Rates of adverse events and infections were comparable between groups. Similar results were seen in the randomized, placebo-controlled trial of rituximab or placebo on background mycophenolate mofetil for the treatment of lupus nephritis [4]. No differences between groups were seen regarding the proportion of subjects achieving complete renal response or partial renal response achieved (45.9% complete and partial responders in placebo vs. 57% in rituximab). Again,

statistically significant improvements in anti-dsDNA and complement levels were seen in the rituximab groups. Results of these much anticipated studies were disappointing; however, it is very possible that issues related to trial design were at least in part responsible for the lack of apparent efficacy. These studies have been criticized for setting a very high hurdle for clinical response (all BILAG scores of C or better without any flares for 52 weeks), and use of high doses of corticosteroids at study onset, the effectiveness of which may have masked distinctions in response between rituximab and placebo. In addition, it is possible that rituximab works best in combination with cyclophosphamide, and this combination was not studied in the two RCTs.

Despite disappointing results in the multi-center randomized controlled trials, rituximab remains an attractive potential treatment for refractory SLE and has demonstrated clinical effectiveness in numerous, albeit uncontrolled, published reports [5–7]. All patients were treated for severely active SLE that was unresponsive or poorly responsive to traditional immunosuppressant therapy. In several recently published reports of large series of patients (50–136 SLE patients) response rates (complete + partial) ranged from 71% to 88%, substantially higher rates than were seen in the RCTs. A recent systematic-review of off label use of rituximab for SLE evaluated a total of 456 treated patients reported in 27 studies [8]. Analyses of these data found a mean decrease in SLEDAI score by 59% (from 14.8 to 5.4) and a mean decrease in BILAG score of 61% (from 14.7 to 7.0) following treatment. When looking specifically at outcomes following rituximab treatment for lupus nephritis, the systematic review found an overall complete renal response rate of 27% and a partial renal response rate of 39%, leaving 30% without change in renal disease and 4% who deteriorated.

The use of biologic agents, particularly with concomitant immunosuppressive therapies and corticosteroids, raises concerns about increased risks for infections. Notably, a few cases of progressive multifocal leucoencephalopathy (PML) have been reported in subjects with SLE being treated with rituximab in combination with other immunosuppressive agents [9]. Attribution of these cases solely to the use of rituximab is not warranted, as most cases occurred in patients with longstanding active SLE (which in itself may increase risk for PML) who were treated with multiple immunosuppressive medications as well as corticosteroids. In the published RCTs as well as the growing literature on off-label use of rituximab in refractory SLE, no new cases of PML have been reported and rates of infections do not appear to be dramatically different than in patients treated with placebo [3,4,8].

Because of conflicting data between RCTs and uncontrolled case series, use of rituximab as a first-line agent for SLE or for the treatment of mild-to-moderate disease activity is not warranted. However, substantial data has accumulated to support the use of rituximab in cases of profound disease that is refractory to multiple traditionally used agents. In these cases, the potential for clinical benefit may outweigh the risks for infections. Patients should be appropriately informed about the potential risks and benefits of rituximab before proceeding with treatment.

Belimumab

Following a 50 year period in which there have been no new drug approvals for the treatment of SLE, the positive results of two phase III trials of belimumab in moderate-severe SLE have brought hope and excitement to the lupus community. Belimumab is a fully human monoclonal antibody targeting B-lymphocyte stimulator, a cytokine that is essential for B cell survival and differentiation (Human Genome Sciences, Inc.). In comparison to rituximab, belimumab causes a lesser degree of B cell depletion. In the phase I dose escalation trial, belimumab reduced CD20+ B cells by a median of 43% and serum immunoglobulins by 16% (IgM) and 9% (IgG) [10]. In the phase II, double-blind, placebo-controlled trial in 449 patients with active SLE, belimumab did not improve disease activity as measured by the Systemic Lupus Disease Activity Index (SLEDAI) and did not decrease time to first SLE flare [11]. However, it was noted that only 72% of the patients were ANA and/or anti-dsDNA positive at the time of study entry. Post-hoc analyses suggested that limiting inclusion to only the antibody positive patients would have demonstrated improved clinical efficacy of belimumab over placebo. This finding led to a series of analyses that resulted in the development of a novel SLE Responder Index (SRI). The SRI incorporated components of the SLEDAI, the British Isle Lupus Assessment Group (BILAG) disease activity instrument, and the physician's global assessment (PGA). This instrument was chosen as the primary endpoint in the two pivotal phase III trials (BLISS-52 and BLISS-76). Both of these large-scale, randomized, double-blind, placebo-controlled trials compared belimumab (1mg/kg or 10mg/kg) to placebo, both added to background standard of care treatment in ANA and/or anti-dsDNA positive patients with moderate to severe disease activity. Importantly, patients with organ threatening disease including severe lupus nephritis and central nervous system (CNS) lupus were excluded. Although the trial duration of BLISS-52 was 52 weeks and BLISS-76 was 76 weeks, the SRI primary endpoint was assessed at week 52 in both trials.

BLISS-52 enrolled 865 patients and was conducted primarily in South America and Asia. 57.6% of the belimumab 10mg/kg group compared to 43.6% of the placebo group achieved the primary endpoint at 52 weeks. Notably, belimumab demonstrated improved efficacy over placebo in multiple secondary endpoints including each component of the SRI, reduction of daily prednisone dose, time to first flare, and rate of severe flare [12]. In the BLISS-76 trial, conducted primarily in the United States, Canada, and Mexico, 43.2% of the high dose belimumab group compared to 33.8% of the placebo group achieved the primary endpoint at 52 weeks [13]. Lastly, a 5-year, open-label extension study of patients in the original phase II trial reassuringly showed that belimumab was well tolerated over the 5 year period [14]. Although the positive results of BLISS-52 and BLISS-76 are very promising, several questions remain. For example, it is yet to be determined if belimumab would be most useful for the treatment of active SLE, or would be best utilized to maintain disease quiescence or remission. The use of belimumab in patients with organ-threatening disease such as lupus nephritis was not studied in the BLISS-52 and BLISS-76 trials as those trials excluded such patients. Thus, the role of belimumab in the treatment of nephritis patients remains unclear. Lastly, the cost of belimumab will most likely be an important factor influencing its use. One might ask if the magnitude of the effect compared to placebo (14%

in BLISS-52 and 9.4% in BLISS-76) outweighs the cost and potential risks. We anticipate that many of these issues will be unraveled over time as belimumb is used with increasing frequency in the clinic.

Epratuzumab

Following extensive experience with B-cell depletion via anti-CD20 monoclonal antibodies (MAbs), attention has been drawn to alternative molecular targets on B-cells. CD22 is a cell surface marker present on the surface of mature B cells. Hence, targeting CD22 may prove to be an attractive alternative to a pan B-cell depletion of the more ubiquitously expressed CD20. Epratuzumab (UCB, Inc) is a humanized IgG1 monoclonal antibody targeting CD22. After initial studies in subjects with hematologic malignancies, epratuzumab was initially studied in a small, phase II open-label study to evaluate tolerability and clinical efficacy [15]. In this study, 14 patients with seropositive active SLE (13 with BILAG Bs and 1 with BILAG C, no BILAG A level of disease activity) were treated with 360 mg/m2 epratuzumab intravenously every other week for a total of 4 doses. Study drug was added on to background immunosuppressive medications including methotrexate, azathioprine, mycophenolate mofetil, corticosteroids (mean 12 mg daily prednisone) and antimalarials. Main clinical efficacy measures included reduction in total BILAG score at weeks 6, 10, and 18. Nearly all patients in this open label study showed improvement in BILAG scores at all time points, with 77% of patients experiencing a >50% decrease in total BILAG score by week 6; 38% of whom showed a sustained response of >50% at 18 weeks following study drug infusion. Aside from non-invasive infections and transient grade I infusion reactions, the study did not reveal any concerning safety or tolerability issues.

Based upon preliminary data suggesting efficacy at reducing signs and symptoms of moderately active SLE and a reasonable safety profile, epratuzumab was studied in a larger, randomized, placebo controlled, dose ranging phase IIb study of 227 patients with moderate to severely active non-renal lupus [16]. To date, results of this study have been published only in abstract form. This study utilized a novel responder index based upon BILAG criteria: reduction in all baseline BILAG scores by at least 1 level (BILAG A to B/C/D or BILAG B to C/D) without worsening of BILAG in other organ systems, worsening of SLEDAI, or physicians global assessment, or increase in prednisone or immunosuppressive medications. At week 12, 43.2% of patients receiving 2400 mg epratuzumab (600 mg weekly for 4 weeks or 1200 mg every other week for 2 doses) met response criteria compared to 21.1% of patients receiving placebo. Furthermore, more than 35% of patients receiving 2400 mg epratuzumab met criteria for enhanced BILAG improvement (improvement of all BILAG domains to C or better) compared to 22% in the placebo group. Although specific details were not provided, safety and tolerability of epratuzumab did not differ significantly from placebo. The striking response signal for epratuzumab in these early reports make targeting CD22 an exciting candidate for further development. Results of larger phase III studies are eagerly anticipated.

Atacicept

In addition to belimumab, several other agents targeting the BAFF pathway are currently under development. Atacicept, a chimeric fusion protein of the extracellular domain of the TACI receptor joined to a human IgG1 domain, blocks both BLyS and APRIL mediated B cell stimulation (Serono, Inc.). Both murine and human studies have shown a marked reduction in immunoglobulin (including autoantibody) levels following treatment. A phase Ib double-blind, placebo-controlled, dose-ranging study of single and multiple does (4 weekly doses) of atacicept administered subcutaneously showed a dose-dependent reduction in immunoglobulin levels and peripheral mature B cells [17]. Because this phase I study was small (24 subjects) and enrolled patients with quiescent or mildly active SLE, clinical efficacy was not formally assessed. However, there was a suggestion that subjects with elevated SLEDAI scores and decreased C3 levels at the baseline visit had improvements in the multiple-dose cohorts compared to placebo and single-dose cohorts. Although injection site reactions were more common in the atacicept group, infections or other adverse events were comparable between active drug and placebo treated subjects.

This very encouraging preliminary data lead to the initiation of larger, phase II/III studies in both lupus nephritis and non-renal SLE. A phase II study of atacicept or placebo on background mycophenolate mofetil for the treatment of active lupus nephritis was halted due to opportunistic infections arising in subjects receiving combination mycophenolate mofetil and abatacept. Following these reports of an increased infection risk, the phase II/III study of active non-renal SLE was amended to exclude patients on background mycophenolate mofetil. The non-renal study is currently enrolling patients with active (BILAG A or B) lupus in non-renal domains who may be on background methotrexate or azathioprine as well as antimalarials and corticosteroids. Primary efficacy outcomes for this study include the proportion of patients who experience a new BILAG A or B flare after disease control (BILAG C or better) is achieved with initial steroid taper. As enrollment has not been completed, data regarding safety and efficacy is unavailable, but will undoubtedly provide invaluable data regarding antagonism of both the BLyS and APRIL pathways.

Other SLE targets

Although B-cells are critical to the immune dysregulation of SLE, it is clear that many other cell types and soluble mediators are involved in the development, maintenance, and disease activity of SLE. Activated T cells are necessary for acceleration of the humoral immune response, making blockage of T cell activation an intriguing therapeutic possibility. More recently, plasmacytoid dendritic cells and interferon alpha have been shown to play a critical role in active SLE.

Abatacept

While belimumab and rituximab target the B cell arm of the immune response, abatacept (CTLA4-Ig) inhibits T cell costimuation. Abatacept is a soluble fusion protein composed of the extracellular domain of CTLA4 and the modified CH2 and CH3 domains of IgG1. Abatacept binds to B7-1 and B7-2 on antigen presenting cells and inhibits T cell activation by disrupting the CD28-B7 costimulatory interaction. Abatacept was compared to placebo in

a randomized, placebo controlled trial of patients with active non-renal SLE characterized by arthritis, serositis, or rash. There was no difference in the percentage of patients who experienced the primary endpoint of flare, as defined by BILAG, over 52 weeks [18]. Despite this overall negative result, there was a suggestion of possible activity of abatacept. At each visit throughout the course of the trial, the study investigators were asked to judge whether or not they believed the patient was experiencing a disease flare. By this measure, the investigators discerned a difference in flare rates between the abatacept group (64%) and the placebo group (83%). This difference was especially pronounced in the subgroup of patients with arthritis. It remains to be determined whether this difference can be replicated in a randomized, controlled trial. Currently, abatacept is being studied in two ongoing trials for the treatment of lupus nephritis, one in conjunction with MMF and one in conjunction with the low dose pulse IVC.

Interferon alpha

Increasing data has suggested a critical role of interferon-alpha (IFNα) in the initiation and maintenance of systemic lupus erythematosus. IFNa (13 subtypes) and interferon b compose the type I interferons, which are criticial for first line innate defense against viral infections. Type I IFNs are synthesized by plasmacytoid dendritic cells (PDCs), among other cells, following infection by DNA or RNA viruses, likely via toll like receptors, and exert pleotropic effects activating the humoral immune system by binding to type I IFN receptors (IFNAR) on many cell types [19]. Administration of exogenous IFNa to patients for the treatment of hepatitis C has led to the development of SLE-like illness in some cases [20]. Increased levels of IFNa as well as the "interferon signature", a pattern of IFN α-inducible genes, has been associated with disease activity among several distinct populations of lupus patients [21, 22].

The identification of the central role of interferona in lupus disease activity has naturally lead to interest in the therapeutic potential of IFNα blockade [19,23]. To date, two monoclonal antibodies directed against IFNα are in clinical trials for the treatment of SLE. Results of a phase I trial of sifalimumab (MedImmune, Inc.), a human monoclonal anbody that binds to and inhibits the majority of IFNα subtypes, have recently been published [24]. The study recruited 60 patients with mild to moderately active SLE with cutaneous involvement. Concomittant immunosuppressive therapy, including cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, immunoglobulins, or prednisone >20 mg daily, were excluded. The manuscript focused on examining efficacy of IFNα neutralization via changes in a 21-panel gene signature for type I IFN family members and IFNα/β inducible genes. Interestingly, only 60% of patients had a moderate to high overexpression of IFNα/β gene signature, the remainder having weak or no overexpression. Among patients with moderate to high IFNα/β overexpression, there was a dose dependent neutralization of the gene signature that diminished, but had not returned to baseline, over the 84 days studies post administration. Skin biopsy specimens were available at baseline and day 14 following administration in 16 patients; eight of whom exhibited IFNα/β overexpression in both skin and whole blood. The majority (7/8) of these patients showed similar patterns of changes in IFNα/β gene expression in both skin and whole blood. Furthermore, immunohistochemical staining of skin biopsy specimens corresponded to

IFNα/β neutralization. These encouraging results of mechanistic studies have lead to the development of further clinical trials to better understand the effects of sifalimumab on active SLE.

A randomized, placebo controlled phase I dose escalating single and multiple dose study of rontalizumab in patients with mild SLE has recently been completed. Rontalizumab (Genentech, Inc.) is a human monoclonal antibody that neutralizes 12 IFNα subtypes without IFNβ binding. Early results are available although not yet in the peer-reviewed literature [25]. This study enrolled 60 patients with mild disease activity, none of whom were permitted to take prednisone >20 mg daily or immunosuppressive therapies. Doses ranged from 0.0 to 10 mg/kg administered subcutaneously or intravenously. Overall, side effects following administration of rontalizumab were similar to that seen with placebo. One patient developed appendicitis and one developed leukemia during the trial: both were deemed to be not related to study drug by the investigator.

Mechanistic studies were incorporated into this study as well. Similar to what is seen in other populations, approximately 50% of patients had an elevated interferon signature at baseline. Investigation into changes in the interferon signature following dose administration revealed decreases in a dose response fashion; all returned to pre-dose levels over time. Based upon these results, a large multi-center phase II randomized controlled trial of rontalizumab in subjects with moderate to severely active SLE is currently underway.

New data on "old" medications

Medications such as mycophenolate mofetil (MMF) and hydroxychloroquine (HCQ) have been considered among the mainstays of effective treatment for moderate-to-severe lupus, lupus nephritis, and mild-to-moderate disease. Additionally, they have a more favorable safety and tolerability profile compared to cyclophosphamide, a medication that is commonly used for lupus nephritis but associated with hemorrhagic cystitis, premature ovarian failure, and opportunistic infections. As the arrival of new therapies begin to change the landscape of the treatment of lupus, evidence continues to emerge regarding the mechanism of action, efficacy, safety, and long term effects of MMF and HCQ that will maintain them among the first line agents for the treatment of active and quiescent disease.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) has been increasingly used for the treatment of SLE and lupus nephritis over the past decade. MMF is a potent inhibitor of lymphocyte proliferation via reversible inhibition of the enzyme inosine 5-monophosphate dehydrogenase (IMPDH) which is critical for the de novo synthesis of guanosine nucleotides. The selectivity of MMF for lymphocytes is due to the fact that lymphocytes are dependent on the de novo pathway for cell proliferation. In addition, there is evidence to suggest that the immunosuppressive effects of MMF extend beyond the effects on lymphocyte proliferation. For example, MMF has been shown to induce apoptosis of activated T lymphocytes and inhibit adhesion molecule expression. MMF was approved for the prevention of acute allograft rejection in 1995 and has been studied in controlled trials in lupus nephritis for over ten years. An initial study in lupus nephritis demonstrated that MMF plus prednisolone had equivalent efficacy

and superior safety to oral cyclophosphamide plus prednisone [26,27]. Ginzler and colleagues then performed an open-label trial of MMF versus monthly pulse intravenous cyclophosphamide (IVC) for the induction treatment of lupus nephritis. While the primary objective of this trial was to demonstrate equivalent efficacy of MMF, MMF was shown to be more efficacious than IVC at 6 months [28].

These promising results set the stage for the multi-national Aspreva Lupus Management Study (ALMS) of 370 patients which was composed of a 6 month induction phase and a 36 month maintenance phase. The induction phase consisted of a comparison of MMF and monthly pulse IVC for induction treatment of lupus nephritis. In the maintenance phase, patients who met the response criteria in the induction phase were re-randomized to receive either MMF or azathioprine for maintenance therapy. Concomitant treatment with prednisone was not allowed to exceed 10mg/d. The induction phase did not achieve its primary endpoint in that MMF was not superior to IVC. The overall rate of renal response at 6 months was 56% in the MMF group and 53% in the IVC group, with only 8% of patients in each arm achieving a complete renal response [29]. Surprisingly, there was no difference in the safety profile of MMF compared with IVC. Despite these disappointing results, post-hoc analyses led to some interesting findings. There appeared to be an interaction between treatment group and race in that Black and Hispanic patients were more likely to respond to MMF than to IVC [30]. An analysis combining the pure membranous nephritis patients from Ginzler's original trial and the ALMS trial demonstrated that there was no difference in the rate of response to MMF and IVC in the induction treatment of membranous lupus nephritis- a class of lupus nephritis that has not been typically included in large scale lupus nephritis treatment trials [31]. Lastly, ALMS was one of the only lupus nephritis studies to allow enrolled patients with an eGFR < 30 ml/min. A subgroup analysis of these patients showed equivalent efficacy of MMF and IVC.

In contrast to the induction phase, the ALMS maintenance phase demonstrated superiority of MMF over IVC in decreasing the time to treatment failure. Treatment failure was defined by one of the following components: renal flare, sustained doubling of serum creatinine, initiation of rescue therapy for nephritis, end stage renal disease, or death. The cumulative incidence of treatment failure at 36 months was 16% in MMF group vs. 32% in the azathioprine group [32]. This difference was consistent among all racial groups. Importantly, the pattern and frequency of adverse events was consistent with what has been reported previously for MMF and azathioprine. Notably, the ALMS trial is the first trial to demonstrate a statistically significant difference in efficacy between treatments for lupus nephritis. The maintenance results from the ALMS trial differ from those demonstrated in a European trial of 105 lupus nephritis patients who were randomized to MMF or azathioprine following induction therapy with low dose IVC (500mg IV every two weeks x 12 weeks) [33]. In this trial, the cumulative incidence of renal flare at 5 years was not statistically different between the MMF groups versus the azathioprine group (19% versus 25%). There are various possible explanations for the difference in results between the ALMS trial and the European trial including the sample size of the trials and the demographics of the patient population. The ALMS trial was larger and enrolled an ethnically and racially diverse patient population while the European trial was smaller and predominantly enrolled

Caucasians. How these factors impacted the study results remains to be determined over time.

Hydroxychloroquine

Far from a new therapy for the treatment of SLE, hydroxychloroquine (or other antimalarials including chloroquine), continues to be a mainstay of therapy because of its safety and efficacy. Elegant randomized controlled trials of hydroxychloroquine withdrawal in subjects with stable SLE have demonstrated a decrease in flares, both mild-to-moderate, as well as severe flares in subjects who continue HCQ in comparison to those who discontinue treatment [34,35]. More recent evidence has demonstrated further effects of HCQ in mitigating other manifestations commonly seen in patients with SLE as well as some insights into the mechanism of action of HCQ.

For many years, HCQ has been established as an effective therapy for the maintenance of SLE despite a clear understanding of the mechanism of action. Several mechanisms have been proposed in the past, including interference with antigen presentation via lysosomal acidification, and inhibiting production of IL-1 and IL-6 by macrophages [36,37]. More recently, exciting data has emerged to suggest that antimalarial agents may inhibit activation of intracellular, nucleic-acid binding Toll-like receptors (TLR). They are thought to affect nucleic-acid binding to TLR 3,7, and 9, by altering lysosomal acidification and disrupting endosomal maturation. TLR 7 and 9 have been implicated in the production of elevated type I interferons in response to RNA and DNA-containing immune complexes [38]. This provides a potential pathway for the recognition of nucleic-acid particles by autoantibodies and the subsequent activation of the immune system via type I interferons.

A comprehensive systematic review, including 95 individual articles, of the clinical efficacy and toxicity of antimalarials in SLE has recently been published [39]. Eleven studies included in the review had data on lupus activity. Lupus activity was found to be reduced by over 50% in these studies, both in pregnant and non-pregnant patients with a high level of evidence. A high level of evidence was similarly found in support of a >50% improvement in mortality. There was a moderate level of evidence to suggest that antimalarials have anti-thrombotic effects, and protective effects against accrural of organ damage. Evidence on the effect of antimalarials on lipids, atherosclerosis, and metabolic syndrome, although favorable, was rated of lower quality. Retinal toxicity among antimalarial users was relatively low, but was found to be worse among subjects taking chloroquine in comparison to hydroxychloroquine. The rate of probable or definite retinal toxicity was 0.3% among HCQ users compared to 2.6% in chloroquine users. A more detailed study of retinal toxicity among HCQ users (SLE and rheumatoid arthritis) found an extremely low rate within the first 7 years of treatment (< 3 per 1,000 users) compared to 20/1000 users (2%) in greater than 10 years of continuous use [40]. Neither age, weight, nor daily dose were associated with increased risk of toxicity.

Very recently, a observational study was published that evaluated the role of HCQ on cardiac neonatal lupus in a population of SSA+/SSB+ pregnant lupus patients [41]. Congenital heart block is a devastating manifestation of trans-placental transfer of maternal

SSA/SSB antibodies that occurs in approximately 2% of exposed neonates. The rate increases to approximately 20% in pregnancies with a previous child born with heart block. To date, no pharmacologic interventions have been conclusively shown to reduce the rate of congenital heart block. This case-control study of 201 pregnancies found an unadjusted odds ratio of 0.28 (95%CI 0.12–0.63, p<0.002) of developing congenital heart block among women who used HCQ throughout pregnancy. When adjusted for variables including birth year, use of fluorinated steroids, maternal race, antibody status, and history of neonatal cardiac manifestations, the OR was reduced to 0.46 (95% CI 0.18–1.18, p=0.1).

Conclusion

These are indeed exciting times for those who live with, study, or treat lupus. Our improved understanding of the complex interplay of the innate and adaptive immune systems and more specific regulators of the immune disturbances of lupus have lead to a myriad of potential therapeutic targets. And for the first time in many decades, new therapies specifically designed to treat lupus are advancing in clinical trials, and finally reaching the FDA approval process. Most studies of new therapies that are currently performed include mechanistic studies to better understand how each molecule works on an immunologic basis in addition to clinically relevant outcomes of safety and efficacy. With each study, there is potential to learn more about the immune system abnormalities of lupus and to better subset lupus patients into groups who may respond to different types of therapies. Thus, we are in a period of an exciting self-perpetuating cycle of increased understanding of the immunology of lupus and the development of targeted therapeutics.

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