The American College of Rheumatology Annual Scientific Meeting 2006: advances in the treatment of connective tissue diseases

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This is the second part of two articles on the 70th Annual Scientific Meeting of the American College of Rheumatology held in Washington, DC, USA, from 10–15 November, 2006. This review will highlight abstracts and presentations on the treatment of systemic lupus erythematosus (SLE), Sjogren's syndrome (SS) and systemic sclerosis (SSc).

Systemic lupus erythematosus

The current treatment approach of SLE includes the use of antimalarials, immunosuppressive drugs, steroids and nonsteroidal agents. The development of new biotherapies that target both the immune cells and cytokine pathways has resulted in a radical change in the management strategy of SLE. Several abstracts addressed the use of immunosuppressive agents, while presentations on new biological therapies provided insights into the changing therapeutic landscape.

Immunosuppressive agents

The accepted standard of care for the treatment of proliferative lupus nephritis, intravenous cyclophosphamide in doses of 0.75–1 g/m^2 body surface area given monthly for 6 months followed by quarterly doses for a total of 2 years, is based on the NIH trials [1,2]. Michelle Petri *et al.* reported on a trial comparing the NIH protocol with high-dose (immunoablative) cyclophosphamide [3]. Of 51 patients enrolled for the trial, 26 were treated with the monthly regimen, 22 with the high-dose regimen and three declined treatment. The response index for SLE was used to determine benefits of therapy. At 5 months both treatment regimens were shown to be effective in inducing responses. Interestingly, it was noted that the monthly regimen was superior to the high-dose regimen for renal lupus.

Azathioiprine and mycophenolate mofetil (MMF) are effective agents for the treatment of renal, as well as several extrarenal, manifestations of lupus [4]. Few studies are available on the calcineurin inhibitors, cyclosporine A and tacrolimus. A multicenter, randomized, controlled trial compared the use of cyclosporine, with azathioprine in patients with severe SLE [5]. A total of 47 patients were assigned to receive cyclosporine while 42 received azathioprine. At 12 months no difference was detected in measures of disease activity, damage and quality of life, suggesting that cyclosporine may be an alternative in SLE patients who are unable to tolerate azathioprine. A Japanese study assessed the efficacy and safety of cyclosporine for the treatment of refractory lupus nephritis [6]. After 6 months of cyclosporine therapy, a response was seen in 15 of 19 patients. Two patients showed no response while another two patients had to discontinue cyclosporine due to a transient increase in serum creatinine. Based on these results the authors conclude that cyclosporine is effective and safe for the treatment of refractory lupus nephritis. A study from Hong Kong compared the use of tacrolimus with MMF in patients with biopsy confirmed class IV or V lupus nephritis [7]. Of the 48 enrolled, 25 were randomized to receive tacrolimus and 23 to receive MMF, for 6 months. Although both medications, in combination with prednisone, were effective for initial treatment of lupus nephritis, MMF was found to be more potent in alleviating proteinuria and improving renal function. MMF was, however, associated with a slightly higher rate of infections.

Biologic agents

Although the role of B lymphocytes and antibodies in SLE was recognized several years ago, treatment modalities aimed at modulating or depleting the number and/or function of B cells have only been studied in the past decade [8]. The immunologic effects of B-cell depletion following rituximab was presented at one of the plenary sessions [9]. Several abstracts addressed novel approaches of depleting B-cell function or altering other cytokine pathways.

Rituximab

Rituximab is a chimeric mouse/human monoclonal antibody against the B-cell-specific antigen CD20 [10]. The US FDA approved the use of rituximab for the treatment of rheumatoid arthritis in 2006. Small open-label studies suggest that rituximab may also be effective for the treatment of SLE [11–13]. Further evidence of this effect, as well as data on the efficacy and safety of rituximab in the pediatric population, were presented at this conference [14–16].

The efficacy of rituximab is thought to roughly correlate with peripheral B-cell depletion [17]. Van Vollenhoven *et al.* attempted to identify predictors of clinical response in patients with severe SLE following treatment with a combination of rituximab (four doses of 375 mg/m^2) and cyclophosphamide (two doses of 500 mg/m^2). They noted that patients with higher baseline

lymphocyte counts had less likelihood of achieving a major clinical response, defined for this study as a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) of less than three. On the other hand, greater reductions in IgA anti-DNA were seen to be strongly associated with major clinical responses [18]. The same authors had previously reported on the beneficial effects of rituximab in patients with proliferative lupus nephritis [19]. At this conference they presented an abstract proposing that rituximab may also be effective in the treatment of severe membranous lupus nephritis [20].

Early studies noted that rituximab had no effect on immunoglobulins and vaccine-induced antibodies [17]. Albert *et al.* measured antibody titers to pneumovax and tetanus toxoid in SLE patients after treatment with rituximab (four doses of 375 mg/m^2) [21]. Patients were immunized 7 months after completing their rituximab course and antibody titers were measured 1 month after immunization. In this trial, patients with depleted circulating B cells for longer than 6 months responded poorly to immunization but did not experience increased infections.

Belimumab

B-lymphocyte stimulator (BlyS) or B-cell activation factor (BAFF) is a cytokine that plays a pivotal role in autoreactive B-cell survival and proliferation. Phase I trials of lymphostat-B, a fully human monoclonal antibody to BlyS, have previously been reported [22]. Phase II studies on the efficacy and safety of belimumab were presented at the ACR meeting. A randomized trial of 449 patients with active SLE, defined as Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA) SLEDAI scores equal to or greater than four, were randomized to receive belimumab 1, 4 or 10 mg/kg or placebo, in a 52-week trial [23]. The primary end points were a reduction in both SELENA SLEDAI scores at 24 weeks and time to SLE flares over 52 weeks. Other assessments included SLE flare index, British Isles Lupus Assessment Group (BILAG) score, physician global assessment (PGA) and Short Form (SF)-36. No significant improvements were detected in the primary outcomes or in the BILAG. Significant improvements were, however, noted in the PGA and physical component score of the SF-36. A 76-week extension of this trial suggested that all three doses were equally effective and showed no significant differences in safety [24]. An attempt was also made to correlate therapeutic responses with peripheral blood B-cell subsets [25]. Activated, memory, plasmacytoid and total CD20$^+$ B cells were stable or reduced after 52 weeks of belimumab therapy. IgG, IgM, IgA and IgE levels were all reduced. The anti-dsDNA levels were also decreased and this was associated with an improvement in SELENA SLEDAI scores. Another abstract reported a statistically significant and clinically meaningful improvement in quality of life measures in the above study [26].

Atacicept

An alternative approach to inhibiting BAFF is with the use of soluble BAFF receptors such as TACI-Ig. Dall'Era *et al.* reported on a Phase Ib double-blind, placebo-controlled, dose-escalating trial of atacicept [27]. Patients with mild to moderate SLE were administered different dosing regimens of atacicept and were followed for 6–9 weeks. A decrease in total and mature B-cell numbers was noted, especially in the cohorts that received multiple doses. No difference in adverse events between placebo and medication were recorded, leading to a conclusion that atacicept is well tolerated in SLE patients.

Tocilizumab (humanized anti-IL-6 receptor monoclonal antibody)

The discovery that IL-6, a proinflammatory cytokine secreted predominantly by macrophages and T cells, is increased in SLE sera has prompted suggestions that IL-6 blockade might be beneficial in SLE patients [28]. In a Phase I, open-label, dose-escalating study, 16 patients with mild-to-moderate disease activity were treated with tocilizumab, every 2 weeks for 12 weeks [29]. Swollen joint counts, SLEDAI and systemic lupus activity measure (SLAM) scores and acute-phase reactants decreased significantly. Tocilizumab was well tolerated but absolute neutropenia was noted at higher doses.

Anti-TNF therapy for SLE

Aringer *et al.* had previously reported improvement in joint and renal manifestations in lupus patients treated with infliximab infusion [30]. The long-term follow-up of this trial was presented at the conference [31]. The improvement in arthritis was not maintained when therapy was stopped. Interestingly, six out of nine patients with renal disease had sustained reduction in proteinuria at 43 months. Long-term therapy was, however, associated with increased risk for infections.

Sjogren's syndrome

SS is a chronic autoimmune disorder of the exocrine glands that is associated with organ-specific and systemic manifestations. The characteristic symptoms are dry eyes and dry mouth. Approximately 30% of patients also have extraglandular features including nephritis, neuropathies, CNS manifestations, interstitial lung disease (ILD) and arthritis. Sicca symptoms are treated with moisture preservation and replacement. Muscarinic-receptor stimulators are used in those not adequately controlled with symptomatic therapy. Treatment of extraglandular manifestations often involves the use of immunosuppressive agents or low-dose steroids.

Muscarinic agents

While it is known that pilocarpine stimulates the M1 and M3 receptors present on salivary glands, resulting in increased salivary function [32], the effect of pilocarpine on the salivary protein profile in patients with primary SS (pSS) is not known. Inzitari *et al.* studied the effect of pilocarpine on salivary peptide and protein profiles in pSS patients [33]. Saliva specimens from four pSS patients were compared with saliva from four healthy subjects at baseline and after pilocarpine.

It was noted that while salivary acinar proteins levels were lower in pSS patients at baseline, the protein levels increased after pilocarpine use. The authors also suggest that some salivary proteins may be used as biomarkers for pSS.

DHEA & Immunosuppressive agents

A double-blind placebo study of 59 females with pSS treated with dehydroepiandrosterone (DHEA) or placebo for 12 months, demonstrated improvements in measures of general fatigue and in the mental and physical component scores of the SF-36 [34]. This finding contradicts results of a previous trial that demonstrated no efficacy with DHEA in SS patients [35].

The use of immunosuppressive drugs in SS is based on the theory that exocrine dysfunction is secondary to inflammation of these structures. The results of trials using methotrexate, cyclosporine and azathioprine and low-dose steroids, however, have been disappointing [36]. A pilot study of 13 pSS patients demonstrated that treatment with leflunomide decreased the spontaneous production of IL-1β, TNF-α and IFN-γ [37]. Furthermore, a decrease in T-cell mediated cytokines following leflunomide therapy correlated with an improvement in sicca symptoms. These findings call for further evaluation of leflunomide in pSS.

A Russian study compared the risk for non-Hodgkin's lymphoma (NHL) in pSS patients treated with prednisone alone or in combination with chlorambucil or cyclophosphamide [38]. A total of 402 pSS patients were included in the study. They were divided into three groups; group I comprised 147 subjects treated with low-dose prednisone (5 mg daily or 5 mg every other day) in combination with chlorambucil or cyclophosphamide; group II comprised 151 patients, treated with low-dose prednisolone alone; and group III was comprised of 114 patients who refused therapy with immunosuppressive medications. The incidence of NHL was significantly less common in group I when compared with groups II and III, as well as when compared with group III alone, implying that a small dose of prednisone in combination with alkylating agents may suppress the risk for NHL in pSS.

Biologic agents

B-cell activation with hypergammaglobulinemia is a prominent finding in SS. Additionally, dysregulation of the BAFF system has been proposed to play an important role in the pathogenesis of SS [39]. These observations led to the initial trials of rituximab for treatment of SS. Seror *et al.* showed that the efficacy of rituximab for systemic features of pSS was associated with decreased levels of rheumatoid factor, γ-globulin and β-2 microglobulin and increased serum BAFF levels [40]. Pijpe initially reported on the benefits of rituximab in pSS, in 2003 [41]. A long-term follow up of 14 of 15 patients from the initial Phase II trial, demonstrated that benefits of therapy were seen for 6–9 months after initial therapy in patients with pSS and for even longer in patients with mucosa-associated lymphoid tissue type lymphoma [42]. Five patients were retreated with rituximab, again with significant improvements of the salivary flow rate and subjective symptoms. Of note, however, 21% of patients developed serum sickness.

Mavragani *et al.* studied the role of IFN-α and BAFF levels in pSS patients and investigated the effect of etanercept therapy on BAFF levels [43]. A total of 17 patients with pSS were treated with etanercept or placebo for 12 weeks. BAFF and IFN-α levels in these patients at baseline were also compared with levels in 29 healthy controls. IFN-α plasma activity and BAFF levels were increased in pSS patients at baseline compared with healthy controls. In the etanercept group, a statistically significant increase in IFN-α plasma activity and BAFF levels was detected after 3 months of treatment, while no difference was found in patients treated with placebo. The authors postulate that the increase in the IFN-α pathway activation and BAFF overexpression might provide a possible explanation for the lack of efficacy of anti-TNF agents in SS.

Systemic sclerosis

SSc is a systemic multiorgan, autoimmune, connective tissue disease characterized by excessive collagen deposition. Current use of immunosuppressive therapy for SSc is based on treatment regimens for other connective tissue diseases. Increased understanding of the pathogenesis of SSc, however, has led to the development of novel therapeutic agents.

Immunosuppressive therapy

A double-blind, randomized, placebo-controlled trial of cyclophosphamide for ILD in SSc reported significant improvements in lung function at 12 months of treatment. These improvements were maintained at 24 months [44]. *Post hoc* analyses presented at the ACR meeting suggested that although 24-month outcomes in pulmonary function between the cyclophosphamide and placebo groups were minor, measures of skin score, breathlessness, activities of daily living and general wellbeing were better in the cyclophosphamide group [45]. Various pulmonary function test parameters were best predicted by their value at baseline [46]. Similarly, statistical analysis suggested that the use of cyclophosphamide results in a small but persistent gain in quality adjusted life years (QALY) compared with no cyclophosphamide, for patients with scleroderma lung disease [47]. A retrospective analysis of 37 subjects investigated whether treatment with cyclophosphamide for a minimum of 6 months for ILD with SSc prevented a decline in lung function (defined as a greater than 10% decline in forced vital capacity [FVC]) [48]. At a median of 3.6 years, 68% of subjects had a stable percentage predicted FVC and 63% had a stable diffusion capacity (DLCO). This analysis implies that treatment with cyclophosphamide results in long-term lung-function stability.

A pilot study investigated the efficacy and safety of a combination of MMF and intravenous methylprednisolone in 16 patients with early diffuse SSc with active ILD (defined as abnormal lung function tests in the presence of ground glass appearance on high resolution CT scan and/or bronchoalveolar lavage

analysis) or extensive skin disease (modified Rodnan score [mRSS] of >15) [49]. Significant improvements in total skin score, forced expiratory volume and DLCO were noted in those treated for ILD, suggesting that the combination of MMF and methylprednisolone may be effective in treating patients with early diffuse scleroderma. No cases of renal crisis were reported.

A study from the USA compared the use of rapamycin versus methotrexate in early diffuse SSc [50]. Improvements in skin score, patient global assessment and FVC were comparable to that with methotrexate. It should, however, be noted that only 11 of 18 patients who enrolled completed the 48-week study. Of those who withdrew, four patients were in the rapamycin arm.

Biologics

Preliminary results from a Phase I study of rituximab for patients with diffuse cutaneous SSc were reported at the meeting [51]. Subjects were treated with two intravenous doses of rituximab (1000 mg). Of 13 patients enrolled to date, 6-month results revealed stabilization of skin disease and improvements in the Health Assessment Questionnaire (HAQ) and FVC measures. No severe adverse events were noted.

A multicenter study of infliximab (5mg/kg body weight at weeks 0, 2, 6, 14 and 22) for diffuse cutaneous SSc showed no significant improvements in skin scores, HAQ-disability index, SSc functional score or PGA at 26 weeks [52]. A total of ten serious adverse events were reported, in six subjects.

Stem cell transplant

Stem cell transplantation using high-dose cyclophosphamide has been tried in the treatment of a severe, progressive form of SSc [53]. Nash *et al.* presented data on the 5-year follow-up of patients treated with high-dose immunosuppressive therapy (HDIT) for SSc [54]. In this trial, 34 patients with early, diffuse SSc and visceral organ involvement were treated with cyclophosphamide (120mg/kg), antithymocyte globulin and total body irradiation. A significant improvement in the mRSS and overall function (HAQ-disability index) were noted at 4 years. Patients surviving at 1 year after HDIT continued to have sustained responses at 4 years and required no DMARD therapy. The 5-year overall survival was 64%. A European study of 26 patients with severe diffuse cutaneous SSc treated with hemopoietic stem cell transplantation also revealed significant improvements in the mRSS years and performance status within 1 year of therapy, with results being sustained for up to 7 years after transplantation [55]. Wigley *et al.* reported the results of treatment with high dose cyclophosphamide (50 mg/kg daily for 4 days) followed by granulocyte stimulating factor, in four patients with severe, active SSc [56]. An improvement of greater than 25% in mRSS was recorded in three patients. An improvement was also noted in the PGA assessment and HAQ scores. One patient died at week 7 from a lung infection.

Conclusion

The Annual Meeting of the American College of Rheumatology continues to be the premiere meeting in the field of rheumatology. Over the last few years the ACR meeting has grown in size with the 2006 meeting setting new records for attendance. The discovery of novel disease pathways and the rapidly growing field of biologic therapies in rheumatology will probably lead to even larger meetings over the next few years. Future ACR conferences, however, will hopefully continue to facilitate the exchange of scientific information between clinicians and scientists and ultimately help us provide better care for our patients.

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