Systemic Lupus Erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disorder that can affect virtually any organ in the body, including the skin, joints, heart, lungs, serous membranes, kidneys, hematologic system, and nervous system.¹ It is a connective tissue disease (CTD) characterized prototypically by the presence of autoantibodies, with almost all SLE patients having a positive antinuclear antibody (ANA) test. Young women in their 20s and 30s are affected more frequently than men. The most common pattern of manifestations in SLE is a mixture of constitutional complaints with skin, musculoskeletal, mild hematologic, and serologic involvement. However, some patients may have predominantly renal, hematologic, central nervous system, or cardiopulmonary involvement, as well as antiphospholipid syndrome.²

This review will briefly review the diagnosis of SLE, as well as provide an update on B-cell-targeted therapies that have recently been investigated in treating this complex disease.

Diagnosis of SLE

Patients with SLE may present with many different clinical manifestations, which often makes diagnosis difficult. Most physicians rely on the classification criteria for SLE that were developed by the American College of Rheumatology (ACR) to aid in making a diagnosis of SLE.³-⁴ These criteria were actually developed for the classification of SLE patients when SLE was compared to other rheumatic diseases for study purposes.⁵ These criteria that state a diagnosis is made if four of the following 11 criteria are met, either serially or simultaneously, with a sensitivity and specificity of approximately 96%:⁶
1. Malar rash: fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash: erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity: skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers: oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. Arthritis: nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis: pleuritis (convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion), or pericarditis (documented by EKG, rub or evidence of pericardial effusion)
7. Renal disorder: persistent proteinuria >0.5 g/day or >3+ if quantitation not performed, or cellular casts: may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder: seizures or psychosis (in the absence of offending drugs or known metabolic derangements)
9. Hematologic disorder: hemolytic anemia (with reticulocytosis), or leukopenia (<4,000/mm³ total on two or more occasions), or thrombocytopenia (<100,000/mm³ in the absence of offending drugs)
10. Immunologic disorders: positive antiphospholipid (APL) antibody, or anti-DNA (antibody to native DNA in abnormal titer i.e., dsDNA), or anti-Sm (presence of antibody to Sm nuclear antigen), or false positive serologic test for syphilis known to be positive for at least six months and confirmed by treponema pallidum immobilization of fluorescent treponemal antibody absorption test
11. Antinuclear antibody (ANA): an abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with “drug-induced lupus” syndrome

Other clinical manifestations that are seen in SLE, but not included in the above ACR criteria, include constitutional symptoms such as fevers, chills, fatigue, and unexplained weight loss; Raynaud’s phenomenon; alopecia (especially if patchy or scarring, but also may be generalized); sicca symptoms (dry eyes and dry mouth); recurrent miscarriages and/or thromboembolic phenomena (due to APL syndrome); lymphadenopathy; gastrointestinal disorders (abdominal pain, elevated liver enzymes, pancreatitis); pneumonitis; interstitial lung disease; pulmonary hypertension (HTN); and vasculitic complications (e.g., alveolar hemorrhage, retinal vasculitis, scleritis/episcleritis, cutaneous small vessel vasculitic lesions, mononeuritis multiplex). Although also not included in the above ACR classification criteria, hypocomplementemia is a frequent finding in SLE and may be associated with disease activity; hence, measurements of serum complement levels C3 and C4 are helpful. Other laboratory testing routinely performed to provide diagnostically useful information when SLE is suspected include a complete blood count and differential, comprehensive metabolic profile, inflammatory markers (erythrocyte sedimentation rate and/or C-reactive protein), creatine kinase, urinalysis, urine protein/creatinine ratio (and/or 24-hr urine protein quantitation), ANA, dsDNA, anti-Sm antibodies, and APL antibodies.

The ANA test is the best screening test for SLE (with a high sensitivity but low specificity at negative or low titers of 1:40), and should be performed whenever SLE is suspected. In virtually all patients with SLE, the ANA test is positive in significant titer (usually 1:160 or higher). ANA may be present, usually in lower titer, in a variety of other autoimmune rheumatic disorders, including Sjogren’s syndrome (68%), scleroderma (40% to 75%, usually speckled pattern), rheumatoid arthritis (RA) (25% to 50%), and juvenile idiopathic arthritis (16%). Additional autoantibodies are frequently checked in the initial diagnostic workup for SLE, since they tend to be associated with certain clinical settings and/or overlap with other CTDs (see Table 1). Diagnostic imaging that may be helpful, if indicated by the presence of symptoms, clinical findings, or laboratory abnormalities, include radiographs of involved joints; chest radiography; renal ultrasonography when there is evidence of renal impairment; echocardiography when there is concern for pericardial involvement or pulmonary HTN; computed tomography (CT) for evaluation of abdominal pain or pancreatitis; magnetic resonance imaging (MRI) for evaluation of neuropsychiatric complaints; and angiography if there is concern for vasculitis, such as mesenteric or limb-threatening ischemia.

Tissue biopsy of involved organs, such as skin or kidney, can be very helpful in confirming a diagnosis of SLE. A review of typical histopathologic findings in various organs in SLE is beyond the scope of this article.
Of note, the ACR criteria for SLE discussed previously have some inherent weaknesses. For example, a patient with biopsy-proven lupus nephritis or skin biopsy-proven lupus (but not malar or discoid rash per se) may still fail to fulfill criteria. A consensus group is actually in the final stages of validating new SLE criteria. A potentially useful classification system would group patients with many of the ACR criteria as “classical SLE,” with four or more ACR criteria as “definite SLE,” and those who have a positive ANA and evidence of inflammation clinically, but who do not meet the ACR criteria for SLE or other autoimmune disorder, as having “undifferentiated CTD (UCTD).”

Case series have been published on outcomes of patients who initially presented as UCTD. Up to one-third have resolution of signs and symptoms over a 10-year follow-up period; 40% to 60% continue with their initial clinical features; and 5% to 35% evolve and meet classification criteria for a definite disease such as SLE, RA, scleroderma, or myositis. Hence, patients with UCTD should be followed carefully over time by a rheumatologist to assess for the emergence of new clinical or laboratory findings.

**Update on B-Cell-Targeted Therapies in SLE**

In recent years, there have been multiple clinical trials evaluating agents that target B cells for the treatment of SLE, which have led to exciting therapeutic advances. These agents have recently been reviewed by Looney, Lateef and Petri, and Gunnarsson and van Vollenhoven and include rituximab, ocrelizumab, belimumab, epratuzumab, and atacicept. This update will include important phase II or III double-blind, placebo-controlled clinical trials that have been completed and/or are ongoing for these agents.

Of importance, the Food and Drug Administration (FDA) recently approved belimumab (Benlysta®) for the treatment of adult SLE patients with active, autoantibody positive disease who are receiving standard therapy. This was the first drug approved for SLE in more than 50 years. However, in clinical practice, rituximab (Rituxan®) has been in use longer than belimumab, with a multitude of anecdotal and uncontrolled trial reports of efficacy in refractory severe SLE. The conflicting negative results of the large, controlled clinical trials in rituximab (RTX) leave open the debate about its efficacy in SLE, because the inability to detect a statistically significant difference in the randomized trials may have been due to trial design issues, particularly the high background doses of prednisone and immunosuppressives used in both groups, and the avoidance of cyclophosphamide (CYC). Of note, in many of the open-label trials suggesting efficacy of RTX, CYC was used as background therapy. Since both RTX and CYC target B cells, there may be synergy in using them together.

**Rituximab**

Rituximab is a chimeric anti-CD20 monoclonal antibody targeting B cells in humans, originally used to treat B-cell lymphomas. CD20 is expressed selectively on B cells, including

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**TABLE 1:**

**Association of Specific Antibodies with Specific Clinical Manifestations**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Clinical Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-ribonucleoprotein (RNP)</td>
<td>SLE, undifferentiated CTD, scleroderma</td>
</tr>
<tr>
<td>Antibodies to Ro (SSA) and La (SSB)</td>
<td>SLE, Sjogren’s syndrome, neonatal lupus</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>Lupus nephritis, active systemic disease</td>
</tr>
<tr>
<td>Anti-U1 RNP</td>
<td>Myositis, Raynaud’s phenomenon, and less severe SLE</td>
</tr>
<tr>
<td>Anti-SSA</td>
<td>Subacute cutaneous lupus erythematosus (SCLE)</td>
</tr>
<tr>
<td></td>
<td>Lymphopenia</td>
</tr>
<tr>
<td></td>
<td>Photosensitivity</td>
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<tr>
<td></td>
<td>C2 deficiency</td>
</tr>
<tr>
<td></td>
<td>Sjogren’s syndrome</td>
</tr>
<tr>
<td></td>
<td>Neonatal lupus</td>
</tr>
<tr>
<td>Anti-ribosomal P</td>
<td>Neuropsychiatric lupus</td>
</tr>
</tbody>
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immature, naïve and memory B cells, but not stem cells or mature plasma cells. Typically, treatment with rituximab spares plasma cells and does not result in significant decreases in serum immunoglobulin (Ig)-G or IgA. B cells are known to be critical in the pathogenesis of SLE, including cytokine production, presentation of self-antigen, T-cell activation, and autoantibody production. Multiple small uncontrolled trials have suggested potential efficacy of rituximab in SLE.15

The EXPLORER (Exploratory Phase II/III SLE Evaluation of Rituximab) trial19 was a recent randomized, double-blind, placebo-controlled trial of RTX in nonrenal lupus patients with moderate to severe disease activity. Inclusion criteria were: (1) age 16 to 75 years; (2) meeting four ACR criteria for SLE (including positive ANA); (3) active disease at screening, with one British Isle Lupus Activity Group (BILAG) A (severe activity in an organ system) or two BILAG Bs (moderate activity in two organ systems); (4) stable use of one immunosuppressive drug at entry (e.g., azathioprine, methotrexate [MTX] or mycophenolate mofetil), which could be continued during the trial. Exclusion criteria included: (1) moderate or severe lupus nephritis, including anyone with serum creatinine >2.5 mg/dL; (2) severe CNS or organ-threatening lupus; (3) active conditions requiring significant use of steroids or recent treatment with cyclophosphamide or calcineurin inhibitors; (4) history of cancer or serious chronic/recurrent infections; (5) pregnancy; (6) previous treatment with B-cell-targeted therapy; (7) severely elevated liver or pancreatic enzymes; (8) severe cytopenias; and (9) uncontrolled medical disease.

The trial was performed in 55 centers in North America. A total of 257 patients were randomized in a 2:1 fashion (169 RTX; 88 placebo) to receive intravenous (IV) RTX (two 1,000 mg doses given 14 days apart) vs. placebo on days 1, 15, 168, and 182 (i.e., at 0 and 6 mo.). The trial was designed to detect a beneficial effect of RTX on both the induction and maintenance of a clinical response, using the BILAG as the primary outcome measure. The grading system of BILAG is from A to E, representing severe to inactive disease, respectively, among each of eight organ systems. A major clinical response (MCR) was defined as achieving a BILAG C or better at week 24, with no severe flares at any time and no moderate flares after week 24.

A partial clinical response (PCR) was defined as fulfilling at least one of three criteria: (1) BILAG C or better in all organ systems at 24 weeks and maintaining this for another 16 weeks; (2) BILAG C in almost all organ systems (i.e., no more than one BILAG B) at 24 weeks, with no new BILAG A or B after 24 weeks; and (3) in patients with high initial disease activity, achieving at most two BILAG Bs at 24 weeks, with no new BILAG A or B up to week 52. A severe flare was defined as one new BILAG A or two new BILAG Bs, and a moderate flare was defined as a new BILAG B. The primary outcome measured was the proportion of patients achieving MCR, PCR, or no clinical response between the two treatment groups.

The study population in both groups was more than 90% female, about 55% Caucasian, about 25% African-American, and with mean disease duration of about 8.5 years. At baseline, the median prednisone dose was 40 mg/day. Most of the SLE manifestations included mucocutaneous and musculoskeletal symptoms. The results of the study revealed no significant differences in the proportion of patients with MCR, PCR, or no response at 52 weeks between the two treatment groups. However, in African-American/Hispanic subgroup analyses, there was significantly more MCR in the rituximab group (13.8%) than placebo (9.4%), as well as more PCR in rituximab (20%) vs. placebo (6.3%) (P=0.0408). None of the primary or secondary end points were met in the subgroup of patients on background immunosuppressive drugs. However, an ad hoc analysis showed that RTX-treated patients in the MTX subgroup had improved mean BILAG global scores at week 52 compared with placebo (P=0.007). Although clinical responses were not found in the overall group, those in the RTX group had a significantly better serologic response, with rapid depletion of CD19-positive B cells; decrease in anti-dsDNA levels; and greater increases in C3 and C4 levels than those in the placebo group.

RTX appeared to be relatively safe over the course of the EXPLORER trial. The proportion of patients with any serious adverse events (SAEs) was similar in the placebo (36.4%) and RTX (37.9%) groups. The proportion with herpes virus infections was lower in the placebo group (8%) than in the RTX group (15.4%). There were more grade 3 and grade 4 neutropenia events in the RTX group (7.7%) compared with the placebo group (3.4%). Infusion-related adverse events (AEs) occurred in similar percentages of both groups during the first course, and decreased more in the placebo group than in the RTX group during the second course. These were primarily mild and transient responses. There were three deaths (1.8%) in the RTX group versus one death (1.1%) in the placebo group.
The LUNAR (Lupus Nephritis Assessment with Rituximab) trial was presented at the 2009 ACR national meeting, but has not yet been published in a peer-reviewed medical journal. This trial was a randomized, double-blind, placebo-controlled trial of rituximab in proliferative lupus nephritis (LN), with the objective to determine the efficacy and safety of RTX compared to placebo added on to background therapy of corticosteroids and mycophenolate mofetil. Inclusion criteria were: (1) age 18 to 75 years; (2) ACR criteria for SLE; (3) Class III or IV proliferative lupus nephritis by International Society of Nephrology (ISN) classification on a biopsy within 12 months of entry; and (4) urine protein to creatinine ratio (UPCR) >1. Exclusion criteria included: (1) >50% of glomeruli with sclerosis and/or interstitial fibrosis on renal biopsy; (2) estimated glomerular filtration rate (GFR) <25 ml/min/1.73 m²; (3) serious CNS manifestations; and (4) severe thrombocytopenia.

A total of 144 patients were randomized in a 1:1 fashion (72 in each arm) to receive IV RTX (two 1,000 mg doses given 14 days apart) vs. placebo on days 1, 15, 168, and 182 (i.e., at 0 and six mos), similar to the EXPLORER trial. Both arms received high-dose corticosteroids consisting of two doses of IV methylprednisolone 1000 mg at the onset of treatment, and oral prednisone 0.75 mg/kg/day with taper down to 10 mg/day by 16 weeks. Both arms also received mycophenolate mofetil (MMF) 3 g/day in divided doses. The primary endpoints were the percentages of patients with complete renal response (CRR) or partial renal response (PRR) at week 52. A CRR was defined as: (1) normalization of serum creatinine or if the initial creatinine was normal then ≤15% above baseline; (2) inactive urinary sediment; and (3) UPCR <0.5. A PRR was defined as: (1) serum creatinine ≤15% above baseline; (2) no significant worsening of urinary sediment; and (3) 50% improvement in the UPCR, plus UPCR <1.0 if baseline was ≤3.0 or UPCR <3.0 if baseline was >3.0.

The study population’s mean age was ~30 yrs, ~90% female, 28% African-American, 36% Hispanic, 31% white ethnicity; 67% had Class IV LN. The baseline mean UPCR was 4.0 and serum creatinine of 1.0 mg/dL. The mean daily MMF dose was 2.4 g in the placebo and 2.7 g in the RTX group. The results of the study did not show a statistically significant difference in any of the primary or secondary clinical end points. However, there was numerically a higher percentage of responders in the RTX group compared to placebo (57% vs. 46%). In subgroup analyses, there was a trend toward a response in the RTX group among blacks and Hispanics, but statistical significance was not achieved. RTX did have a greater effect on levels of dsDNA and complement at week 52, similar to what was observed in the EXPLORER trial.

Rates of SAEs and infectious SAEs were similar between the two groups (placebo 35% vs. RTX 30% for SAEs; placebo 17% vs. RTX 16% for infectious SAEs). However, neutropenia, leukopenia, and hypotension were more frequent in the RTX group. Two deaths (sepsis and pneumonitis) occurred in the RTX group, and none in the placebo group.

Ocrelizumab

The BELONG trial was a Genentech-sponsored, phase III trial of the humanized anti-CD20 antibody (as opposed to RTX, which is a chimeric anti-CD20 antibody) for lupus nephritis. The trial design was similar to LUNAR, with immunosuppressive medications and high-dose corticosteroids used as background therapy. However, in the BELONG trial, subjects could have been treated with either MMF or CYC at the EuroLupus dosing of 500 mg IV every two weeks for six doses, with plans for treatment over a longer time period of two years; however, the BELONG trial was halted due to serious and opportunistic infection signals detected by the trial’s Data and Safety Monitoring Board in 2010.

Belimumab

Belimumab is a fully human monoclonal antibody against B-lymphocyte stimulator (BLyS), a.k.a. B-cell-activating factor (BAFF), which is part of the tumor necrosis factor (TNF) superfamily. BLyS binds to BLyS receptor 3 (BR3), transmembrane activator, calcium modulator, cyclophilin ligand interactor (TACI), and B-cell maturation antigen (BCMA) on the B-cell surface, which then promotes B-cell survival and differentiation. BAFF has been found to be overexpressed in mouse models of lupus-like disease, and in humans, BAFF levels are elevated and correspond with SLE disease activity.

The BLISS-52 study was a large phase III multicenter, randomized, placebo-controlled study assessing the efficacy and safety of belimumab in SLE. It was designed based on results found in the phase II, dose-escalating, double-blind, placebo-controlled trial, in which subgroup analyses found a modest but
statistically significant benefit of belimumab over placebo only in patients who were serologically active, i.e., had a positive ANA or dsDNA at study entry. The study was performed in 90 centers in 13 countries. Inclusion criteria were: (1) age ≥ 18 years; (2) ACR criteria for SLE; (3) active disease at entry (score ≥ 6 on the Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index [SELENA-SLEDAI]); (4) unequivocally positive ANA (≥ 1:80) or dsDNA (≥ 30 IU/mL); and (5) stable treatment regimen with fixed doses of prednisone (0–40 mg/day), nonsteroidal anti-inflammatory drugs (NSAIDs), or other immunosuppressive agents for the past 30 days. Exclusion criteria were: (1) Severe active lupus nephritis or CNS lupus; (2) pregnancy; and (3) previous treatment with any B-lymphocyte-targeted drug (including RTX), IV CYC within six months of enrollment, and IVIG or high doses of prednisone (>100 mg/day) within three months.

A total of 865 patients were randomized in a 1:1:1 fashion to receive either IV belimumab 1 mg/kg, belimumab 10 mg/kg, or placebo on days 0, 14, 28, and then every 28 days. The primary outcome measure was the percent of subjects at week 52 with ≥ four-point reduction from baseline in SELENA-SLEDAI score, no worsening in physician global assessment (PGA), and no new BILAG A organ domain score or two new BILAG B organ domain scores were compared with baseline at the time of assessment (SLE Response Index [SRI]). Baseline study characteristics of the patients were ~95% female, mean age ~35 years, ~25% white, ~4% African-American, ~40% Asian, ~50% Hispanic or Latino ethnicity, ~30% indigenous American, and average disease duration of ~5 years. Disease manifestations in a majority of subjects were primarily musculoskeletal and mucocutaneous. Mean baseline prednisone dose was ~12 mg/day.

The results showed a statistically significant SRI at 52 weeks for both the low- and high-dose belimumab groups compared to placebo (57.6% for the 10 mg/kg belimumab group vs. 43.6% for the placebo group). Furthermore, these secondary outcomes also were positive for both the low- and high-dose belimumab groups: (1) percent of subjects with four-point reduction from baseline in SELENA-SLEDAI score; (2) no worsening in PGA; (3) no new BILAG A or two new BILAG B at week 52. The proportions of patients with at least a 50% reduction in prednisone dose were significantly greater with belimumab 10 mg/kg at every visit from weeks 24 to 52. In addition, the occurrence of AEs and SAEs were similar between belimumab and placebo groups, including infusion reactions. Nine patients died during the study (three in the belimumab groups from infections, and one in the placebo group from cardiac arrest and sepsis). No malignant diseases were reported.

The BLISS-76 study was the second phase III trial of belimumab for SLE. The trial design was identical to BLISS-52, including the primary end point of SRI at week 52. However, the double-blind study was continued for an additional 24 weeks to see if there was an increased response with time. The SRI at week 52 was again significant in favor of belimumab 10 mg/kg group over placebo (43.2% vs. 33.8%), with a trend toward significance in the 1 mg/kg group.

**Epratuzumab**

Epratuzumab is a humanized monoclonal antibody against CD22, a B-cell-specific surface antigen involved in the regulation of B-cell signaling. An open-label trial in 14 subjects treated with epratuzumab 360 mg/m² every two weeks showed the drug was well-tolerated with ≥ 50% improvement in the total BILAG scores in all 14 patients at some point during the study. Preliminary results from a phase II trial (EMBLEM) demonstrated significant improvements in disease activity and quality of life and decreases in corticosteroid doses compared to placebo in moderate-to-severe SLE. A phase III trial of this agent is still ongoing (www.clinicaltrials.gov identifier NCT00383513).

**Atacicept**

A proliferation-inducing ligand (APRIL) is another member of the TNF super-family, which like BAFF binds to receptors expressed on B cells and plasma cells, and promotes B-cell survival and differentiation. Both BAFF and APRIL bind to TACI on B-cell surfaces. Atacicept is a chimeric molecule, with the extracellular domain of TACI fused to the constant regions of human IgG1 (i.e., IgG-TACI). A phase I study in lupus patients showed subcutaneous atacicept to be well-tolerated. However, a phase II study of atacicept plus mycophenolate in lupus nephritis patients was discontinued due to infectious complications (www.clinicaltrials.gov identifier NCT00573157). A phase II/III study of atacicept in nonrenal lupus patients is ongoing (www.clinicaltrials.gov identifier NCT00624338).
References


ONLINE CME OPPORTUNITIES

Gout: New Treatments for a Familiar Disease
Robyn T. Domsic, MD, and Marc C. Levesque, MD, PhD, from the UPMC Arthritis and Autoimmunity Center, review therapies like febuxostat for the treatment of gout.

Understanding Musculoskeletal Pain: Focus on Fibromyalgia
Rheumatologist Terence W. Starz, MD, discusses the causes, symptoms, and treatment of pain associated with fibromyalgia. This presentation was part of UPMC’s Update in Internal Medicine.

Rheumatoid Arthritis Comparative Effectiveness Research (RACER)
In this recent UPMC Medical Grand Rounds, Marc C. Levesque, MD, PhD, reviews the recognition and management of rheumatoid arthritis, as well as the use of diagnostic criteria in characterizing RA patients in the clinical care setting.

Treatment of Inflammatory Myopathy (Myositis):
Fall 2011 UPMC Rheumatology Grand Rounds
The treatment of myositis is challenging for both internists and rheumatologists, and its rarity and heterogeneity add further complexity. This review by Chester V. Oddis, MD, and Rohit Aggarwal, MD, MSc, discusses conventional and some newer agents used in treating myositis.

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  > Myositis
  > Vasculitis
  > Scleroderma
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