Latest Research in Vasculitis Reviewed

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The term vasculitis encompasses various inflammatory and autoimmune disorders affecting blood vessels. Recent research in several different types of vasculitis was reviewed by Salvatore de Vita, MD, University of Udine, Udine, Italy. Tocilizumab (TCZ), an interleukin (IL)-6 antagonist, which is approved for the treatment of rheumatoid arthritis, has been studied in giant cell arteritis (GCA). In 14 published case studies of TCZ treatment of GCA, 36 of 38 patients (95%) responded. However, whether this represents control or cure of GCA is unclear based on the current data.

The Phase 3 Giant Cell Arteritis Clinical Research study [GiACTA; Unizony SH et al. *Int J Rheumatol* 2013] is a large, double-blind study of TCZ in patients with GCA. For this trial, 250 patients will be enrolled at ~100 centers and randomized into 1 of 4 treatment arms: TCZ 162 mg weekly plus a 6-month prednisone taper (n=100); TCZ 162 mg on alternate weeks plus a 6-month prednisone taper (n=50), placebo plus a 6-month prednisone taper (n=50), or placebo plus a 12-month prednisone taper (n=50). All patients will receive corticosteroid therapy. The primary end point is sustained remission at 52 weeks. The double-blind period will be followed by a 104-week open-label extension. Prof. de Vita stated that he believes that this is the most important ongoing study for GCA.

The double-blind, multicenter Belimumab in Remission of Vasculitis [BREVAS; NCT01663623] trial aims to examine whether targeting the B-cell activating factor (BAFF) with the monoclonal anti-BAFF antibody, belimumab (BEL), will sustain remission in patients with Wegener's granulomatosis polyangiitis (GPA) or microscopic polyangiitis (MPA). BAFF is increased in patients with GPA and targeting this may be effective in patients with an inadequate response to rituximab (RTX). This ongoing, international Phase 3 trial is randomizing patients one of 2 arms: BEL 10 mg/kg intravenously plus oral azathioprine (AZA) 2 mg/kg/day or placebo plus oral AZA 2 mg/kg/day. BEL will be administered on Days 0, 14, 28, and then every 28 days until the end of the study. The primary outcome is the time to first major relapse, as defined by having at least one major item on the Birmingham Vasculitis Activity Score (BVAS).

In the Rituximab in ANCA-Associated Vasculitis study [RAVE; Stone JH et al. *New Eng J Med* 2010], 197 patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) were randomly assigned to either intravenous RTX 375 mg/m^2 of body surface weekly for 4 weeks or to cyclophosphamide (CP) 2 mg/kg/day. All patients received the same glucocorticoid (GC) regimen. In this double-dummy trial, rituximab-treated patients, who were in remission between Months 3 and 6, were switched to AZA 2 mg/kg/day; in the control arm, patients were eligible to switch to AZA 2 mg/kg/day. Disease remission by 6 months was the primary end point. RTX was shown to be non-inferior to CP therapy.

Although the primary end point was met in the RAVE study, approximately 24% of patients did not achieve GC-free remission at 6 months. Relapsing AAV was found to be worse than the newly diagnosed disease, with more frequent and severe flares in Months 1 to 6. For patients with proteinase (PR) 3 antibodies, remission was less frequent than for those testing positive for myeloperoxidase (MPO) antibodies. In a subsequent publication, RTX was shown to be superior to CP in relapsing disease [Specks U et al; *New Eng J Med* 2013]. Prof. de Vita said that CP appears to be the preferred induction therapy in new AAV patients. However, RTX should be used first in patients with a contraindication to CP therapy or younger patients for whom fertility is a concern.

How long to continue immunosuppressive treatment remains unclear, but the current thinking is at least 18 months, with long-term maintenance for all patients with GPA, when possible. Maintenance with RTX has been investigated in several different studies. Overall, it appears that maintenance with RTX is more effective than is initiating treatment at the time of relapse, though whether RTX should always be used for maintenance is still an unanswered question. Although

Peer-Reviewed Highlights From the

European League Against Rheumatism 2014 Annual Scientific Meeting

June 11-14, 2014
Paris, France

there are currently no adequate biomarkers for relapse, two have been recently suggested: The presence of Fc receptor-like protein 5 (RLP5) mRNA at baseline levels predicted complete response to RTX but not CP for patients from the RAVE trial [Owczarczy K et al. EULAR 2014 (OP0232)] and detectable naïve B cells at sites of B-cell repopulation was indicative of no or low relapse [Yusof MY et al. EULAR 2014 (OP0231)].

The preliminary classification criteria for cryoglobulinemic vasculitis (CV) [De Vita S et al. *Ann Rheum Dis* 2011] have been validated by 643 cases from 23 centers in Italy, France, Spain, Greece, Slovenia, Egypt, and Japan [Quartuccio L et al. *Rheumatology (Oxford)* 2014]. The classification criteria are easy to use and were developed by specialists from different branches of medicine.

Prof. de Vita noted that CV in patients with Sjogren's syndrome and those with chronic hepatitis C virus (HCV) infection differ biologically. CV in Sjogren's syndrome has been shown to be a predictive marker for lymphoma [Quartuccio L et al. *J Autoimmun* 2014]. Prof. de Vita's group treated 30 patients with severe HCV-related CV with RTX for >2 years, and concluded that long-term RTX monotherapy was safe and effective, with a low rate of hypogammaglobulinemia. Relapses with life-threatening complications such as intestinal vasculitis were uncommon (7%) [Quartuccio L et al. EULAR 2014 (OP0228)].

Prof. de Vita reviewed a recently published case of a patient with CV and Sjogren's syndrome [De Vita S et al. *Clin Exp Rheumatol* 2014]. A parotid gland biopsy indicated the presence of low-grade, mucosa-associated lymphoid tissue lymphoma and B-cell non-Hodgkin lymphoma. The patient had elevated levels of BAFF. The patient did not respond to sequential treatment with RTX, a prolonged course of RTX with high-dose GC, or BEL. However, the patient was effectively treated with another course of RTX given 49 days after the last infusion of BEL. The lymphoma and CV disappeared, and the rheumatoid factor and BAFF levels returned to normal. This represents a potential novel strategy for further research, he stated.