Biologic agents in systemic vasculitis

The treatment of systemic necrotizing vasculitis has made great strides in both efficacy and outcomes. Standard therapies, however, are associated with numerous side effects, and not all patients will respond to conventional immunosuppression. These realities have prompted the search for safer and more efficacious treatments, most notably among biologic agents. For example, the role of TNF-α in the pathophysiology of several vasculitides has led to the investigation of targeted inhibitors of this cytokine, albeit with mixed results. There have been some disappointing results in the area of giant cell arteritis and Wegener's granulomatosis (granulomatosis with polygiitis), but anti-TNF therapy has shown promise in the treatment of Takayasu's arteritis, although additional trials to demonstrate its efficacy are required. Anti-B-cell therapy seems to be the most promising advance in the management of these diseases. Complete and partial responses have been seen in both primary and secondary mixed cryoglobulinemic vasculitis. Recent trials have demonstrated that rituximab is effective for the treatment of Wegener's granulomatosis and microscopic polyangiitis. These trials have, however, raised concerns regarding the long-term safety of these agents. The future holds promise for additional targeted therapies with improved patient response and fewer side effects.

Charles F Henderson[1] & Philip Seo[†1]

[1]5501 Hopkins Bayview Circle, JHAAC, Room 1B.1A, Johns Hopkins University Division of Rheumatology, MD 21224, USA
[†]Author for correspondence:
Tel.: +1 410 550 6825
Fax: +1 866 752 7405
seo@jhmi.edu

The systemic necrotizing vasculitides are a broad family of conditions characterized by injury or destruction of the blood vessel walls by inflammatory cells (TABLE 1) [1]. Untreated, these diseases can be devastating, with high rates of morbidity and mortality. Over the past few decades, the use of high-dose glucocorticoids and cytotoxic agents has dramatically improved the prognosis of these patients, leading to remission in many patients who, in the past, would have succumbed to their illnesses. However, current standard therapies, are far from ideal. Some patients with systemic vasculitis will not respond to conventional immunosuppression; a far greater number will relapse, or develop morbidity as a direct result of the drugs used to treat the disease [2]. This was illustrated in a cohort of 158 granulomatosis with polyangiitis (GPA; Wegener's granulomatosis) patients treated with a combination of cyclophosphamide and prednisone. In this cohort, 91% of subjects demonstrated a marked improvement in their disease and 75% had complete remission. It was observed, however, that 86% experienced significant morbidity, 50% relapsed within 5 years and 13% died as a result of either their disease or adverse events associated with therapy [3].

For this reason, despite the great strides that have been made in the treatment of the systemic vasculitides, there is clearly a need for therapies with better efficacy and fewer adverse effects. The advent of biologic therapy has resulted from advances in our understanding of the pathogenesis of autoimmune diseases, allowing increasingly specific, targeted therapies to be developed for clinical use. In broad strokes, these therapies may be classified as falling into one of two distinct approaches: anticytokine strategies, and drugs that target specific subsets of immune cells. The ultimate goal of these therapies is to target pathways that contribute to disease initiation and propagation, while avoiding the disruption of pathways that are necessary for the health of the patient. Although there has been widespread enthusiasm for the use of biologic agents to treat systemic vasculitis, the literature supporting this approach has only recently become robust. This article will focus on the use of the two most popular classes of biologic agents.

Anti-TNF therapy

TNF-α, along with its sister compound lymphotoxin (or TNF-β), is a proinflammatory cytokine produced by a variety of cells, but primarily by lipopolysaccharide-stimulated macrophages and monocytes, as well as by T lymphocytes. TNF-α has receptors on many cells, including macrophages and monocytes, thereby allowing

future medicine part of **fsg**

Table 1. Names and definitions of vasculitis adopted by the Chapel Hill Consensus Conference (NC, USA) on the nomenclature of systemic vasculitis.

Diagnosis	Description
Granulomatosis with polyangiitis	Granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small-to-medium sized vessels (e.g., capillaries, venules, arterioles and arteries). Necrotizing glomerulonephritis is common
Giant cell arteritis	Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. Often involves the temporal artery. Usually occurs in patients older than 50 years of age and is often associated with polymyalgia rheumatica
Takayasu's arteritis	Granulomatous inflammation of the aorta and its major branches. Usually occurs in patients younger than 50 years of age
Microscopic polyangiitis	Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e., capillaries, venules or arterioles). Necrotizing arteritis involving small- and medium-sized arteries may be present Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs
Essential cryoglobulinemic vasculitis	Vasculitis, with cryoglobulin immune deposits, affecting small vessels (i.e., capillaries, venules or arterioles), and is associated with cryoglobulins in serum. Skin and glomeruli are often involved
Data taken from [57].	

it to stimulate its own production and release. It has been shown to be a key cytokine in the host inflammatory response [4]. Its actions are modulated through various mechanisms, which include adhesion molecule expression, proinflammatory cytokine release, synthesis of chemokines, inhibition of regulatory T cells and activation of a variety of immune cells [5]. More specifically, in GPA, TNF-α has the effect of priming neutrophils for the degranulating effects of antineutrophil cytoplasmic autoantibodies (ANCA), which may be central to the pathogenesis of GPA and microscopic polyangiitis [6].

TNF-α is increasingly being implicated in the pathophysiology of autoimmune diseases, including systemic vasculitis, and therefore provides an interesting target for the treatment of these diseases. There are presently five TNF-α inhibitors available. Infliximab is a chimeric monoclonal antibody composed of a murine variable region attached to human Fc (constant) portion of IgG κ. It is administered as an infusion every 4–6 weeks. Adalimumab is a fully humanized monoclonal antibody and is dosed every second week as a subcutaneous injection. Etanercept is a dimeric fusion protein composed of two extracellular TNF-receptor domains bound to the Fc portion of human IgG and is injected twice weekly. It effectively binds soluble TNF, thereby blocking TNF-receptor activation. Two newer TNF inhibitors, certolizumab and golimumab have been genetically engineered for improved TNF affinity and less complement activation [7,8].

The three most studied TNF inhibitors are strikingly different in their binding characteristics and ability to induce apoptosis [9]. Unlike infliximab and adalimumab, etanercept does not induce apoptosis in cells that express transmembrane TNF, which has been suggested as a possible reason for differences in efficacy in certain autoimmune diseases such as Crohn's disease. Because of the purported involvement of TNF-α in the pathogenesis of granulomatous disease [10], hopes have been raised that it might be an effective treatment for the vasculitides characterized by granulomatous inflammation, such as giant cell arteritis (GCA), Takayasu arteritis (TAK) and GPA.

Safety concerns have been raised for TNF inhibition, primarily related to infection, malignancy and cardiovascular disease. An analysis of Medicare beneficiaries enrolled in the Pharmaceutical Assistance Contract for the Elderly in Pennsylvania, USA demonstrated that among almost 16,000 patients with rheumatoid arthritis over the age of 65 years old, treatment with TNF inhibitors did not lead to an increase in serious bacterial infections when compared with patients who had received treatment with methotrexate [11]. However, a review of three European registries suggested an increased risk of several types of infections among patients treated with TNF inhibitors, including tuberculosis [12]. The role of TNF in tumor surveillance has raised concerns for an increased risk of solid tumors due to TNF inhibition. A recent analysis of the Lombardy Rheumatology Network (LORHEN) registry demonstrated no increase in the overall cancer risk beyond that found in the general population, although the risk of hematological cancers was significantly increased, particularly among men over the age of 65 years old [13]. This finding must be balanced against the increased risk of lymphoma

that may be inherent to certain inflammatory diseases such as rheumatoid arthritis [14]. Despite fears of the effects of TNF inhibition on the heart, an analysis of the cardiovascular risk in rheumatoid arthritis patients treated with TNF inhibitors demonstrated no difference in cardiovascular events when compared with patients treated with conventional disease-modifying antirheumatic drugs [12].

■ GCA

Giant cell arteritis is a granulomatous vasculitis that affects large- and medium-sized arteries, including the aorta and its major branches. The standard treatment for GCA is glucocorticoids, but unfortunately 80% of treated patients ultimately have a single significant adverse effect of glucocorticoid therapy, while 60% have two or more adverse effects [15], necessitating an alternative treatment for this disease. TNF is one of several cytokines linked to the vascular injury found in GCA [16], and encouraging reports of success with infliximab [17–19] initially gave hope that TNF blockade might be used successfully for treatment of this disease.

In 2007, a randomized, controlled trial was conducted [15] in which patients with newly diagnosed GCA who had achieved remission with glucocorticoid therapy were randomized to receive adjunctive therapy with infliximab. A total of 44 subjects were enrolled, and they were randomized in a 2:1 ratio to receive infliximab 5 mg/kg or placebo prior to glucocorticoid taper. This trial was terminated at week 22, because interim analysis demonstrated no significant difference in the percentage of patients successfully tapered off of glucocorticoids (71 vs 56%, though the difference did not reach clinical significance). Moreover, subjects randomized to receive treatment with infliximab had a higher infection rate. Because of this experience, TNF-α inhibitors are not routinely used for the treatment of GCA.

■ GPA

The majority of information available regarding the use of TNF-α inhibition for the treatment of the ANCA-associated vasculitides has been extrapolated from studies of GPA, which is a systemic inflammatory disorder characterized by the presence of a small- and medium-vessel vasculitis and the presence of necrotizing granulomatous inflammation, primarily of the upper and lower respiratory tract. The Wegener's Granulomatosis Etanercept Trial (WGET) [20] was a double-blind study in which 180 patients

with GPA were randomized to receive etanercept or placebo in addition to standard-of-care therapies to determine if etanercept was effective for remission maintenance. Standard induction therapy with prednisone and cyclophosphamide (for severe disease) or methotrexate (for limited disease) was given to all patients, followed by randomization to either subcutaneous etanercept 25 mg twice weekly or placebo. Glucocorticoids were tapered within 6 months. The primary end point was sustained remission, which was defined as the absence of disease activity off of glucocorticoids after 6 months of therapy. There was no increase in the rate of cytopenias, infections, congestive heart failure, or venous thrombotic events associated with the use of etanercept. Although the rate of solid tumor malignancies was slightly higher than expected among patients who had received treatment with both cyclophosphamide and etanercept, this increased risk did not persist over time. This trial demonstrated that the use of etanercept had no impact on the rate of achieving sustained remission (69% for etanercept vs 75% for placebo, p = nonsignificant).

Doubts have been raised about the ability to extrapolate these results to other TNF inhibitors given the differences in their mechanism of action, as discussed above. Case series and open label trials have raised hope that other TNF inhibitors might be effective [21–25]. Infliximab, for example, may be more effective for the treatment of GPA [26,27]. Unfortunately, these questions are difficult to answer definitively with the available data.

■ TAK

Takayasu's arteritis is a rare, chronic, systemic panarteritis of unknown etiology characterized by granulomatous inflammation of the aorta and its major branches (occasionally including the pulmonary arteries as well) that typically presents in women before the age of 40 years old and results in progressive fibrosis and stenosis of the affected vessel wall and, less commonly, in aneurysm formation [28–30]. Glucocorticoids and methotrexate have been the mainstays of treatment [31]. There have been several case series [32,33] and case reports [34–36] that have shown clinical benefit of TNF inhibition for TAK. Hoffman *et al.* published a case series of 15 patients with treatment-resistant TAK who were treated with either infliximab or etanercept for disease relapse. Prior to institution of anti-TNF therapy, the median prednisone dose among study subjects was 20 mg (range: 12.5–40 mg); after introduction of anti-TNF therapy, the median

prednisone dose dropped to 0 (range: 0–20 mg). Of these 15 patients, 93% demonstrated marked improvement and 67% experienced a glucocorticoid-free sustained remission for up to 3 years of follow-up [37]. One patient experienced an injection site reaction, and there were two infections reported in patients (i.e., herpes zoster and disseminated histoplasmosis) that might be attributable to TNF inhibition. Randomized, controlled trials are necessary to further characterize the effectiveness of TNF inhibition and before any recommendations can be made for its use in TAK. There are also occasional reports of TAK developing in a patient while undergoing TNF inhibition for other diseases [38].

■ Other diseases

The effect of TNF inhibition on Behçet's disease is complicated by the diverse manifestations of the disease and the lack of extensive randomized trials. Much of what is known has been obtained from case reports and case series. Keino *et al.* retrospectively evaluated 14 patients with ocular Behçet's disease who received infliximab (5 mg/kg at 0, 2, and 6 and then every 8 weeks) with a median follow-up of 19 months. Over half of patients (57%) experienced no disease flares at 12 months, and the frequency of attacks was reduced compared with the 6 month period prior to infliximab use. Both the background retinal disease and visual acuity improved in the majority of patients (79 and 93%, respectively) over a 12 month period. With the exception of two infusion reactions, no serious adverse events were reported. Of specific interest, although six patients were purified protein derivative positive and received isoniazid prophylaxis, no patients developed tuberculosis during the study period. This study suggests that infliximab is effective in the treatment of uveoretinitis associated with Behçet's disease, although randomized control trials with longer follow-up periods are not available at this time [39]. TNF inhibition may be a valuable alternative for Behçet's patients who have proven refractory to more commonly used treatments. TNF has been suggested as an important cytokine in the active phase of coronary disease in mouse models of Kawasaki disease [40]. Clinically, infliximab has been used for the treatment of Kawaski's disease that has failed to respond to intravenous immunoglobulin [41]. There is very little known about the use of TNF inhibition in Churg–Strauss syndrome, polyarteritis nodosa, idiopathic leukocytoclastic angiitis, or cryoglobulinemic vasculitis.

Anti-B-cell therapy

B lymphocytes are well known as cells that produce antibodies and are therefore key players in autoimmune-mediated disease. However, their activities are more diverse, and they are also known to act as antigen-presenting cells, cytokine producing cells and are involved in costimulation of T cells via membrane associated molecules [42]. CD20 is a membrane protein that appears in the late pre-B-cell stage and persists until the differentiation of B cells into plasma cells. Rituximab is a monoclonal antibody that targets the CD20 marker present on B cells. B-cell forms that lack CD20, such as plasma cells, are unaffected by rituximab. Rituximab has been used effectively for the treatment of B-cell lymphoma [43]. B-cell depletion associated with such treatment raised the hope that rituximab might be useful for patients with autoimmune diseases driven by autoantibody production. Diseases that have been investigated in this regard include cryoglobulinemic vasculitis and ANCA associated vasculitis.

■ Cryoglobulinemic vasculitis

Cryoglobulinemic vasculitis is an antigen-antibody complex disease characterized by the presence of antibodies that precipitate at low temperature (cryoglobulins). There are three classes of cryoglobulins. Type I is a monoclonal antibody. Type II (mixed cryoglobulins) is characterized by both polyclonal γ globulins as well as a monoclonal (usually IgM) antibody with rheumatoid factor activity. Type III is composed of only polyclonal antibodies. The clinical triad of purpura, weakness and arthralgias is known as 'Meltzer's triad' [44], but the disease often includes the involvement of the peripheral nervous system and kidneys. In one investigation, the vast majority of patients with renal involvement had type II cryoglobulinemic vasculitis (74%), and 87% of patients with type II cryoglobulins were found to be hepatitis C positive [45]. Mixed cryoglobulinemic vasculitis is classified as either 'essential,' that is, with no associated cause, or 'secondary' if there is an associated condition. Such conditions include connective tissue disorders, lymphoproliferative disorders, chronic infections, noninfectious hepatobiliary diseases or immunologically mediated glomerular disease [45].

Despite its name, we now know that many cases of 'essential' cryoglobulinemic vasculitis are induced by chronic hepatitis C infection. The hepatitis C virus infects B cells, resulting in clonal expansion and stimulation of autoantibody

production [46]. Eradication of hepatitis C with interferon and ribavirin has been tried, but is often ineffective [45], particularly with genotype 1, and interferon has many side effects. On the other hand, treatments such as cyclophosphamide and plasmapheresis are generally reserved for life- or organ-threatening disease.

The rationale behind anti-B-cell therapy in mixed cryoglobulinemic vasculitis includes the presence immune complex deposition as the cause of symptoms in the so-called 'hepatitis C virus syndrome', in which chronic stimulation by hepatitis C virus induces the production of cryoglobulins by infected B cells [46]. A recent literature review compiled a total of 142 patients with cryoglobulinemic vasculitis treated with rituximab; 83% of the patients were hepatitis C positive [47]. Most of these patients were treated after lack of efficacy of other treatments. Of these patients, 60% demonstrated a complete response to treatment and 23% had a partial response. Neuropathy and cutaneous vasculitis were the most common clinical features. In this article, patients with type I cryoglobulins were less responsive to therapy with rituximab. Untoward effects, including serum sickness, flares of vasculitis, serious infections, thrombosis of the retinal artery and cold agglutinin disease, were noted in 27/142 (19%) of patients. Three factors were found to be associated with increased risk of side effects: high complement activation, higher rituximab doses and elevated level of cryoglobulins.

ANCA-associated vasculitis

Standard treatment of ANCA-associated vasculitis generally consists of a remission induction regimen that includes the use of cyclophosphamide and high-dose glucocorticoids, followed by a remission maintenance regimen using methotrexate, azathioprine or another, less toxic, antimetabolite therapy. The advent of these drugs has led to a dramatic improvement in the prognosis of patients with these diseases, and achieving remission has become commonplace. In fact, remission rates of greater than 70% are now commonly seen. Despite these advances, conventional immunosuppression fails to achieve remission in a substantial minority of patients; furthermore, many patients either have relative contraindications to cytotoxic agents, or will relapse despite appropriate therapy. This highlights a need for alternate therapies. While TNF inhibition may still play a role for a select subset of patients with these diseases, it is clearly an inadequate solution [20].

B-cell activation is believed to play an important role in the pathogenesis of the ANCA-associated vasculities [48], and autoantibodies may have a pathogenic role in these diseases, perhaps by activating TNF-primed neutrophils, leading to premature degranulation and resultant endothelial damage. It is also interesting to note that patients who develop undetectable ANCA titers after treatment are less likely to experience disease relapse than patients who remain ANCA positive [49]. Given the role of B cells and antibody production in the pathogenesis of this disease, it is attractive to consider rituximab as a potential treatment. Rituximab may also exert other effects on the immunopathogenesis of these diseases, possibly by altering B-cell and regulator T-cell function [50].

Rituximab has been used successfully for the treatment of the ANCA-associated vasculitides in both open label studies [51–53] and in cohort studies [54]. These early successes led to two landmark studies that support the use of B-cell therapies for these diseases. In 2010, two randomized controlled trials examined the use of rituximab for patients with ANCA-associated vasculitis. There were significant differences in the patient population and in the study design, but both raise hopes for future use of rituximab in this disease population.

RAVE

The Rituximab for ANCA-Associated Vasculitis (RAVE) trial [55] was a multicenter, randomized, double-blind, double-dummy, noninferiority study of patients with severe GPA and microscopic polyangiitis. In this trial, 197 patients with either new or relapsing disease were randomized in a 1:1 ratio to receive remission-induction therapy with either oral cyclophosphamide (2 mg/kg/day) or rituximab (375 mg/m² weekly for 4 weeks). Both groups received the same glucocorticoid regimen (i.e., up to 3 pulses of 1 g of intravenous methylprednisolone, and then prednisone 1 mg/kg/day, followed by a protocolized taper). Approximately 50% of subjects enrolled in this trial had significant renal disease and 28% had alveolar hemorrhage at trial entry, although patients were not eligible for this trial if their serum creatinine exceeded 4 mg/dl or if the patient required mechanical ventilation during the study period. The primary end point of this study was achievement of remission at 6 months in the absence of glucocorticoids.

In this trial, 63/99 patients in the rituximab group (64%) achieved the primary end point compared with 52/98 patients in the control

group (53%), demonstrating that rituximab was noninferior to rituximab for remission induction. Subgroup analysis demonstrated that rituximab was superior to cyclophosphamide among patients with relapsing disease (67 vs 42%, p = 0.01). In this trial, rituximab was as effective as cyclophosphamide for the treatment of subjects with alveolar hemorrhage or glomerulonephritis, with no difference in the frequency of adverse events.

These findings were especially impressive given the relatively rapid glucocorticoid taper (which occurred over 6 months) and strict remission criteria (which required the complete absence of disease activity and no use of chronic glucocorticoids) [50]. Because the study focused on remission induction, the effects of retreatment with rituximab could not be addressed. Also, the results cannot necessarily be extrapolated to patients with life-threatening manifestations, since they were excluded from this trial by design. It was surprising that there was no difference found in adverse effects between the two groups; this implies that the majority of adverse events experienced during the first 6 months of treatment are mainly owing to the use of high-dose glucocorticoids. In addition, although 97% of the rituximab patients had B-cell depletion, 4/5 (80%) of the patients without B-cell depletion still reached the primary end point, suggesting that a second mechanism may have contributed to the effectiveness of treatment.

This trial demonstrates that rituximab is not inferior to cyclophosphamide in the induction of remission in patients with new onset GPA or microscopic polyangiitis, and may be superior to cyclophosphamide in patients with relapsing disease. The significance of these findings may ultimately change the way that patients with ANCA-associated vasculitis are treated in the future. However, longer term follow-up will be necessary to answer questions regarding long-term efficacy and risk.

RITUXVAS

The Randomized Trial of Rituximab Versus Cyclophosphamide in ANCA-Associated Vasculitis (RITUXVAS) trial [56] was a randomized, open-label study that looked at the effectiveness of rituximab for the treatment of 44 patients with new diagnoses of ANCA-associated glomerulonephritis. Subjects were randomized in a 3:1 ratio, stratified by age, diagnosis and baseline renal function. The rituximab group (33 patients) received standard dosing of rituximab (375 mg/m² weekly for 4 doses) as well as two intravenous cyclophosphamide pulses (15 mg/kg) with the first and third rituximab

doses. A third dose of cyclophosphamide was permitted if remission had not been achieved after 6 months of therapy. No maintenance therapy was given in this group. The control group (11 patients) received intravenous cyclophosphamide monthly for 3–6 months followed by azathioprine for remission maintenance. Both groups received up to 2 g of methylprednisolone; some subjects also underwent plasmapheresis. The primary end points were sustained remission at 12 months and severe adverse effects. Remission was defined as the absence of disease activity for 2 months and relapse was defined as any disease activity after remission had been attained.

In this trial, 25/33 (76%) of patients in the rituximab group had a sustained remission at 12 months as opposed to 9/11 (82%) in the cyclophosphamide group. Severe adverse effects were noted in 14/33 (42%) of the rituximab patients and 4/11 (36%) of patients in the control group. A total of eight patients died, six of whom had been randomized to receive rituximab therapy. As in the RAVE study, it was surprising that the adverse effects were not lower in the rituximab group as had been expected. The authors noted that the deaths from infection all occurred early in the treatment course and suggested that this may have been the result of cyclophosphamide exposure that occurred early in the treatment protocol.

RITUXVAS versus RAVE

There are several differences between the two studies (TABLE 2). RITUXVAS patients all had significant renal disease while only half of the RAVE patients had glomerulonephritis. However, subgroup analysis of the RAVE trial indicates that rituximab was as effective as cyclophosphamide for this subset of patients. At the time that RITUXIVAS was designed, it was not clear that rituximab alone would be adequate to treat patients with ANCA-associated vasculitis. RITUXIVAS therefore employed a hybrid schema in which subjects randomized to receive rituximab also received several doses of cyclophosphamide, whereas analogous subjects in RAVE were treated with rituximab alone. This raises an important question as to whether cyclophosphamide should be given with rituximab for induction of remission [50]. Moreover, the relatively short follow-up employed by both of these trials makes it difficult to comment on the long-term efficacy of this treatment strategy.

Finally, it is notable that a treatment strategy that minimizes or eliminates exposure to cytotoxic agents was not associated with a dramatic

Table 2. Demographics of patients enrolled in RAVE and RITUXVAS.		
	RAVE	**RITUXVAS**
Median age (years)	54	68
Male (%)	46	52
Disease process		
Granulomatosis with polyangiitis (%)	75	55
Microscopic polyangiitis (%)	24	36
Renal involvement (%)	66	100
ANCA positivity		
PR3-ANCA (%)	66	61
MPO-ANCA (%)	33	39
ANCA: Antineutrophil cytoplasmic autoantibodies; RAVE: Rituximab for ANCA-associated vasculitis; RITUXVAS: Rituximab versus cyclophosphamide in ANCA-associated vasculitis. Data taken from [55,56].		

decrease in adverse events. These questions will need to be addressed before rituximab is ready to replace cyclophosphamide for the treatment of these diseases.

Future perspective

The 1970s witnessed a revolution in the management of patients with systemic vasculitis. The use of cytotoxic agents for the management of diseases like GPA was transformative, beginning an era in which these diseases could be managed as chronic conditions. We now stand poised at the cusp of a second revolution, this one ushered by the advent of biologic agents, which may allow us to replace indiscriminate agents with a more targeted approach. The potential benefits of this approach are clear: first, conventional immunosuppression is associated with a wide variety of untoward effects, which compound with chronic use, and second biologic therapies provide us with the opportunity to target specific elements of the immune system, while leaving other elements of immunity intact.

We have just begun to explore the potential of this new class of agents for the treatment of systemic vasculitis. Clearly, the greatest success belongs to anti-B-cell strategies, which have already altered the standard-of-care for patients with GPA and microscopic polyangiitis. The next decade will test the boundaries of this new strategy, identifying which patients gain the greatest benefit from this new class of agents. At the same time, with the success of rituximab for the management of patients with this disorder, the next decade will also witness the spread of this strategy to other disorders more far afield. This may eventually lead to randomized clinical trials of other forms of ANCA-associated vasculitis such as the Churg–Strauss syndrome, and other

diseases such as cryoglobulinemic vasculitis, where the need for novel approaches is great, particularly among patients who are not candidates for antiviral treatments. The great limitation of rituximab is that it is not a cure; some patients with GPA or microscopic polyangiitis may need to be retreated following initial treatment. New anti-CD20 agents, or agents that attack different B-cell precursors, may overcome this hurdle, and may enable even longer periods of remission.

The potential of this approach is just beginning to be explored for patients with systemic vasculitis. Abatacept, an inhibitor of T-cell costimulation, is being explored as a potential treatment for GPA, TAK, and GCA. The need for alternate agents for GCA is particularly great because of how poorly the elderly tolerate the high doses of steroids required to achieve remission. It is possible that some of these newer agents, such as anti-IL-6, might enable us to treat patients with shorter courses of lower dose glucocorticoids, which may in turn result in a substantial long-term benefit for these patients.

Executive summary

Anti-TNF therapy
- TNF-α is a proinflammatory cytokine implicated in a variety of autoimmune disorders.
- There are five commercially available anti-TNF-α drugs: etancercept, infliximab, adalimumab, cerolizumab and golimumab.
- Although all of these compounds are directed against TNF-α, they may not be equally effective for all indications.

Anti-TNF therapy & giant cell arteritis
- Giant cell arteritis is a large vessel vasculitis that, untreated, can lead to blindness.
- Glucocorticoids are the only standard therapy for this form of vasculitis.
- A randomized controlled trial of 44 subjects demonstrated no benefit to adjunctive therapy with infliximab 5 mg/kg.
- Despite promising case reports and a plausible mechanism, anti-TNF-α therapy does not seem to be effective for this diagnosis.

Anti-TNF therapy & granulomatosis with polyangiitis (Wegner's syndrome)
- Granulomatosis with polyangiitis is characterized by the presence of a small- and medium-vessel vasculitis, and the presence of granulomatous inflammation, primarily of the respiratory tract.
- TNF is critical to granuloma formation.
- The Wegener's granulomatosis etanercept trial (WGET) demonstrated no benefit to adjunctive etanercept for a variety of end points, including remission maintenance.
- Owing to differences in mechanism, WGET does not completely rule out the possibility that other anti-TNF agents might be more effective for the treatment of antineutrophil cytoplasmic autoantibodies (ANCA)-associated vasculitis.

Anti-TNF therapy & Takayasu's arteritis
- Takayasu's arteritis is a large vessel vasculitis that predominantly affects young women, not necessarily of Asian ancestry.
- Methotrexate is a standard therapy for Takayasu's arteritis, but is often not effective.
- One case series has demonstrated that patients with Takayasu's arteritis may respond to infliximab or etanercept when they have failed conventional immunosuppression.

Anti-B-cell therapy
- Monoclonal antibodies to CD20 induce apoptosis of B-cell precursors.
- Rituximab, an anti-CD20 monoclonal antibody, has been effective for the treatment of several autoimmune diseases, such as idiopathic thrombocytopenia purpura.

Anti-B-cell therapy & cryoglobulinemic vasculitis
- Cryoglobulinemic vasculitis is commonly associated with chronic hepatitis C infection.
- Although antiviral therapy would be ideal in theory, many patients either cannot tolerate treatment or do not respond.
- In a case series, 83% of subjects with cryoglobulinemic vasculitis will have some response to rituximab.

Anti-B-cell therapy & ANCA-associated vasculitis
- B-cell activation is central to the pathogenesis of granulomatosis with polyangiitis and microscopic polyangiitis.
- The Rituximab in ANCA associated Vasculitis (RAVE) trial demonstrated that rituximab was noninferior to cyclophosphamide for achieving remission in patients with granulomatosis with polyangiitis and microscopic polyangiitis.
- The RITUXIVAS trial demonstrated that for patients with newly diagnosed ANCA-associated glomerulonephritis, rituximab was not superior to cyclophosphamide.
- Neither trial demonstrated significant reduction in adverse events, which may be owing to the short length of follow-up, or because the majority of adverse events early in the disease course are owing to the high-dose glucocorticoids used to treat these diseases.

Bibliography

Papers of special note have been highlighted as:
- of interest
- of considerable interest

1   Roane DW, Griger DR. An approach to diagnosis and initial management of systemic vasculitis. *Am. Fam. Physician* 60(5), 1421–1430 (1999).

2   Little MA, Nightingale P, Verburgh CA. Early mortality in systemic vasculitis. relative contribution of adverse events and active vasculitis. *Ann. Rheum. Dis.* 69, 1036–1043 (2010).

3   Hoffman GS, Kerr GS, Leavitt RY *et al.* Wegener's granulomatosis. An analysis of 158 patients. *Ann. Intern. Med.* 116(6), 488–498 (1992).

4   Vassalli P. The pathophysiology of tumor necrosis factors. *Annu. Rev. Immunol.* 10, 411–452 (1992).

5   Chung SA, Seo P. Advances in the use of biologic agents for the treatment of systemic vasculitis. *Curr. Opin. Rheumatol.* 21, 3–9 (2009).

6   Aries PM, Lamprecht P, Gross WL. Biological therapies: new treatment options for ANCA-associated vasculitis? *Expert Opin. Biol. Ther.* 7(4), 521–533 (2007).

7   Nesbitt A, Fossati G, Bergin M *et al.* Mechanism of action of certolizumab pegol (CDP870): *in vitro* comparison with other anti-tumor necrosis factor agents. *Inflamm. Bowel Dis.* 13, 1323–1332 (2007).

8   Shealy D. Characterization of golimumab (CNTO 148), a novel monoclonal antibody specific for human TNFα. *2007 ACR Poster Pres.* (2007).

9   Brande JMVD, Braat H, Brink GRVD *et al.* Infliximab but not etanercept induces apoptosis in lamina propria T-lymphocytes from patients with Crohn's disease. *Gastroenterology* 124, 1774–1785 (2003).

10 Buonuomo PS, Bracaglia C, Campana A *et al.* Infliximab therapy in pediatric Takayasu's arteritis: report of two cases. *Rheumatol. Int.* 31(1), 93–95 (2011).

11 Schneeweiss S, Setoguchi S, Weinblatt ME *et al.* Anti-tumor necrosis factor α therapy and the risk of serious bacterial infections in elderly patients with rheumatoid arthritis. *Arthritis Rheum.* 56(6), 1754–1764 (2007).

12 Zink A, Askling J, Dixon WG, Klareskog L, Silman AJ, Symmons DP. European biologicals registers: methodology, selected results and perspectives. *Ann. Rheum. Dis.* 68, 1240–1246 (2009).

13 Pallavicini FB, Caporali R, Sarzi-Puttini P *et al.* Tumour necrosis factor antagonist therapy and cancer development: analysis of the LORHEN registry. *Autoimmun. Rev.* 9, 175–180 (2010).

14 Heldmann F, Dybowski F, Saracbasi-Zender E, Fendler C, Braun J. Update on biologic therapy in the management of axial spondyloarthritis. *Curr. Rheumatol. Rep.* 12, 325–331 (2010).

15 Hoffman GS, Cid MC, Rendt-Zagar KE *et al.* Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis. *Ann. Intern. Med.* 146(621–630), (2007).

16 Martinez-Taboada VM, Alvarez L, RuizSoto M, Marin-Vidalled MJ, Lopez-Hoyos M. Giant cell arteritis and polymyalgia rheumatica: role of cytokines in the pathogenesis and implications for treatment. *Cytokine* 44, 207–220 (2008).

17 Cantini F, Niccoli L, Salvarani C, Padula A, Olivieri I. Treatment of longstanding active giant cell arteritis with infliximab: report of four casses. *Arthritis Rheum.* 44(12), 2932–2935 (2001).

18 Andonopoulos AP, Meimaris N, Daoussis D, Bounas A, Giannopoulos G. Experience with infliximab (anti-TNFα monoclonal antibody) as monotherapy for giant cell arteritis. *Ann. Rheum. Dis.* 62, 1116 (2003).

19 Tan A, Holdsworth J, Pease C, Emery P, McGonagle D. Successful treatment of resistant giant cell arteritis with etanercept. *Ann. Rheum. Dis.* 62, 373–374 (2003).

20 Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. *N. Engl. J. Med.* 352(4), 351–361 (2005).

21 Josselin L, Mahr A, Cohen P *et al.* Infliximab efficacy and safety against refractory systemic necrotising vasculitides: long-term follow-up of 15 patients. *Ann. Rheum. Dis.* 67, 1343–1346 (2008).

22 Lamprecht P, Voswinkel J, Lilienthal T *et al.* Effectiveness of TNF–α blockade with infliximab in refractory Wegener's granulomatosis. *Rheumatology* 41, 1303–1307 (2002).

23 Booth AD, Jefferson HJ, Ayliffe W, Andrews PA, Jayne DR. Safety and efficacy of TNF α blockade in relapsing vasculitis. *Ann. Rheum. Dis.* 61, 559 (2002).

24 Bartolucci P, Ramanoelina J, Cohen P *et al.* Efficacy of the anti-TNF-α antibody infliximab against refractory systemic vasculitides: an open pilot study on 10 patients. *Rheumatology* 41, 1126–1132 (2002).

25 Booth A, Harper L, Hammad T *et al.* Prospective study of TNFα blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. *J. Am. Soc. Nephrol.* 15, 717–721 (2004).

26 Fujikawa K, Kawakami A, Eguchi K. Recovery from multiple cranial nerve palsy of Wegener's granulomatosis with infliximab. *J. Rheumatol.* 35(7), 1471–1472 (2008).

27 Hermann J, Reittner P, Scarpatetti M, Graninger W. Successful treatment of meningeal involvement in Wegener's granulomatosis with infliximab. *Ann. Rheum. Dis.* 65, 691–692 (2006).

28 Pariser KM. Takayasu's arteritis. *Curr. Opin. Cardiol.* 9, 575–580 (1994).

29 Johnston SL, Lock RJ, Gompels MM. Takayasu arteritis: a review. *J. Clin. Pathol.* 55, 481–486 (2002).

30 Mason JC. Takayasu arteritis – advances in diagnosis and management. *Nat. Rev. Rheumatol.* 6, 406–415 (2010).

31 Kerr GS, Hallahan CW, Giordano J *et al.* Takayasu arteritis. *Ann. Intern. Med.* 120(11), 919–929 (1994).

32 Rossa AD, Tavoni A, Merlini G *et al.* Two Takayasu arteritis patients successfully treated with infliximab: a potential disease-modifying agent? *Rheumatology (Oxford)* 44, 1074–1075 (2005).

33 Karageorgaki ZT, Mavragani CP, Papathanasiou MA, Skopouli FN. Infliximab in Takayasu arteritis: a safe alternative? *Clin. Rheumatol.* 26, 984–987 (2007).

34 Tanaka F, Kawakami A, Iwanaga N *et al.* Infliximab is effective for Takayasu arteritis refractory to glucocorticoid and methotrexate. *Intern. Med.* 45, 313–316 (2006).

35 Jolly M, Curran JJ. Infliximab-responsive uveitis and vasculitis in a patient with Takayasu arteritis. *J. Clin. Rheumatol.* 11, 213–215 (2005).

36 Tato F, Rieger J, Hoffmann U. Refractory Takayasu's arteritis successfully treated with the human, monoclonal antitumor necrosis factor antibody adalimumab. *Int. J. Angiol.* 24, 304–307 (2005).

37 Hoffman GS, Merkel PA, Brasington RD, Lenschow DJ, Liang P. Anti-tumor necrosis factor therapy in patients with difficult to treat Takayasu arteritis. *Arthritis Rheum.* 50 (7), 2296–2304 (2004).

▪ **Often cited in support of the use of infliximab for the treatment of Takayasu's arteritis.**

38 Katoh N, Kubota M, Shimojima Y *et al.* Takayasu's arteritis in a patient with Crohn's disease: an unexpected association during infliximab therapy. *Intern. Med.* 49(2), 179–182 (2010).

39 Keino H, Okada AA, Watanabe T, Taki W. Decreased ocular inflammatory attacks and background retinal and disc vascular leakage in patients with Behçet's disease on infliximab therapy. *Br. J. Ophthalmol.* DOI: 10.1136/bjo.2010.194464 (2010) (Epub ahead of print).

40 Hui-Yuen JS, Duong TT, Yeung RSM. TNF-α is necessary for induction of coronary artery inflammation and aneurysm formation in an animal model of Kawasaki disease. *J. Immunol.* 176(10), 6294–6301 (2006).

41 Son MBF, Gauvreau K, Ma L *et al.* Treatment of Kawasaki disease: analysis of 27 US pediatric hospitals from 2001 to 2006. *Pediatrics* 124, 1–8 (2009).

42 Chen M, Kallenberg CGM. ANCA-associated vasculitides – advances in pathogenesis and treatment. *Nat. Rev. Rheumatol.* 6, 653–664 (2010).

43 Plosker GL, Figgitt DP. Rituximab: a review of its use in non-hodgkin's lymphoma and chronic lymphocytic leukaemia. *Drugs* 63(8), 803–843 (2003).

44 Meltzer M, Franklin EC, Elias K, McCluskey RT, Cooper N. Cryoglobulinemia-a clinical and laboratory study. *Am. J. Med.* 40, 837–856 (1966).

45 Roccatello D, Fornasieri A, Giachino O *et al.* Multicenter study on hepatitis C virus-related cryoglobulinemic glomerulonephritis. *Am. J. Kidney Dis.* 49 (1), 69–82 (2007).

46 Roccatello D, Baldovino S, Rossi D *et al.* Rituximab as a therapeutic tool in severe mixed cryoglobulinemia. *Clin. Rev. Allergy Immunol.* 34, 111–117 (2008).

47 Wink F, Houtman PM, Jansen TL. Rituximab in cryoglobulinaemic vascultis, evidence for its effectivity: a case report and review of literature. *Clin. Rheumatol.* 30(2), 293–300 (2011).

48 Popa E, Stegeman C, Bos NA, Kallenberg CG,Tervaert JW. Differential B- and T-cell activation in Wegener's granulomatosis. *J. Allergy Clin. Immunol.* 103, 885–894 (1999).

49 Sanders JSF, Huitma MG, Kallenberg CGM, Stegeman CA. Prediction of relapses in PR3-ANCA-associated vasculitis by assessing responses of ANCA titres to treatment. *Rheumatology (Oxford)* 45, 724–729 (2006).

50 Falk RJ, Jennette JC. Rituximab in ANCA-associated disease. *N. Engl. J. Med.* 363 (3), 285–286 (2010).

51 Keogh KA, Wylam ME, Stone JH, Specks U. Induction of remission by B lymphocyte depletion in eleven patients with refractory antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum.* 52(1), 262–268 (2005).

52 Smith KGC, Jones RB, Burns SM, Jayne DRW. Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitis: remission, relapse, and re-treatment. *Arthritis Rheum.* 54, 2970–2982 (2006).

53   Keogh KA, Ytterberg SR, Fervenza FC, Carlson KA, Schroeder DR, Specks U. Rituximab for refractory Wegener's granulomatosis: report of a prospective, open-label pilot trial. *Am. J. Resp. Crit. Care Med.* 173, 180–187 (2006).

54   Jones RB, Ferraro AJ, Chaudhry AN *et al.* A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum.* 60(7), 2156–2168 (2009).

55   Stone JH, Merkel PA, Spiera R *et al.* Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N. Engl. J. Med.* 363(3), 221–232 (2010).

■■   **Randomized, placebo-controlled trial that supports the use of rituximab for the treatment of microscopic polyangiitis and severe granulomatosis with polyangiitis (Wegener's granulomatosis).**

56   Jones RB, Tervaert JWC, Hauser T *et al.* Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N. Engl. J. Med.* 363(3), 211–220 (2010).

57   Jennette JC, Falk RJ, Andrassy K *et al.* Nomenclature of systemic vasculitides. proposal of an international consensus conference. *Arthritis Rheum.* 37 (2), 187–192 (1994).