



Targeted therapies in systemic vasculitis

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In the near future, the ability to target specific components of the immune system that have gone awry has the potential to revolutionize the treatment of systemic vasculitis. By targeting aberrant or dysregulated parts of the immune system, “biologic” interventions offer the prospect of fewer adverse effects and greater efficacy than conventional treatments. However, many challenges must be overcome before the potential benefits of this new class of therapies can be realized (**Table 1**). I will address several issues related to biologic therapies in systemic vasculitis:

- Hurdles to the development of targeted therapies
- Challenges in the evaluation of efficacy
- Candidate targets
- Results of early studies
- The path to progress.

■ HURDLES TO THE DEVELOPMENT OF TARGETED THERAPIES

The development of biologic therapies in systemic vasculitis confronts major intellectual challenges. The most daunting of these is that, without exception, definitions of the underlying immunoregulatory defects in the systemic vasculitides are still incomplete. The contributions of genetic predispositions (inborn or acquired), epidemiologic risk factors (age, gender, ethnicity), and environmental exposures to the development of vasculitis remain poorly understood. Although there are clear precedents for microbial pathogens causing systemic vasculitides (eg, hepatitis B and polyarteritis nodosa; hepatitis C and mixed cryoglobulinemia), the relationships between most forms of vasculitis and potential microbial pathogens are still only speculative. Finally, the absence of adequate animal models for most types of vasculitis is a major impediment to the development and assessment of new treatment approaches.¹

Economic hurdles exist, as well. Based on estimates of the prevalence of giant-cell arteritis (GCA) and polymyalgia rheumatica (PMR) alone, the prevalence of

TABLE 1
HURDLES TO THE DEVELOPMENT OF TARGET THERAPIES IN SYSTEMIC VASCULITIS

- Knowledge of immunoregulatory defects incomplete
- Understanding of genetic/epidemiologic/environmental risk factors poor
- Uncertain relationships between disease and potential microbial pathogens
- Few animal models
- Reluctance of patients to enroll in randomized trials
- Complexity of disease assessment
- Difficulty in determining incremental effectiveness of new therapies compared with conventional treatments
- Length of time required for rigorous trials
- Market forces

vasculitis in the United States easily exceeds half a million cases.² However, the common perception is that all forms of vasculitis are rare. The pharmaceutical industry is far more likely to devote resources to the development of therapies for diseases that have larger perceived markets.

■ CHALLENGES IN THE EVALUATION OF EFFICACY

For any new therapy, the determination of efficacy requires randomized trials. The first challenge in the evaluation of novel therapies for vasculitis, therefore, is to enroll sufficient numbers of patients into clinical trials. With regard to GCA/PMR (the most common form of systemic vasculitis in the developed world), the perception among many practicing physicians is that this disorder does not require referrals to specialists at academic medical centers. This is because for decades, glucocorticoids have been a remarkably effective therapy for the treatment of GCA (albeit a toxic one), and there have been few new therapies introduced. Since academic centers have had nothing new to offer patients in terms of treatment, the understandable position of most practitioners has been that “my prednisone works as well as yours.” In order to optimize enrollment in trials of new vasculitis therapies, therefore, the intervention must be both truly novel and not widely available.

A second challenge to the evaluation of efficacy is reluctance on the part of patients to be randomized. (This is not a drawback that is exclusive to trials of biologic agents in systemic vasculitis). The tendency of patients with dread diseases—and often of the physicians who treat

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them—is to embrace all new therapies as superior, even before these therapies have been tested adequately. This may be particularly true for systemic vasculitis, because of the enormous potential toxicities associated with most conventional therapies. As the experience with tumor necrosis factor (TNF) inhibition in multiple sclerosis illustrates, however, *newer is not always better*. (Quite contrary to expectations, multiple sclerosis patients experienced dramatic *worsenings* after treatment with anti-TNF agents. These drugs are now contraindicated in this disease.) The experience with anti-CD40 ligand therapy in systemic lupus erythematosus illustrates this lesson again (investigations of this agent were terminated abruptly because of life-threatening thrombotic events). Because of the many redundancies, counter-regulatory mechanisms, and unknowns that characterize our current state of knowledge about the immune system, the belief that “newer is better” may be particularly dangerous with regard to biologic therapies.

Another major challenge to evaluating the efficacy of new treatments in vasculitis is the complexity of disease assessments (eg, activity, remission, and damage). Vasculitides are the prototypes of multi-organ system diseases. Consequently, distilling the concept of “active disease” into a number as quantifiable as the counts of swollen or tender joints is difficult. The 1990s observed substantial improvements in the methods of vasculitis assessment, with the creation and validation of several disease assessment indices.^{3–6} All of these indices are imperfect yardsticks of disease activity, but they are the best clinical measurements currently available. Teaching investigators to use these instruments in a uniform fashion in clinical trials is no small task.

Although conventional therapies for systemic vasculitis are toxic, they *are* effective, at least in the short-term. (The principal shortcomings of conventional treatments are their side effects, not their lack of efficacy.) Daily cyclophosphamide and high doses of prednisone, for example, lead to significant improvement in >90% of patients with WG.⁷ Thus, determining the *incremental effectiveness* of new medications—if any—is not easy. Furthermore, new therapies must be employed *in addition to* the old ones: failure to use therapies known to be effective in these potentially lethal diseases would not be ethical.

The effectiveness of conventional therapies in the control of disease and the requirement for using these “old” medications along with new agents to be tested have another implication for the determination of efficacy: proving that a new medication works requires a lengthy study, with prolonged patient follow-up. Given the relatively crude state of outcome measures in vasculitis, hard endpoints—sustained remission, number of disease relapses over time, and death—require time to accumulate. The length of time required to test a new agent adds substantially to the expense of performing such trials and heightens the bar when it comes to performing trials of high quality.

Finally, market forces also complicate the evaluation of new treatments’ efficacy. *The dose of a biologic agent that is effective for one disease may be subtherapeutic for another.*

Thus, when testing a new therapy for a specific disease, one would like to be certain of employing the optimal dose. However, pharmaceutical sponsors, eager to get their products into general use—whether approved for a given indication or not—are usually unenthusiastic about dose-finding studies in relatively uncommon conditions.

■ SEVERAL POSSIBLE BIOLOGIC APPROACHES TO TREATMENT

There are many possible candidate molecules for biologic approaches to treatment. A partial list is shown in **Table 2**. Many of these potential targets are drawn from our current understanding of GCA. Although there remains much to learn about GCA, research over the past decade has highlighted many potential targets for biologic intervention in this disease.

Tumor necrosis factor

Tumor necrosis factor (TNF) is a critical mediator of inflammation in a variety of conditions. TNF release, principally by macrophages, leads to activation of the vascular endothelium, including the expression of adhesion molecules and the upregulation of class II major histocompatibility (MHC) molecules. These events orchestrate the recruitment of inflammatory cells and increase production of immunoglobulins and complement proteins. As a major cytokine in the Th1 inflammatory pathway, TNF stimulates the release of other pro-inflammatory cytokines, including interleukins (IL)-1, -6, and -8. At least two different approaches to the inhibition of TNF are now commercially available. Others will be shortly. The early results of treating WG with TNF inhibition are discussed below.⁸

Interferon-gamma

IFN- γ , a cytokine produced by Th1 lymphocytes and natural killer cells, induces class II MHC expression and morphologic changes in both endothelial cells and macrophages. IFN- γ also increases the expression of adhesion molecules on endothelial cells, and has effects that are synergistic with those of TNF.^{9,10}

In giant-cell arteritis, IFN- γ produced by CD4+ T-cells within the adventitia appears to drive the inflammatory response. Strong evidence supports the concept of GCA as an antigen-driven, T-cell mediated disease, and the adventitia appears to be the site of immunologic recognition events.¹¹ IFN- γ + T-cells appear to be recruited to the adventitia by a specific antigen or antigens (which, of course, remain unidentified). From this location, the T-cells—via the production of IFN- γ —orchestrate a cascade of inflammation that permeates the entire vessel wall, culminating in some patients in ischemic events that result from luminal occlusion (eg, anterior ischemic optic neuropathy).

IFN- γ is an appealing target for a biologic intervention because of the central role it appears to play in both GCA (and WG; see below). The implications of blocking IFN- γ , however, are presently unclear. Data emerging from a mouse model of large vessel arteritis indicate that strategies for blunting the inflammatory response (eg, by the in-

TABLE 2
POTENTIAL TARGETS FOR BIOLOGIC INTERVENTIONS IN SYSTEMIC VASCULITIS

- Tumor necrosis factor
- Interferon gamma
- Matrix metalloproteinases and reactive oxygen species
- Platelet-derived growth factors and vascular endothelial growth factor
- Interleukin-6
- The interleukin-10/interleukin-12 balance
- Interferon-alpha
- Interleukin-1/interleukin-1 receptor antagonist
- CTLA-4 and other co-stimulatory molecules

hibition of IFN- γ) are likely to lead to the persistence of the inciting agent/antigen,¹² with consequences that may be ultimately deleterious to the host.

Interleukin-1 and interleukin-6

In addition to TNF, several other macrophage products constitute potential targets for biologic interventions. In GCA, for example, both circulating macrophages and those homing to the site of antigen recognition in the adventitia produce IL-1 β and IL-6.¹³ These cytokines probably account in large measure for the profound constitutional complaints, polymyalgia rheumatica symptoms, and elevated erythrocyte sedimentation rates so characteristic of many GCA patients.

In addition to its secretion by monocytes/macrophages, IL-6 is secreted by vascular smooth muscle cells and endothelium in response to TNF and IL-1. IL-6 is a potent activator of acute phase response proteins, stimulates the hypothalamic-pituitary-adrenal axis, helps propagate Th1 cytokine responses, and has recently been implicated in the pathogenesis of atherosclerosis.¹⁴ In vitro, animal, and human studies of this molecule over the past decade have implicated it in the pathogenesis of a variety of vasculitides, including GCA, Takayasu's arteritis (TA), rheumatoid vasculitis (RV), vasculitis associated with SLE, Wegener's granulomatosis (WG), and microscopic polyarteritis (MPA).

Plasma concentrations of IL-6 are increased during flares of GCA, TA, WG, and RV.¹⁵⁻¹⁸ In general, IL-6 concentrations parallel disease activity in these disorders. Temporal artery biopsy specimens in GCA reveal an increase in IL-6 producing cells within the arterial media (macrophages) and intima (fibroblasts). Following the treatment of GCA, IL-6 levels normalize.¹⁵ Recent evidence, however, suggests that IL-6 suppression by conventional GCS doses in GCA is incomplete, and that IL-6 elevations correlate with disease flares.¹⁹ IL-6 may be a more sensitive indicator of persistent vascular inflammation than the ESR, and persistently elevated IL-6 levels may indicate patients who will require additional treatment. Trials of anti-IL-6 therapies are under way in RA. Whether the inhibition of IL-6 production and monocyte activation will result in clinical and immunologic improvement in patients with vasculitis is an intriguing question.

Matrix metalloproteinases and reactive oxygen species

In GCA, macrophages lining the media and media-intima border synthesize other products under the direction of IFN- γ : matrix metalloproteinases (MMP) and reactive oxygen species (ROS).¹¹ MMP, which play an important role in joint destruction in inflammatory arthritis, probably contribute substantially to the fragmentation of the internal elastic lamina in GCA. MMP are also required for the mobilization of smooth muscle cells (ultimately contributing to luminal occlusion). ROS production leads to lipid peroxidation and destruction of cellular membranes. Whether or not these targets can be inhibited by specific approaches—and whether such approaches would have meaningful clinical effects—both remain to be seen.

Platelet-derived growth factors and vascular endothelial growth factor

Macrophage (and multi-nucleated giant cell [MNGC]) products also lead directly to arterial failure and clinical events in GCA. Products elaborated by these cells lead to smooth muscle migration, intimal hyperplasia, and luminal occlusion. Intimal proliferation is mediated by the in situ production of platelet-derived growth factors A and B (PDGF-A & -B) and vascular endothelial growth factor (VEGF), all of which are produced by MNGC.²⁰ The presence of MNGC correlates strongly with the concentration of IFN- γ within the arterial wall.²¹ Therapies targeting intimal proliferation could serve as treatments adjunctive to those designed to abolish “inflammatory” elements of the immune response.

The interleukin-10/interleukin-12 balance

IL-10 downregulates lymphocyte activity in vivo by suppressing macrophage activation. This cytokine is secreted by helper T-lymphocytes, macrophages, and keratinocytes. The inhibition of macrophages by IL-10 leads to a decrease in plasma levels of IL-1, TNF, and IL-12, and ultimately to the suppression of Th1 activity. Conversely, IL-12, produced by activated macrophages, is a potent activator of CD4+ T-cells and natural killer cells and is downregulated by IL-10. Because of the major roles of IL-10 and IL-12 in the regulation of the Th1 inflammatory pathway, manipulation of these cytokines offers the opportunity to alter the inflammatory milieu in ways beneficial to patients.

Monocyte activation and skewing of the Th1:Th2 ratio have been demonstrated in a variety of human vasculitides. As noted, PBMCs isolated from patients with active WG secrete increased amounts of the Th1 cytokines IL-12, IFN- γ , and TNF. Moreover, in vitro levels of IFN- γ are decreased by the exogenous administration of IL-10,²² suggesting a possible therapeutic role for IL-10. To date, however, IL-10 has not been employed in significant numbers of patients with vasculitis.

CTLA-4 and other co-stimulatory molecules

Current experimental approaches to the induction of immunological self-tolerance in autoimmune disorders such as SLE involve the use of biologic agents to block

molecules that promote T-cell activation. In general terms, these strategies are intended to disrupt “co-stimulatory” pathways.²³ Such strategies may also be applicable to certain forms of vasculitis. Potential targets within co-stimulatory pathways include the B7 stimulators of CD28, B7-1, and B7-2.

Among the many molecules involved in co-stimulation, molecules of the B7:CD28/CTLA4 pathway are described most completely. CTLA4-Ig is a soluble chimeric protein consisting of the extracellular domain of human CD152 and a fragment of the Fc portion of human IgG1.²⁴ CTLA4-Ig binds to both B7-1 and B7-2 molecules on antigen-presenting cells, thereby blocking the CD28-mediated co-stimulatory signal for T-cell activation. There is early evidence, based on studies of candidate genes, that WG may be an appropriate disease in which to test this approach.²⁵

■ RESULTS OF EARLY STUDIES

Anti-TNF investigations in Wegener’s granulomatosis

Preliminary results of etanercept use in vasculitis include data from a six-month open-label study of 20 WG patients.⁸ This trial was conducted to evaluate the safety of etanercept combined with the potentially hazardous conventional therapies used to treat WG. (Prior to this trial, etanercept had never been employed in combination with cyclophosphamide.) Etanercept (25 milligrams subcutaneously twice a week) was added to standard therapies for WG that were prescribed according to disease severity. All patients enrolled had histories of refractory WG: the mean time since original diagnosis was 63.6 months (range: 14-189 months), and 14 patients (70%) had never achieved remissions permitting the successful discontinuation of GCS. Sixteen patients (80%) had limited WG at entry, and 4 (20%) had severe disease. Eighteen of the patients (90%) were receiving GCS and 18 (90%) were receiving another immunosuppressive agent (8 methotrexate, 6 cyclophosphamide, 4 azathioprine). However, 14 of the 20 patients (70%) had etanercept added as the only new therapeutic variable.

The most common etanercept-related adverse event was the occurrence of injection site reactions. Eight injection site reactions occurred in 5 patients (25% of all patients enrolled, but <1% of all injections). All injection site reactions were mild. Two patients had a combined total of 5 hospital admissions (1 patient had 4 admissions), but none were attributable solely to etanercept-related adverse events. One patient with severe subglottic stenosis developed pneumococcal tracheobronchitis and subsequently had a localized *H zoster* infection. Nineteen patients (95%) remained on treatment at 6 months, the single exception being a patient who developed progression of orbital (retro-bulbar) disease at 4 months. There were no deaths.

Although the principal purpose of this open-label trial was to investigate the safety of etanercept in WG, preliminary indications of treatment efficacy were sought in comparisons of disease activity scores at entry and 6 months. The Birmingham Vasculitis Activity Score for

WG (BVAS/WG)⁵ was used to measure disease activity. The mean BVAS/WG at entry was 3.6 (range: 1-8). At 6 months, the mean BVAS/WG score decreased 3.0 points, to 0.6 ($P < 0.001$; 95% confidence interval: -4.0, -2.1). Among the 14 patients in whom etanercept was the only new treatment variable, the mean BVAS/WG score declined 2.7 points, from 3.1 at entry to 0.4 at 6 months ($P < 0.001$; 95% confidence interval: -4.5, -1.8). The mean daily prednisone dose in this subset decreased from 12.9 mg at entry to 6.4 mg at 6 months, but this comparison did not achieve statistical significance (difference: -6.5; $P = 0.19$; 95% confidence interval: -16.6, +3.6). Sixteen of the patients (80%) achieved BVAS/WG scores of 0 at some point during the trial. *However, intermittently active disease was observed in 15 patients (75%).* There were 3 severe flares during the course of the trial (two flares of pre-existing orbital disease and one de novo flare of glomerulonephritis).

Randomized trials to assess the efficacy of etanercept in WG have begun. The Wegener’s Granulomatosis Etanercept Trial (WGET), a randomized, double-blinded, placebo-controlled study, is under way at 8 medical centers in the United States.²⁶ In this trial, patients are randomized to either etanercept and placebo in addition to conventional WG treatments (which all patients receive at entry). The conventional treatments are tapered after the achievement of remission. The principal outcome measure is the ability of etanercept to maintain disease remissions. Enrollment in WGET is now 75% complete, but no outcomes related to efficacy are available at this time.

A single-center trial (randomized but unblinded) is being conducted at the National Institutes of Health. This trial involves the combined use of etanercept and methotrexate (versus methotrexate alone) for patients with non-life-threatening WG. All patients receive etanercept and methotrexate initially. At 6 months, those patients in remission are randomized to either continue etanercept, or to stop receiving etanercept but to continue methotrexate.²⁷ Follow-up in this trial continues at the present time. No efficacy data are currently available.

■ THE PATH TO PROGRESS

Despite the challenges noted above, investigations in systemic vasculitis have made tremendous advances in recent years. Both the International Network for the Study of the Systemic Vasculitides (INSSYS) and the European Union Vasculitis Study Group (EUVAS), organizations with overlapping memberships but separate funding sources, have completed large randomized trials of non-biologic therapies in systemic vasculitis.^{28,29} Under the auspices of INSSYS, WGET—the first multi-center, randomized, double-blinded trial of a biologic agent in vasculitis—is presently under way.

To advance the therapy of vasculitis, randomized, double-blind, placebo-controlled trials will be required. Continued improvements in outcome measures will facilitate the rigorous conduct of clinical trials. Evaluations of new therapies should include small studies aimed at determining the optimal dose for larger trials.

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