Published in final edited form as:

Curr Opin Rheumatol. 2009 January ; 21(1): 3–9. doi:10.1097/BOR.0b013e32831d28b3.

Advances in the use of biologic agents for the treatment of systemic vasculitis

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Abstract

Purpose of review—Due to the well-known toxicities of cyclophosphamide, substantial interest exists in finding other therapies to treat primary systemic vasculitis. Biologic agents have been proposed as an alternative to cyclophosphamide for these disorders because of their recent success in treating other rheumatic diseases. This article reviews the current state-of-the-art with regards to the use of biologic agents as a treatment for systemic vasculitis.

Recent findings—The greatest amount of experience with these agents for the treatment of systemic vasculitis is with anti-tumor necrosis factor agents, pooled intravenous immunoglobulin, and anti-B cell therapies such as rituximab. Intravenous immunoglobulin is already a standard therapy for Kawasaki's disease, but should also be considered for the treatment of ANCA-associated vasculitis when standard therapies are either ineffective or contraindicated. Early experience with tumor necrosis factor inhibitors indicates that they may be effective for the treatment of Takayasu's arteritis, but their role in the treatment of other forms of vasculitis remains controversial. Early experience with rituximab for the treatment of several forms of vasculitis has been quite promising, but must be confirmed by ongoing randomized clinical trials.

Summary—Biologic agents represent the next evolution in treatment for the primary systemic vasculitides. Greater understanding of these diseases has allowed use to move further away from non-specific, highly toxic therapies towards a more directed approach. As our experience with these agents increases, they will likely form the keystone of treatment in the near future.

Keywords

vasculitis; anti-TNF; intravenous immunoglobulin; rituximab

Introduction

Cytotoxic agents are the cornerstone of treatment for many forms of primary systemic vasculitis. Drugs such as cyclophosphamide have vastly improved the previously dismal prognosis associated with many of these diseases. Due to the toxicities associated with cyclophosphamide, however, there has been substantial interest in finding alternate agents

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for treatment of these disorders. With the recent success of biologic agents for the treatment of many autoimmune disorders, there has been great interest to expand the use of these agents to treat systemic vasculitis. .

Anti-tumor necrosis factor agents

Tumor necrosis factor α (TNF) is a pro-inflammatory cytokine produced primarily by cells of the macrophage-monocyte lineage. The biologic effects of TNF are varied, and include adhesion molecule expression, synthesis of proinflammatory cytokines, synthesis of chemokines, activation of other immune system cells (T-cells, B-cells, and macrophages), and inhibition of regulatory T-cells. TNF exists in both cell membrane-bound and soluble forms. Three agents directed against TNF are currently approved for use: infliximab (Remicade), etanercept (Enbrel), and adalimumab (Humira). Infliximab is a chimeric monoclonal antibody comprised of the human IgG1 constant region fused with the murine variable region recognizing TNF. Adalimumab has a similar structure, but is fully humanized. Infliximab and adalimumab can bind to circulating and membrane bound TNF, and can induce apoptosis in cells expressing TNF. Etanercept is a fusion protein composed of 2 extracellular p75 TNF receptor domains linked by the F_C portion of human IgG1. Unlike infliximab and adalimumab, etanercept does not induced apoptosis in TNF-expressing cells [1].

Giant cell arteritis (GCA)

Since up to 80% of patients with GCA experience complications from corticosteroid therapy, an effective adjunct therapy to allow corticosteroid reduction is needed. Small case series and a case report presented evidence that infliximab could be used as a steroid sparing agent for GCA [2-4]. Based on these reports, a randomized, multicenter trial of infliximab versus placebo was conducted to determine the efficacy of infliximab in GCA [5]. Forty-four patients newly diagnosed with GCA were randomized to receive infliximab (5 mg/kg) or placebo in a 2:1 ratio, in addition to prednisone. At 22 weeks, the proportion of patients without relapse were similar between the infliximab and placebo groups (43% versus 50% respectively, $p=0.65$). In addition, the proportion of patients on prednisone tapered to 10 mg/day without relapses was similar between both groups (61% for infliximab versus 75% for placebo, $p=0.31$). The incidence of infection was 71% in the infliximab group and 56% in the placebo group (difference of 15%, 95% CI -14-45%). With the results of this study, the authors concluded that infliximab was unlikely to have substantial efficacy in the treatment of GCA. Although there is some evidence that etanercept and adalimumab could have a role in the treatment of GCA, the data are inconclusive [6*,7].

Takayasu's arteritis (TA)

The successful use of anti-TNF therapy for the treatment of TA has been reported by multiple investigators [8-13]. The largest case series examined 25 patients with active, relapsing TA who were TA treated with infliximab ($n=21$) or etanercept ($n=9$), and followed for a median of 28 months [14*]. Of the 9 patients initially treated with etanercept, 4 underwent complete remission and 2 experienced partial remission. Of the 6 patients who achieved remission on etanercept, 3 had disease relapses. Three patients who did not respond to etanercept were switched to infliximab and achieved complete remission.

Of the 21 patients treated with infliximab (including the 5 previously treated with etanercept), 12 achieved a complete remission and 6 achieved a partial remission. Three patients discontinued infliximab; 12 of the remaining 18 patients relapsed, and required treatment with higher doses of infliximab administered at shorter intervals.

While the positive results from these case series and case reports of the use of anti-TNF agents for refractory TA are encouraging, they need to be replicated in larger, randomized clinical trials. Currently, there is more evidence to support the use of infliximab compared to etanercept or adalimumab. One should note, however, that doses frequently had to be escalated above the baseline 3 mg/kg dose to achieve remission.

ANCA-associated vasculitis (AAV)

Little is known regarding the efficacy of anti-TNF strategies for the treatment of microscopic polyangiitis (MPA) and Churg-Strauss syndrome (CSS) [15-17]. Our understanding of the potential role of these drugs for the treatment of AAV is extrapolated from our experience with Wegener's granulomatosis (WG) [18,19]. The Wegener's granulomatosis Etanercept Trial (WGET) was conducted to determine if etanercept is effective for the maintenance of remission in WG. In this multicenter, placebo-controlled trial, 180 patients were randomized to receive adjunctive therapy with etanercept versus placebo, in addition to standard-of-care immunosuppression (with either cyclophosphamide or methotrexate) [20].

No difference in the rates of sustained remission was observed between the etanercept and placebo groups (69.7% vs. 75.3%, $p=0.39$). In addition, no difference in the relative risk of disease flares was observed between the 2 groups (0.89, $p=0.54$). One concerning finding was the increased rate of malignancy in the etanercept group. Six solid tumors developed in patients in the etanercept group, while none were observed in the placebo group ($p=0.01$). Based on age- and sex-specific incidence rates from the Surveillance, Epidemiology, and End Results (SEER) database, only 1.92 solid cancers were expected in the etanercept group, leading to a standardized incidence ratio (SIR) of 3.12 (95% CI 1.15-6.80). Additional follow-up of 140 participants in the WGET showed that this increased risk in solid cancers in the etanercept group persisted 3.5 years following the conclusion of the study ($SIR_{\text{etanercept}} 4.4$, $SIR_{\text{placebo}} 1.5$, $p=0.01$) [P. Seo, personal communication].

The negative results of the WGET were surprising. Several potential explanations exist. First, the dose of etanercept used in the WGET may not have been sufficient. Studies of etanercept in psoriasis show an increased therapeutic effect at higher doses (e.g., 50 mg subcutaneous twice weekly) [21,22]. In addition, etanercept may not be effective in diseases marked by granulomatous inflammation. For example, etanercept is not effective in Crohn's disease and sarcoidosis, which are both characterized by granulomatous inflammation. In a randomized, double-blind, placebo-controlled trial of 43 patients with moderate to severe Crohn's disease, use of etanercept (25 mg subcutaneously twice weekly) was not associated with an improvement in clinical response or clinical remission rates at 2, 4, or 8 weeks when compared to placebo [23]. In an open-label study of etanercept in stage II/III sarcoidosis, enrollment was stopped after 17 patients since the use of etanercept was associated with both early and late treatment failure [24].

No randomized clinical trials have been conducted to study the efficacy of other anti-TNF agents (i.e., infliximab or adalimumab) for AAV. Four case series and a prospective open-label trial [Table 1] have been published describing the use of infliximab in WG [15,16,25-27]. Results of these case series cannot be combined due to the use of different treatment regimens and outcome measures. In general, the majority of patients appear to respond and enter either a complete or partial remission. However, some patients did experience flares while receiving infliximab, and serious infections were reported.

The role of anti-TNF therapy for the treatment of AAV remains uncertain. Based on the WGET, etanercept should not be used as monotherapy or adjunctive treatment to cyclophosphamide or methotrexate for induction or maintenance of remission in WG.

Without randomized clinical trials, the ability of infliximab (or adalimumab) to induce or maintain remission cannot be fully assessed. Therefore, neither should not be used as first-line therapies for these vasculitides, and could be considered for refractory disease after review of the risks and benefits of therapy. Lastly, combination therapy with an anti-TNF therapy and cyclophosphamide should be used cautiously, given the increased risk of malignancy seen in the WGET and its subsequent analyses.

Intravenous Immunoglobulin (IVIG)

IVIG contains pooled IgG immunoglobulins extracted from the plasma of blood donors, and was initially used to treatment immunodeficiencies. However, at higher doses (up to 2g/kg), IVIG has also been used to treat autoimmune diseases such as dermatomyositis and systemic lupus erythematosus. The exact mechanism of IVIG's immunomodulatory effects for the vasculitic syndromes is unclear. Proposed hypotheses include the clearance of anti-idiotypic antibodies, blockade of Fc receptors on phagocytic cells, downregulation of T- and B-cell function, and anticytokine effects [28]. Recent work by Ravetch et al. suggests that IVIG acquires its anti-inflammatory activity from sialylation of the Fc core polysaccharide [29]. IVIG is well established as the treatment of choice for the prevention of coronary artery aneurysms in Kawasaki's disease (reviewed in [30]). IVIG has also been used for the treatment of polyarteritis nodosa [31] and Henoch-Schönlein purpura [32]. However, the role of IVIG for the treatment of other forms of systemic vasculitis has not been clearly defined.

ANCA-associated vasculitis

IVIG has previously been suggested to be effective for WG and MPA based on case series and small prospective, open-label trials [33-37]. However, only one randomized clinical trial investigating the use of IVIG in persistent WG and MPA has been reported [38]. Thirty-four patients (24 with WG, 10 with MPA) were randomized to receive one course of IVIG (0.4 g/kg/day for 5 days) or placebo. All patients were required to have received 2 months of treatment with prednisolone and cyclophosphamide or azathioprine prior to the trial, and continued on these medications for at least 3 months after IVIG was initiated. At 3 months, a partial or complete remission was observed in 14/17 (82%) of the IVIG group and 6/17 (35%) of the placebo group ($p=0.015$). However, subsequent vasculitic activity, relapse frequency, and immunosuppression exposure was the same in both groups, indicating that the benefit of a single infusion of IVIG did not extend beyond 3 months.

To study the efficacy of adjunctive IVIG for remission maintenance, Martinez et al. conducted a prospective, open-label study of 22 patients (19 with WG, 3 with MPA) who received 6 monthly courses of IVIG (0.5 gm/kg/day for 4 days) in addition to standard immunosuppressive therapies [39]. At 9 months, 13 of the 21 remaining patients were in complete remission, 1 patient had a partial remission, and 7 patients had relapsed. Seven of the 13 patients in complete remission at 9 months were still in complete remission at 24 months. The remaining patients underwent treatment changes at the discretion of the treating physicians, and therefore, the results for these patients are difficult to interpret. One serious adverse event, renal insufficiency, developed in 1 patient. Three infections were reported in 2 patients: a staphylococcal infection, and Kaposi sarcoma and *E. coli* urinary tract infection in the same patient.

In summary, IVIG is not a panacea but may have a role as adjunctive therapy for AAV refractory to routine immunosuppression. IVIG may also be useful for patients in whom immunosuppression is undesirable or contraindicated [40,41].

Rituximab

Rituximab is a chimeric monoclonal antibody directed against CD20, a B-cell marker expressed from the pre-B cell phase to the mature B-cell phase of B-cell development. CD20 is not expressed by pro-B cells, memory cells, plasma cells, or antibody-secreting B-cells. Binding of rituximab to CD20+ B-cells results in cell death. While the mechanism for cell death is not known, in vitro experiments have shown that antibody-dependent cellular cytotoxicity, complement-mediation B-cell lysis, apoptosis, and sensitization to cytotoxic agents or corticosteroids may all play a role. Use of rituximab results in selective depletion of peripheral B cells which can last for 6 months or longer [42].

Rituximab is most commonly used to treat malignancies, such as B-cell non-Hodgkin's lymphoma [43]. However, it has developed an important role in the treatment of autoimmune diseases such as rheumatoid arthritis [44] and immune-mediated thrombocytopenia [45]. More recently, its use for the treatment of both cryoglobulinemic vasculitis and AAV has been explored.

Mixed cryoglobulinemic vasculitis (HCV-MC)

More than 80% of mixed cryoglobulinemic vasculitis cases are attributable to hepatitis C viral (HCV) infection. Previous studies have shown that treatment with pegylated interferon and ribavirin can achieve remission in up to 70% of cases [46]. However, this antiviral regimen is ineffective, poorly tolerated, or contraindicated for some patients. Therefore, additional treatment options have been sought.

A recently published review combined the results of 2 larger case series (with 20 and 15 patients), 2 smaller case series (with 6 and 5 patients), and case reports of using rituximab for HCV-MC [47]. Out of the 57 patients included in this analysis, 43 (75.4%) had cryoglobulinemic vasculitis secondary to HCV. Most patients received rituximab for either non-responsiveness or intolerance to previous treatments (n=52). Partial or complete remissions were observed in 80% of patients with skin involvement, 79% of patients with arthralgias, 93% of patients with neuropathy, and 83% of patients with glomerulonephritis. Fourteen of 36 patients (39%) relapsed after a mean of 6.7 months; 8 of these patients went into complete remission after a second course of rituximab.

Since only 60-70% of patients with HCV-MC respond to antiviral therapy, and the response to antiviral therapy can be slow, additional immunosuppressive treatments may be needed initially to help control life-threatening organ involvement. Therefore, Saadoun et al. studied the use of rituximab in combination with pegylated interferon and ribavirin in an open-label pilot study of 16 patients with refractory HCV-MC [46*]. Participants were given rituximab 375 mg/m² and methylprednisolone 40 mg IV weekly for 4 weeks, followed by 1 year of therapy with pegylated interferon and ribavirin. After a mean of 6 months, 10 patients (62.5%) cleared both their HCV RNA and cryoglobulin load, while another 5 (31.2%) patients had a partial response. Partial or non-responders had cryoglobulinemic vasculitis 3.6 times longer than complete responders. Renal involvement improved in 4 out of 7 patients (57.2%), polyneuropathy in 5 of 13 patients (38.4%), purpura in 11 of 13 patients (84.6%), arthralgias in 5 of 6 patients (83.4%), and leg ulcers in 2 of 2 patients (100%). This open-label pilot study suggests that rituximab in combination with peg-interferon and ribavirin may be efficacious for HCV-MC and should be studied further in a randomized trial.

ANCA-associated vasculitis

Use of rituximab for refractory or relapsing WG has been reported in case reports, case series, and studied in prospective, open-label trials [Table 2] [48-58]. Rituximab appears to be effective for the treatment of the vasculitic manifestations of WG, such as pulmonary

capillaritis and necrotizing glomerulonephritis. Whether rituximab is equally effective for the treatment of the necrotizing granulomatous manifestations of WG, such as orbital pseudotumor and subglottic stenosis, is somewhat more controversial [56], at least in part because these lesions may include some scar tissue that would not be expected to respond to immunosuppression [54]. Some of these lesions may require prolonged treatment to achieve tissue B-cell depletion [59].

The Rituximab for ANCA-associated Vasculitis (RAVE) trial is a randomized, double-blinded, placebo controlled trial currently underway to determine the efficacy of rituximab for the treatment of severe WG and MPA (ClinicalTrials.gov identifier NCT00104299). The results of this trial will help clarify the role of rituximab in the treatment of these diseases.

Conclusions

The advent of biologic therapies for the treatment of the systemic vasculitides is the beginning of a sea change in which highly toxic, broadly immunosuppressive therapies may gradually be replaced by a more targeted approach. Newer therapies directed against B-cells, T-cells, and specific cytokines will continue to profoundly affect the evolving standard of care. Enthusiasm for this new approach, however, must be tempered by our lack of experience with the long-term consequences of these agents, which largely have yet to be defined. Concerns regarding increased risk of malignancy and opportunistic infection in particular may not be clearly defined for many years [60]. Given the rarity of these diseases, international collaboration will be crucial to defining the future role of these agents for the treatment of systemic vasculitis.

Acknowledgments

Dr. Seo is a Lowe Family Scholar in the Johns Hopkins University Center for Innovative Medicine

Funding

American College of Rheumatology Research and Education Foundation's Physician Scientist Development Award

The National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases (1K23AR052820-01)

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Table 1

Infliximab use in Wegener's granulomatosis

WG= Wegener's granulomatosis; RAAV=rheumatoid arthritis associated vasculitis; MC=mixed cryoglobulinemia; CS=corticosteroids; CTX=cyclophosphamide; MTX=methotrexate; AZA=azathioprine; CR= complete remission; PR=partial remission.

Study type	Study author and year	Number of patients and disease	Infliximab regimen	Other immunosuppression	Patient outcomes
Case series	Booth 2002 [15]	3 WG, 3 MPA	200 mg every month $\times$ 3 months	CS, others not reported	5 in remission, 1 relapsed (unclear if pt had WG or MPA).
	Bartolucci 2002 [26]	7 WG (as well as 2 RAAV, 1 MC)	5 mg/kg on days 1, 14, 42, and then every 8 weeks	CS maintained or reduced, other immunosuppressants reintroduced on day 42	4 in CR and 3 in PR at 6 months. 2 flared while still receiving infliximab.
	Lamprecht 2002 [25]	6 WG	3 mg/kg (2 pts) or 5 mg/kg (4 pts) on day 1, 14, 42, and every 4 weeks until remission	CTX and CS	Remission induced for at least 6 months in 5, infliximab stopped in 1 due to suspicion of serious infection.
Prospective open-label trial	Booth 2004 [27]	10 WG (as well as 1 MPA, 3 RAAV, 1 MC; 9 were previously described in [26]); all with refractory disease	5 mg/kg on day 0, 15, 45, and then every 4-6 weeks depending on clinical response	CS and others, including MTX, AZA, and CTX depending on the pt	11 entered remission and 4 with responses by day 45, but 10 subsequently relapsed (median 13 months)—7 after stopping infliximab, 3 while receiving infliximab.
		32 WG (subgroup I: 16 with either first presentation or relapse; subgroup II: 16 with persistent disease)	5 mg/kg at 0, 2, 6, and 10 weeks	CTX and CS	14 in each subgroup (88%) achieved remission by 14 weeks. 2 deaths (pulmonary vasculitis, bronchopneumonia), 6 additional infections. Relapse occurred in 5 of the 28 initial responders (18%) at a mean of 27 weeks.

Table 2
Rituximab use in Wegener's granulomatosis

WG= Wegener's granulomatosis; MPA= microscopic polyangiitis; CSS=Churg-Strauss syndrome; AAV=ANCA-associated vasculitis; CYC=cyclophosphamide; MTX=methotrexate; AZA=azathioprine; MMF= mycophenolate mofetil; CR=complete remission; PR=partial remission.

Study type	Study author and year	Number of patients and disease	Rituximab regimen	Patient outcomes
Case series	Omdal 2005 [48]	3 refractory WG	375 mg/m ² IV qweek × 4 weeks	Remission induced in all, but disease relapse recurred in all and were preceded by the return of B cells. 2 noted to have sinus masses (1 with retro-orbital mass) worsening in spite of rituximab treatment.
	Gottenberg 2005 [49]	2 refractory WG	375 mg/m ² IV qweek × at least 3 doses	1 responded, 1 did not.
	Keogh 2005 [50]	11 refractory AAV (10 WG, 1 MPA)	375 mg/m ² IV qweek × 4 weeks	By 8 months: remission (BVAS/WG=0) achieved in all. 2 (out of 9) whose B lymphocytes returned had disease relapse. 3 treated preemptively with rituximab for rising ANCA titers.
	Eriksson 2005 [51]	9 refractory AAV (7 with WG, 2 with MPA)	500 mg IV qweek × 4 weeks in 5, 375 mg/m ² qweeks × 4 weeks in 1, 500 mg IV qweek × 2 weeks in 3, with concomitant immunosuppression (MMF, AZA, or CYC)	At 6 months: 8 in CR, 1 in PR. 2 minor nasal relapses at 12-13 months treated with increased prednisone dose. 1 relapse of cutaneous herpes infection after rituximab, 2 upper respiratory infections.
	Tamura 2007 [52]	2 refractory WG (both with retroorbital granulomata)	375 mg/m ² IV qweek × 4 weeks	Induction of remission and improvement in retroorbital granulomata for both.
	Brihay 2007 [53]	9 refractory/relapsing WG	375 mg/m ² IV qweek × 4 weeks for 7, 1000 mg IV on days 1 and 15 for 2	At 6 months: 3 with CR, 3 with PR, 2 did not respond. Constitutional and vasculitic symptoms noted to respond within days or weeks, while granulomatous manifestations regressed over several months.
	Seo 2008 [54]	8 refractory limited WG (predominately granulomatous manifestations)	375 mg/m ² IV qweek × 4 weeks	Remission induced in all. 2 treated preemptively for return of peripheral B-cells. 5 retreated for disease recurrence.
Prospective open-label trials	Keogh 2006 [55]	10 refractory WG	375 mg/m ² IV qweek × 4 weeks	At 3 months: All achieved clinical remission. 5 treated preemptively for increase in ANCA titers after B-cell return. 1 flared at 9 months after B-cell return and increased ANCA titers, was retreated with rituximab and steroids. 2 developed herpes zoster during initial infusion, 1 developed influenzae when B-cell depleted, 5 experienced a total of 13 upper respiratory infections.
	Aries 2006 [56]	8 refractory WG (5 with retro-orbital granulomata, 1 with lung nodules, 2 with subglottic stenosis)	375 mg/m ² IV q 4 weeks × 4 doses with CYC or MTX	At 16 weeks: 2 in remission, 1 in PR, 3 with unchanged disease activity, 2 with disease progression

Study type	Study author and year	Number of patients and disease	Rituximab regimen	Patient outcomes
	Stasi 2006 [57]	8 WG, 2 MPA	375 mg/m ² IV qweek × 4 weeks	At 6 months: 9 in CR, 1 in PR. 3 relapsed (between 12-24 months) and were re-treated with rituximab
	Smith 2006 [58]	5 WG, 5 MPA, 1 CSS	375 mg/m ² IV qweek × 4 weeks, and CYC 500 mg IV × 1 with first rituximab infusion; retreatment dose 1000 mg IV administered 2 weeks apart	9 achieved CR, 1 achieved PR, 1 had progressive nasal, sinus, and endobronchial WG. 6 relapsed, 5 of which occurred on or after return of peripheral B-cells and were retreated with rituximab.