

## Review

# Wegener's granulomatosis: current and upcoming therapies

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### Abstract

Wegener's granulomatosis is a complex multisystem disease that can be associated with morbidity and mortality. The introduction of cyclophosphamide and glucocorticoids brought about the potential for long-term survival and provided the opportunity and impetus to explore treatment options that can reduce the toxicity of therapy and lessen the likelihood of relapse. With the growth of knowledge regarding disease pathophysiology and the increasing ability to selectively target the immune system, the potential options for therapeutic investigation have continued to expand. Careful study of new agents through rigorously designed trials is essential to answering questions of safety and efficacy in Wegener's granulomatosis.

**Keywords:** granulomatosis, treatment, vasculitis, Wegener

### Introduction

Wegener's granulomatosis (WG) is a unique clinicopathological disease entity characterized by necrotizing granulomatous vasculitis of the upper and lower respiratory tract, pauci-immune segmental necrotizing glomerulonephritis, and small vessel vasculitis. Because of its wide range of manifestations, WG has a broad spectrum of severity that includes the potential for alveolar hemorrhage or rapidly progressive glomerulonephritis, which are immediately life threatening.

It has long been appreciated that the immune system plays a critical role in the pathogenesis of WG. Among the earliest supportive evidence was the effectiveness of cyclophosphamide (CYC) and prednisone, a potent immunosuppressive regimen, to bring about clinical improvement. This interrelationship between pathophysiology and treatment has continued to deepen, as findings from the laboratory prompt investigation of an expanding range of immunologically selective agents.

The present article will focus on the treatment of WG, examining the challenges that are faced in the exploration

of new therapies, the available data published in peer-reviewed literature on individual regimens, and the general approach to treatment.

### Challenges in therapeutic investigations for WG

The therapeutic goals in WG have expanded dramatically over the past 30 years (Table 1). Prolongation of patient survival was the primary objective prior to the 1970s as 82% of patients with active WG died within 1 year [1]. Long-term survival became possible with the introduction of prednisone and CYC [2], although morbidity and mortality continued to occur as a result of treatment-induced toxicity and disease relapse. This prompted the search for safer treatment options that reduce disease recurrence. The opportunity to explore new therapies in WG has, however, brought challenges in clinical trial design (Table 2).

Outcome measures play an important role in the evaluation of treatment efficacy in WG. Remission and relapse are the most frequently used outcome terms, which are based on disease activity. There remains no unequivocally

ANCA = antineutrophil cytoplasmic antibodies; AZA = azathioprine; CSA = cyclosporine; CYC = cyclophosphamide; Fc = crystallizable fragment; IFN = interferon; IL = interleukin; IVIg = intravenous immunoglobulin; MMF = mycophenolate mofetil; MPA = microscopic polyangiitis; MPO = myeloperoxidase; MTX = methotrexate; T/S = trimethoprim/sulfamethoxazole; Th1 = T helper cell type 1; TNF = tumor necrosis factor; WG = Wegener's granulomatosis.

**Table 1****Goals of treatment for Wegener's granulomatosis**

Patient survival
Induce remission of active disease
Reduce disease relapse
Minimize therapeutic toxicity
Use the least toxic yet effective treatment option
Actively pursue strategies to prevent and monitor for toxicity
Use treatment regimens at doses and schedules on which there are rigorous published data

reliable means by which to confirm active disease, and assessment is based on clinical parameters from physical examination, from the laboratory, and from radiographic studies. The difficulty of determining disease activity is further compounded in multicenter trials, as definitions may not be universal between investigators. A significant area of progress in the conduct of clinical trials for WG has been the recognized necessity of having predefined outcome measures and their definition in the published methods. As a means of standardizing the assessment of disease activity, the development and validation of instruments has been actively sought [3]. This work underscores the importance for definition of outcome measures in all studies of new therapeutic agents.

Clinical trial design in WG is influenced by the effectiveness of available therapies. This is most importantly due to the potential for active WG to be a life-threatening disease. Study design must address the patient population to be enrolled, the patients' severity of disease, and how standard therapies impact the regimen being examined. Current treatment approaches also influence sample size estimates and the length of follow-up. As CYC and prednisone induce remission of active WG in 75–100% of patients [4–6], approximately 200 patients per arm would be required to test a comparative agent of remission induction. Use of sustained remission as a primary outcome measure similarly presents a challenge to following induction treatment with CYC and glucocorticoids, as 80–83% of patients remain in remission at 18 months [6,7].

Conducting therapeutic studies in WG is additionally complicated by the disease rarity. Based upon an analysis using the National Hospital Discharge Survey, the 1986–1990 United States prevalence of WG was estimated to be three per 100,000 persons [8]. While there remains an important role for rigorous standardized, early-phase, open-label studies, randomized, multicenter trials are being pursued to further address comparative issues of efficacy.

**Table 2****Challenges in conducting therapeutic trials in Wegener's granulomatosis**

Rarity of Wegener's granulomatosis
Potential for active disease to be life threatening
Available treatment of established efficacy
Definition of outcome measures
Imprecise means of assessing active disease
Extended follow-up is necessary to fully assess relapse and to reach study endpoints

**Therapeutic data in WG**

When evaluating any therapeutic publication in WG, the study methods must be judiciously examined (Table 3). The peer-reviewed literature to date contains very few sufficiently powered randomized trials in WG, with retrospective series and case reports forming a substantial proportion of the published therapeutic literature. Most of the data on which current treatment is based comes from prospective standardized, open-label trials.

In the following sections, the data for therapeutic agents used in WG and their immunologic effects will be reviewed. The pathogenetic mechanisms through which the currently utilized treatments act in WG remain unclear. With the exception of the selective immunomodulatory agents that are being explored investigationaly, each of these therapies has broad effects on the immune response. While this has probably been instrumental in the efficacy of these agents, it is also frequently responsible for their observed toxicities.

**Glucocorticoids**

Prior to the time when treatment became available, active WG was a rapidly fatal disease in which patients survived a median of 5 months [1]. Glucocorticoids were the first applied therapy and, while some patients transiently improved, the median survival time remained only 12.5 months [9]. In a National Institutes of Health cohort, 96% of patients who had been treated with glucocorticoids alone prior to referral had progressive disease [10]. Of the 45 patients with renal involvement, none experienced sustained improvement with glucocorticoid monotherapy. These data support glucocorticoids alone being insufficient therapy for active WG affecting a major organ, and for glomerulonephritis in particular.

**Cyclophosphamide**

The immunosuppressive properties of cytotoxic agents became appreciated during the 1950s and 1960s. Emerging in concert with these findings was evidence that

**Table 3**

**Points to evaluate in assessing a Wegener's granulomatosis therapeutic study**

Type and design of study	Retrospective, prospective, open-label, randomized Single center or multicenter
Study size	For open-label trials, how many patients were included? For randomized trials, were the sample size per arm and power sufficient to draw conclusions?
Patient population	Did the study enroll patients with other forms of vasculitis? How was Wegener's granulomatosis diagnosed? Were patients enrolled at initial diagnosis or relapse?
Site of organ involvement	What was the distribution of organ involvement? Were there any patients who had disease isolated to nonmajor organ sites such as the skin, the joint, or the sinus? Were patients enrolled for sites known to be of limited medical responsiveness (i.e. subglottic stenosis)? Were methods in place to rule out other processes that could have the appearance of active disease?
Definition of outcome measures	How did the study define active disease, remission, and relapse? Were outcome measures clearly defined in the methods?
Concurrent therapies	Were immunosuppressive therapies used concurrently with the agent or regimen being studied?
Standardization	Did all enrolled patients receive a standardized dose and duration of the study agent? Was the glucocorticoid dose and taper standardized? At what point in time did patients enter the study (i.e. at beginning of induction or at remission)?
Study duration	What was the median follow-up time? Were patients followed for sufficient duration to observe relapses?

immunologic mechanisms played an important role in the pathophysiology of WG. Based upon these observations, case reports began to appear on the use of cytotoxic agents in WG. The efficacy of these approaches remained uncertain until 1973, when Fauci and Wolff explored the immunologic and clinical effects of CYC and glucocorticoids in WG [2].

CYC is an alkylating agent that results in cross-linking of DNA, in decreased DNA synthesis, and in apoptosis. The actions of CYC also impact on a number of components of the immune response including decreasing the number of both T lymphocytes and B lymphocytes, reducing lymphocyte proliferation, decreasing antibody production, suppressing delayed hypersensitivity to new antigens, and interfering with the function of both resting and stimulated B lymphocytes.

In the regimen studied by Fauci and Wolff, 2 mg/kg/day CYC is given together with 1 mg/kg/day prednisone [11]. At the end of 1 month, if there is evidence of improvement, the prednisone is tapered to an alternate day schedule over 3 months and discontinued by 6–9 months. CYC is maintained for 1 year past remission, after which time it is tapered and discontinued. Of 133 patients who were treated with daily CYC and prednisone at the National Institutes of Health over a 24-year span, 91% had a marked improvement in their disease, 75% achieved a

complete remission, and an 80% survival rate was seen [4]. Reinhold-Keller and colleagues similarly observed a median survival of 21.7 years in their series of 155 patients, 92% of whom received CYC and prednisone [12].

Despite the efficacy of daily CYC and prednisone to induce remission, 50% of patients in the National Institutes of Health series later went on to relapse, and 42% experienced serious morbidity from the side effects of treatment [4]. CYC has significant toxicities including bone marrow suppression, infection, infertility, myelodysplasia, and bladder injury. Talar-Williams and colleagues reported that, of 145 WG patients treated with daily CYC, 6% developed transitional cell carcinoma of the bladder, which by Kaplan–Meier estimates may rise to 16% 15 years following the first exposure to CYC [13]. While extended analyses have therefore confirmed the ability of CYC and glucocorticoids to prolong patient survival in WG, they also supported the exploration of further treatment options.

**Intermittent CYC**

Interest in the use of intermittent CYC in WG was encouraged by its successful application in systemic lupus erythematosus. Reduction of toxicity also motivated the use of intermittent CYC, although it remains unclear whether the risk of myelodysplasia, infertility, or bladder cancer is influenced by the frequency of administration or the cumulative CYC dose.

The utility of intermittent administration in WG has remained controversial. Much of the literature in which efficacy has been concluded has come from retrospective nonstandardized series and from prospective inception cohort studies [14]. Prospective standardized data involving more than 10 patients are available from two nonrandomized studies and from three randomized trials. In one open-label prospective study of 14 patients, 93% had initial improvement and 50% achieved remission, but only 21% had a sustained remission [15]. In another open-label series of 43 patients, 42% sustained a partial or complete remission for 6 months after discontinuation of intermittent CYC [16].

In examining the three randomized trials that compared intermittent CYC with daily CYC, two of them included patients with microscopic polyangiitis (MPA) or polyarteritis nodosa and the maximum enrollment was 30 patients per arm [5,17,18]. None of these trials therefore had sufficient power to draw conclusions of equivalence. In examining the results, the two trials found no difference in the rate of survival, remission, or relapse between intermittent CYC and daily CYC. In the one randomized trial that enrolled only patients with WG, a similar rate of remission was seen in both groups, but the relapse rate in the intermittent CYC group was 52% as compared with 18% in those who received daily CYC [5].

de Groot and colleagues performed a detailed examination of the literature where intermittent CYC had been used in the treatment of WG [19]. The tables in their paper illustrate the wide range of CYC doses and administration frequency, concurrent therapies, and vasculitic diseases that have been encompassed by past publications. These authors performed a meta-analysis of the three randomized trials, which suggested that, compared with daily CYC, intermittent CYC was less likely to fail to induce remission and was less toxic, but was associated with a higher relapse rate. However, the diverse designs in the individual trials confound the ability to draw any conclusions from their collective analysis.

Data from the available prospective standardized studies suggest that intermittent CYC in WG is associated with a high frequency of relapse. Although some authors believe intermittent CYC and daily CYC to be of equal efficacy to induce remission, this remains unproven by a sufficiently powered trial.

#### **Staged regimens for induction and remission maintenance**

With the goal of reducing toxicity, recent studies have examined the use of staged regimens whereby the use of CYC is confined to the period of time needed to induce remission, after which time CYC is stopped and remission is maintained with a less toxic medication. Methotrexate

(MTX) and azathioprine (AZA) have been evaluated for remission maintenance.

Langford and colleagues conducted a prospective standardized, open-label trial in which 42 patients with active WG received 2 mg/kg/day CYC and 1 mg/kg/day prednisone to induce disease remission, followed by 20–25 mg/week MTX for remission maintenance [6,20]. Patient survival was 98%, with one death occurring from a myocardial infarction not related to vasculitis. Remission was achieved in 100% of patients at a median time of 3 months, which represented the duration of CYC exposure. Twenty-two patients (52%) relapsed, with glomerulonephritis occurring in 16 patients. Serum creatinine increased by  $\geq 0.2$  mg/dl in four patients (maximum elevation, 0.4 mg/dl) but returned to baseline with treatment. Two patients (5%) had to withdraw from the study as a result of MTX pneumonitis.

In another study, Reinhold-Keller and colleagues treated 71 patients with intravenous 0.3 mg/kg/week MTX after complete or partial remission was induced with daily CYC [21]. The mean duration of CYC was 13.8 months (range, 1–66 months). Seventy patients received glucocorticoids for remission induction and 55 remained on this therapy at the start of the study. Of the 26 relapses (37%) 16 had glomerulonephritis, with 14 patients exhibiting a rise in serum creatinine to 1.5–2.0 mg/dl. One patient relapsed with rapidly progressive glomerulonephritis and pulmonary hemorrhage that was fatal. Leukopenia prompted withdrawal of MTX in two patients and dosage reduction in an additional seven patients, but there were no occurrences of pneumonitis or serious infection.

In contrasting the two open-label studies, both found MTX to be a well-tolerated therapy for the maintenance of remission in WG, but they varied in the severity of renal relapse. The reason for such divergent findings is unclear, although differences in study design were present. Given the potential for glomerulonephritis to be asymptomatic and rapidly progressive, close renal surveillance is important, regardless of the treatment regimen.

AZA has also been evaluated for remission maintenance. Initial reports from open-label series suggested that AZA may be able to maintain remission following induction with daily CYC [11]. The European Vasculitis Study Group conducted a randomized trial investigating CYC or AZA as a remission therapy for vasculitis in patients with active generalized WG or MPA. Preliminary results from this trial have been published in abstract and review publications [7]. All patients in the European Vasculitis Study Group trial received the same regimen of daily CYC and prednisolone until remission (between 3 and 6 months), after which time they were randomized to receive CYC or AZA. There was no difference in relapse rate between the two arms at

18 months. Adverse events were frequent, with a nonsignificant trend to fewer severe, adverse events with AZA.

### Methotrexate

Encouraging results from case reports as well as its potential mechanisms of action prompted the investigation of MTX as a therapeutic agent for WG. MTX inhibits dihydrofolate reductase and, at pharmacologic concentrations, can increase adenosine accumulation and release from cultured fibroblasts and endothelial cells [22]. (Adenosine inhibits neutrophil adhesion to endothelial cells, inhibits generation of toxic oxygen metabolites, inhibits production of tumor necrosis factor [TNF], and may increase the secretion of IL-10.)

The use of low-dose MTX and glucocorticoids to induce remission has been studied in patients with active WG who had nonimmediately life-threatening disease [23]. In a prospective standardized, open-label trial, Sneller and colleagues treated 42 patients with 1 mg/kg/day prednisone and 20–25 mg/week MTX [24]. Remission was induced in 33 of 42 patients (79%). Nineteen patients (58%) experienced a relapse, 79% of which occurred when the MTX dose was  $\leq 15$  mg/week [25]. The MTX and prednisone regimen was ineffective at controlling disease activity in only three (7%) patients, who then achieved remission after treatment with daily CYC. Three fatalities occurred in this study, two from *Pneumocystis carinii* pneumonia and one from a pulmonary embolism. Three patients (7%) withdrew because of MTX pneumonitis.

MTX is contraindicated in the setting of renal insufficiency, which presents a limitation to its use in some patients with WG. Even in the setting of normal renal function, some physicians have expressed concern about using MTX in patients with glomerulonephritis. In the trial by Sneller and colleagues, although patients with poor renal function or rapidly progressive renal failure were excluded, 50% had active glomerulonephritis. The presence of glomerulonephritis did not influence the likelihood of achieving remission, the time to remission, or the duration of remission. An analysis of the long-term renal outcome of this population found that, of the 20 patients who achieved renal remission, two patients had a rise  $>0.2$  mg/dl in their serum creatinine, 12 patients had stable renal function, and six patients had improvement in their serum creatinine [26]. These findings suggest that the use of MTX to treat selected patients with WG-associated glomerulonephritis and a normal or near normal serum creatinine was not associated with a long-term decline in renal function.

Two other studies have examined the use of MTX for the induction of remission in WG. In a prospective open-label study, de Groot and colleagues treated 17 patients with intravenous 0.3 mg/kg/week MTX combined with prednisone [27]. Ten patients (59%) achieved a complete or

partial remission, with the seven patients who did not respond having received a median prednisone dose of only 7.5 mg daily. Significant side effects, including opportunistic infections, did not occur. In a retrospective series of 19 patients treated by Stone and colleagues, the combination of MTX and 20–60 mg prednisone daily brought about remission in 74% of patients [28]. Eight patients (57%) relapsed while taking a mean MTX dose of 10.8 mg/week. Two patients discontinued MTX for elevated liver enzymes, but there were no cases of opportunistic infection, pneumonitis, or cytopenia.

### Azathioprine

The ability for AZA to be given to patients with renal insufficiency and the comparative safety compared with CYC has made it an attractive immunosuppressive agent in WG. AZA is a purine analog and a prodrug of 6-mercaptopurine. Metabolites of AZA have been shown to inhibit *de novo* synthesis of purine ribonucleotides, to inhibit purine ribonucleotide interconversion, and to incorporate into cellular DNA and RNA. Mechanisms through which AZA may impact on immune function include suppression of lymphocyte proliferation, suppression of natural killer cell activity, inhibition of monocyte and antibody production, and inhibition of cell-mediated and humoral immunity.

Limited data examining the use of AZA and prednisone for induction of remission have not supported efficacy. In one series, 10 of 11 patients with active WG treated with AZA did not achieve remission and had progressive organ dysfunction [11]. However, as discussed under staged regimens, data from open-label and randomized trials suggest that AZA can maintain remission after induction with CYC [7].

### Mycophenolate mofetil

Mycophenolate mofetil (MMF) is an ester prodrug of mycophenolic acid, which is a noncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase. Inhibition of inosine monophosphate dehydrogenase blocks the *de novo* synthesis of guanosine nucleotides, which are necessary substrates for DNA and RNA synthesis. Unlike other cell types, lymphocytes rely solely on the *de novo* pathway for the generation of guanosine. *In vitro*, MMF has been shown to inhibit proliferative responses of T lymphocytes and B lymphocytes, to suppress antibody formation by B lymphocytes, and to prevent the glycosylation of glycoproteins involved in intercellular adhesion of leukocytes to endothelial cells. MMF has been successfully used in renal transplantation where randomized trials have found MMF to be superior to AZA in reducing the risk of acute rejection during the first 6 and 12 months following surgery.

Nowack and colleagues performed an open-label, prospective standardized study to examine 1000 mg MMF

twice per day in nine patients with WG and in two patients with MPA following remission induction with daily CYC [29]. Of the 11 patients, one WG patient (9%) relapsed in the 14th month of maintenance therapy. Adverse events included abdominal pain, diarrhea, respiratory infection, leukopenia, and cytomegalovirus colitis. Although encouraging results have also been found in case reports, the experience with this agent remains limited.

#### **Other cytotoxic and immunosuppressive agents**

The experience with other cytotoxic and immunosuppressive agents in the treatment of WG comes solely from case reports and small series. Interpretation of these findings is often further confounded by the lack of outcome measures and concurrent use of other therapies. For each of these agents, there remain insufficient data to assess efficacy, and they should be considered only where a contraindication to CYC, MTX, or AZA exists. The agents now discussed include only those for which there has been published experience in more than five patients.

##### *Cyclosporin*

Cyclosporin (CSA) is a calcineurin inhibitor that blocks the transcription of IL-2 and other cytokines in activated T lymphocytes. A major drawback of CSA in WG is its potential for nephrotoxicity and hypertension. Five patients in one open-label, prospective trial were treated with 5 mg/kg/day CSA [30]. All five patients had stabilization or improvement of their WG, but worsening occurred in two patients upon dosage reduction to 3 mg/kg/day. In another prospective open-label trial, 2 mg/kg CSA was given to three patients with WG and to four patients with MPA after remission had been achieved for 6 months with prednisone and intermittent CYC or daily CYC [31]. No patient developed a relapse during a mean follow-up period of 24 months after the end of CYC treatment.

##### *Deoxyspergualin*

Deoxyspergualin is a synthetic analog of spergualin, a product of *Bacillus laterosporus* that has immunosuppressive properties. The mechanism of action of deoxyspergualin is unclear, although effects on B-cell differentiation and T-lymphocyte maturation have been described. In a prospective open-label study by Birck and colleagues, deoxyspergualin was given to 20 patients with WG or MPA who had resistance or contraindications to standard therapy [32]. Leukopenia was an expected drug effect and occurred in all patients. Mild to moderate infections were observed, not associated with mortality or sepsis. Disease improvement was said to occur in 70% of cases, although outcome measures were not clearly defined.

##### *Intravenous immunoglobulin*

The investigation of intravenous immunoglobulin (IVIg) in WG was prompted by the detection of anti-idiotypic antibodies to antineutrophil cytoplasmic antibodies (ANCA) in

IVIg preparations together with the proven efficacy of IVIg in Kawasaki disease [33]. Three open-label studies and one randomized trial have been published.

In one open-label study, IVIg was given alone or in combination with other therapies for 5 days [33,34]. Reduction of disease activity occurred in 13 of the 14 patients (eight patients with WG, five patients with MPA, and one patient with rheumatoid vasculitis), with remission being achieved in eight patients. In another open-label trial, 14 patients with WG and one patient with ANCA-associated systemic vasculitis were treated with IVIg over 5 days [35]. Six patients experienced musculoskeletal, cutaneous, or otolaryngeal benefit from IVIg, but there was no improvement of ophthalmic, pericardial, pulmonary, or renal manifestations, and no patient achieved complete remission. IVIg alone has also been used to treat six patients with WG or MPA without threatened vital organ involvement [36]. In this open-label study, two patients had a partial response but went on to require conventional treatment and four patients entered remission, two of which later relapsed. In the single randomized trial, 34 patients with active ANCA-associated systemic vasculitis despite 2 months of prednisone and CYC or AZA treatment received 0.4 g/kg/day IVIg for 5 days or placebo [37], in addition to their previous immunosuppressive regimen. IVIg resulted in a statistically significant therapeutic response compared with placebo, but this was not sustained beyond 3 months. While these collective data are small and potentially confounded by the use of concomitant therapies, they do not currently support the use of IVIg in the treatment of active WG involving a major organ.

##### *Trimethoprim/sulfamethoxazole*

DeRemee and colleagues reported in 1985 that trimethoprim/sulfamethoxazole (T/S) brought improvement in 11 of 12 patients with WG [38]. Several investigators believe that T/S is anti-inflammatory through interference with the formation of oxygen-derived radicals by activated neutrophils. Other workers assert that the actions of T/S in WG are related to antimicrobial effects. Mucosal damage predisposes patients with WG to bacterial superinfection. *Staphylococcus aureus* is the organism most frequently cultured from the upper airways of patients with WG and can be found in the absence of clinical infection [11,39]. From *in vitro* and *in vivo* studies, *S. aureus* can stimulate an immune response characterized by proliferation of T lymphocytes and B lymphocytes, by secretion of immunoglobulin, and by increased cytokine production [40]. Investigation of *S. aureus* in WG remains ongoing, but it is currently unclear whether this organism plays a role in triggering or mediating disease pathophysiology.

T/S has been found in several reports to be beneficial in treating WG limited to the upper and/or lower airways. Interpretation of these results is confounded by their retro-

spective nature, by the use of concurrent immunosuppressive agents, by the difficulty in defining active upper airways disease, and by the lack of controlling for infection. In one prospective series of nine patients in which these factors were addressed, three patients improved but failed to achieve remission while the remaining six patients had disease progression [41]. In another prospective study of 19 patients treated with T/S alone for disease limited to the upper and/or lower airways, eight patients (42%) had progression [42]. The role of T/S in the management of isolated upper airways disease remains incompletely defined; however, T/S monotherapy should never be used in the setting of glomerulonephritis or any other severe disease manifestations.

T/S has also been studied for its ability to decrease relapses. Stegeman and colleagues conducted a randomized, placebo, controlled trial in which 81 patients who achieved remission with CYC and prednisone received 160 mg/800 mg T/S twice daily or placebo [43]. At 24 months, 82% of patients in the T/S group were in remission as compared with 60% of the placebo group. Only the recurrence of nasal or upper airway lesions was significantly reduced, however, and no difference was observed in relapses involving other organ systems. T/S was discontinued in 20% of patients because of side effects. Based upon these data, the use of T/S for relapse prevention must be considered on an individual basis. MTX-treated patients can safely receive 160 mg/800 mg T/S three times a week to provide prophylaxis against *P. carinii*, but twice-daily dosing should not be combined with MTX as this may cause life-threatening bone marrow suppression.

One of the most important roles for T/S in WG has been as a prophylactic agent against *P. carinii* [24]. As this infection carries a mortality rate of up to 35%, treatment with T/S to provide prophylaxis against *P. carinii* is recommended for all nonsulfa-allergic WG patients who are receiving a cytotoxic agent combined with glucocorticoids.

### Nonmedical treatment modalities

Subglottic stenosis occurs in about 20% of patients with WG and is typically unresponsive to systemic immunosuppressive therapy. One approach that has been effective is a surgical technique that combines mechanical dilation of the trachea with the intratracheal injection of a long-acting glucocorticoid. In one series of 20 patients treated with intratracheal therapy, none required tracheostomy and six patients with previous tracheostomies were decannulated [44]. Patients who require immunosuppressive treatment for other manifestations of WG should undergo this procedure concurrently. However, in the absence of major organ disease activity, WG-related subglottic stenosis can be optimally managed using this technique alone.

The role of plasmapheresis in the treatment of WG has remained unclear. Plasmapheresis is most commonly considered in the setting of immediately life-threatening disease; in particular, severe glomerulonephritis. The hypothesis for its potential utility has included the removal of inflammatory mediators and ANCA. Plasmapheresis has not been specifically studied in WG, and the available data from polyarteritis nodosa and pauci-immune crescentic glomerulonephritis have not been of sufficient size to resolve the question of its efficacy [45]. The use of plasmapheresis remains actively investigated, but at this time the unknown benefits must be weighed against the risks of a large-bore vascular catheter and potential hemodynamic instability.

### Selective immunomodulatory agents

Monoclonal antibody and recombinant DNA technology has led to an expanding range of therapies capable of directly targeting components of the immune response. The evaluation of these agents in WG may provide both new treatment options and insights into disease pathogenesis. Although reports on the use of biologic agents in WG have begun to appear in the literature, none of these allow any conclusions to be drawn regarding their efficacy. As biologic agents have the potential for unexpected toxicities and effects on disease, it is critical that they be further investigated in WG prior to their use in clinical practice.

#### *Alemtuzumab*

Alemtuzumab (CAMPATH-1H) is a humanized monoclonal antibody directed against cell surface CD52 expressed on normal and malignant B lymphocytes and T lymphocytes, on natural killer cells, and on macrophages. Lockwood and colleagues conducted a series of studies during the 1990s examining alemtuzumab, often with anti-CD4 in selected patients with treatment-resistant systemic vasculitis [46]. The findings included both remissions as well as side effects consisting of infusion reactions, infection, autoimmune events, and prolonged lymphocyte depletion. While these studies suggest the toxicity of alemtuzumab to outweigh its benefits, they provided the first exploration of a monoclonal antibody in WG.

#### *TNF modulation: etanercept and infliximab*

TNF modulatory agents have raised interest in the treatment of WG because of the potential role of Th1 cytokines in this disease. Activated peripheral blood CD4<sup>+</sup> T lymphocytes from patients with active WG have been found to produce 10-fold to 20-fold higher levels of interferon (IFN)- $\gamma$  compared with healthy controls [47]. Increased production of TNF by activated CD4 T lymphocytes and of IL-12 by purified monocytes was also noted, but production of IL-4, IL-5, and IL-10 from patients with WG did not differ from controls. A Th1 pattern of cytokine expression has also been exhibited by T-cell clones

isolated from WG nasal biopsy specimens displaying granulomatous inflammation and, to a lesser extent, T-cell clones and T-cell lines generated from bronchoalveolar fluid [48]. Based on these observations, a hypothetical pathogenic mechanism would be that patients with WG have an immunoregulatory defect that, following exposure to an infection and/or autoantigen, leads to an unbalanced production of Th1 cytokines with initiation and perpetuation of the granulomatous vascular lesion that is characteristic of WG.

Stone and colleagues treated 20 WG patients with etanercept, a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kDa TNF receptor linked to the Fc portion of human IgG<sub>1</sub> [49]. Patients in this 6-month, open-label, phase I study received 25 mg etanercept twice a week in combination with standard therapies for WG. Etanercept was well tolerated with few adverse events, and concurrent treatment with other immunosuppressive agents did not appear to increase toxicity.

Three reports, each including less than 10 patients with WG, have utilized infliximab, a chimeric IgG<sub>1</sub> monoclonal antibody that binds to TNF. Lamprecht and colleagues examined the use of infliximab in six patients with refractory WG [50]. Patients received infliximab (3 mg/kg in two patients and 5 mg/kg in four patients), with a 2-week interval after the first administration and 4-week intervals between infusions until remission, in addition to CYC and glucocorticoids. Remission was induced in five patients and glucocorticoid doses were tapered. No serious side effects occurred, although one patient was withdrawn for a suspected systemic infection.

Booth and colleagues described their experience with 200 mg infliximab given at monthly intervals for 3 months in three patients with WG and in three patients with MPA who had relapsing vasculitis [51]. Five patients had remission of their disease, with treatment allowing glucocorticoid withdrawal in three patients and reduction by more than 50% in two patients. One patient experienced fatigue, myalgia, and blurred vision 24 hours after the first infusion, but infliximab was otherwise well tolerated.

Ten patients with refractory vasculitis (seven patients with WG, two patients with rheumatoid vasculitis, and one patient with cryoglobulinemic vasculitis) were treated by Bartolucci and colleagues. The patients received 5 mg/kg infliximab on days 1, 14, and 42, and then every 8 weeks for 6 months [52]. Immunosuppressive agents were held between days 0 and 42 in eight patients while glucocorticoids were maintained or decreased. Complete or partial remission occurred in all patients. Infliximab was well tolerated, with two patients experiencing a transient cutaneous eruption, one of which discontinued therapy.

### **B-lymphocyte depletion: rituximab**

Specks and colleagues examined the use of rituximab, a chimeric monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes, in a patient with relapsing PR3-ANCA-positive WG who had resistance or intolerance to standard therapies [53]. In this case report, rituximab was used with the hypothesis that elimination of pathogenic ANCA would lead to the induction and maintenance of remission.

First described in 1982, ANCA are antibodies directed against proteins in the primary granules of neutrophils and in the lysosomes of monocytes [54]. More than 80% of patients with typical active WG have detectable antibodies to proteinase-3, a 29 kDa serine proteinase present in neutrophil azurophilic granules. Antimyeloperoxidase ANCA, which are more frequently seen in MPA, can occur in 5–20% of patients with WG.

Although a number of *in vitro* observations have suggested potential mechanisms whereby ANCA could contribute to the pathogenesis of WG, the strongest evidence has come from a recently described animal model. Xiao and colleagues took myeloperoxidase (MPO) knockout mice and immunized them with murine MPO [55,56]. Splenocytes from these mice or from control mice were injected into recombinase-activating gene-2-deficient mice. All mice developed glomerular immune deposits but mice receiving anti-MPO splenocytes developed necrotizing and crescentic glomerulonephritis, granulomatous inflammation, and systemic vasculitis. To test the pathogenic potential of the antibodies alone, purified anti-MPO IgG or control IgG was injected into recombinase-activating gene-2-deficient mice and into wild-type mice. Mice that received anti-MPO IgG but not mice that received control IgG developed a pauci-immune focal necrotizing and crescentic glomerulonephritis. Although these data support direct pathogenicity of ANCA in the mouse model, there remain unanswered questions in human disease. While this evidence would support the direct pathogenicity of ANCA, the observation that patients with high-titer ANCA can lack glomerulonephritis and may remain in remission suggests that additional factors modulate disease occurrence in humans.

In the patient described by Specks and colleagues, ANCA became negative by the end of the four weekly infusions of 375 mg/m<sup>2</sup> rituximab, which was followed by evidence of clinical improvement [53]. The ANCA titer started to increase 9 months after treatment, which was preceded by a return of CD19<sup>+</sup> B cells. Although the patient remained in remission, the decision was made to treat him with a second course of rituximab. Following these infusions, the patient's ANCA persisted at high levels but the disease remained in clinical remission. The persistence of ANCA after the second course of rituximab in this patient



**Table 4**

**Points to consider when deciding on a treatment regimen for a patient with active Wegener's granulomatosis**

Is the disease active?	Differentiate active disease from: <ul style="list-style-type: none"> <li>Chronic sequelae of disease</li> <li>Medication toxicity</li> <li>Other diseases (in particular, infection)</li> </ul>
How severe is the active disease?	Immediately life-threatening disease necessitates initial treatment with cyclophosphamide and glucocorticoids
What organ sites are being affected?	Certain sites of organ involvement, particularly subglottic stenosis, may not require or may not respond to systemic immunosuppressive therapy
What is the data on different therapeutic regimens?	What is the data for the regimen being considered (see Table 3)? <ul style="list-style-type: none"> <li>Has the regimen improved survival?</li> <li>What is the likelihood of inducing remission?</li> <li>What is the relapse rate?</li> <li>What are the known toxicities?</li> </ul>
Consideration of individual patient factors	History of medication toxicity Contraindications to certain medications Presence of previous organ damage Relapse history with past treatment regimens Age Gender

and his continued remission raises new questions about the role of ANCA and B lymphocytes in disease pathogenesis, about the origin of ANCA, and about the longevity of plasma cells. Further therapeutic exploration of B-lymphocyte depletion together with the recent advances in the mouse model may shed new insights into the role of ANCA and humoral immunity in WG.

**General therapeutic approach**

With the expansion of therapeutic options in WG, physicians will increasingly need to choose between different treatment approaches in the care of their patients. In the absence of direct comparative trials, decisions regarding a management plan for an individual patient can be assisted by considering several points, outlined in Table 4.

Glucocorticoids combined with CYC or MTX are the only two regimens that have thus far been shown to induce remission of active WG affecting a major organ. Patients with alveolar hemorrhage, rapidly progressive glomerulonephritis, central nervous system disease, or other manifestations that are immediately life threatening should initially be treated with CYC and glucocorticoids. Once remission has been induced, consideration can be given to stopping CYC and beginning AZA or MTX treatment to maintain remission. As there have been no randomized trials comparing non-CYC maintenance agents, the choice

of maintenance therapy should be based on medication contraindications and toxicity profiles, on the patient's relapse and disease history, and on physician experience with each medication. In patients with active WG that is not immediately life threatening, the decision whether to use CYC or MTX for remission induction must again be based on individual factors as there have been no head-to-head assessments. Because of its potential toxicity, CYC is rarely if ever justified for treating disease activity isolated to the sinus, to the skin, or to the joint.

Monitoring and prevention of therapeutic toxicities play an important role in overall patient management. This includes pneumocystis prophylaxis as discussed earlier (see Trimethoprim/sulfamethoxazole section), osteoporosis prevention regimens with concurrent glucocorticoid treatment, as well as medication-specific strategies (Table 5).

**Conclusion**

The therapeutic literature in WG has provided physicians not only with current life-saving treatments, but also with an important foundation for planning the future study of new approaches. Although substantial progress has been made, challenges remain in the search for regimens that reduce disease relapse and therapeutic toxicity. Exploration of the pathophysiology of WG together with the development of targeted immunomodulatory agents may

**Table 5****Cytotoxic medications frequently used in the treatment of Wegener's granulomatosis: strategies to monitor for and prevent toxicity**

Medication	Toxicity	Strategy for monitoring or prevention
Cyclophosphamide	Bone marrow suppression	Complete blood counts every 1–2 weeks to maintain the total leukocyte count above 3000/mm <sup>3</sup>
	Bladder injury	Administer all at once in the morning with a large amount of fluid Consideration of MESNA if intermittent dosing is given
	Transitional cell carcinoma of the bladder	Urinalysis every 3–6 months
		Cytology every 6 months Cystoscopy in patients with nonglomerular hematuria or abnormal cytology If bladder injury present, cystoscopy every 1–2 years
Methotrexate	Bone marrow suppression	Complete blood counts weekly while adjusting dose, and every 4 weeks thereafter Consider use of 5–10 mg calcium leucovorin weekly 24 hours after methotrexate, or 1 mg folic acid daily
	Hepatic injury and fibrosis	Monitor liver function tests every 4 weeks Liver biopsy based on guidelines established by the American College of Rheumatology Alcohol consumption prohibited
	Mucositis	Consider use of 5–10 mg calcium leucovorin weekly 24 hours after methotrexate, or 1 mg folic acid daily
Azathioprine	Bone marrow suppression	Complete blood counts weekly for the first 2 weeks and every 4 weeks thereafter
	Transaminase elevation	Monitor liver function tests every 2 weeks for the first month, every 1–3 months thereafter

MESNA, sodium 2-mercaptoethanesulphonate.

provide increasing treatment options. As new therapeutics are introduced, careful study is essential in order to understand their disease mechanisms and, more importantly, their safety and efficacy in WG. Until such time when these data become available, conventional immunosuppressive agents will continue to provide an efficacious means of inducing remission of active disease in patients with WG.

### Competing interests

Amgen Corporation provides the study drug for a clinical trial on which CL is the Principal Investigator.

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