

Advances in the therapy of Wegener's granulomatosis

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Purpose of review

In the past, recommendations for the treatment of Wegener's granulomatosis were primarily based on findings reported from open-label clinical trials. Results from several randomized controlled trials in patients with Wegener's granulomatosis and other antineutrophil cytoplasm antibody-associated vasculitides have recently been reported that have a great impact on patient care.

Recent findings

In view of the considerable toxicity of cyclophosphamide, strategies to limit exposure to it have recently been evaluated. The replacement of cyclophosphamide by azathioprine after the successful induction of remission has been demonstrated not to increase the rate of relapse compared with continued cyclophosphamide. In patients with early antineutrophil cytoplasm antibody-associated vasculitides without critical organ manifestations low-dose methotrexate can replace cyclophosphamide for induction treatment with similar remission rates. As the early discontinuation of immunosuppressive treatment is associated with unacceptably high relapse rates, however, treatment for the maintenance of remission is mandatory. Besides azathioprine, leflunomide and methotrexate were efficacious in preventing relapses in Wegener's granulomatosis. Data on anticytokine therapy in Wegener's granulomatosis are controversial, possibly related to differences in study design. Open-label clinical studies suggest a beneficial effect of infliximab in addition to standard therapy in refractory Wegener's granulomatosis. In contrast, a recent randomized controlled trial showed that etanercept in addition to standard therapy, with the subsequent tapering of standard medications, is not effective for the maintenance of remission.

Summary

Despite recent progress, the prevention of relapses and treatment of refractory cases remain the greatest challenges in the treatment of Wegener's granulomatosis.

Keywords

cyclophosphamide, methotrexate, tumour necrosis factor, Wegener's granulomatosis

Abbreviations

AAV	antineutrophil cytoplasm antibody-associated vasculitis
ANCA	antineutrophil cytoplasm antibody
BVAS	Birmingham Vasculitis Activity Score
EUVAS	European Vasculitis Study Group
MMF	mycophenolate mofetil
MPA	microscopic polyangiitis
NORAM	Non-Renal Wegener's Granulomatosis Treated Alternatively with Methotrexate trial
WG	Wegener's granulomatosis
WGGET	Wegener's Granulomatosis Etanercept Trial

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Introduction

As a result of the lack of randomized controlled clinical trials, recommendations for the treatment of Wegener's granulomatosis (WG) need to be largely based on the evaluation of certain treatments across different clinical studies. One basic requirement for such comparisons across clinical trials is a comparable trial methodology. This, however, has not been the case in many recent studies. First, although in most studies the same criteria were used for the classification of WG, investigators from both sides of the Atlantic have often used divergent definitions for disease stages for subclassification into clinical subgroups (Table 1) [1–10,11^{**},12–14]. Second, definitions of outcome parameters and disease states have not been uniform across clinical trials. Outcome is usually defined in terms of disease states such as remission or relapse (Table 2) [5,14–17,18^{**},19^{*},20–22,23^{*},24], and is quantified by the use of disease assessment instruments. Although being distinct in some items, the preliminary results of a comparative multicentre case exercise by experienced investigators indicated that the Birmingham Vasculitis Activity Score (BVAS), BVAS 2003, BVAS WG and the Disease Extension Index are highly correlated [25], suggesting that a comparison of these assessment tools across clinical trials is possible to some extent, if the underlying differences between the respective tools are kept in mind. Differences in the disease assessment tools applied, however, may still account for different findings. In summary, variations in trial design and particularly disease assessment are likely to have a major impact on the recently reported outcomes in therapeutic trials in WG that are reviewed below.

General approach to treatment of Wegener's granulomatosis

Treatment for the induction of remission during phases of active disease (Table 1) is usually followed by less

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Table 1 Recommendations for the induction of remission in Wegener's granulomatosis

Protocol	Disease stage	Dose	Category of evidence ^a	Grade of recommendations ^a	References
Cyclophosphamide (daily oral) ^b	Generalized ^c	2 mg/kg per day p.o.	Ib	A	Fauci 1983 [1] Hoffman 1992 [2] Guillemin 1997 [3] Reinhold-Keller 2000 [4] *Jayne 2003 [5] *de Groot 2005 [6]
Cyclophosphamide (pulse) ^b	Generalized ^c	15–20 mg/kg i.v. every 3rd week	Ia	A	Adu 1997 [7] Guillemin 1997 [3] *de Groot 2001 [8] de Groot 1998 [9]
Methotrexate ^b	Early systemic ^c , no life-threatening disease	0.3 mg/kg per week i.v., s.c. or p.o.	Ib	A	Sneller 1995 [10] *de Groot 2005 [11**] *Reinhold-Keller 1996 [12]
Trimethoprim/sulfamethoxazole	Localized ^c	2 × 960 mg/day p.o.	IIa	A	
Plasma exchange ^d	Severe ^c	40–60 ml/kg (4–7×)	Ib	A	*Gaskin 2002 [13]

^aBased on the study(ies)^a with the highest level of evidence or grade of recommendations according to definitions by Woolf [14].

^bPlus prednisone (starting dose 1 mg/kg).

^cFor definitions of disease stages see Table 4.

^dPlus cyclophosphamide (daily oral) and prednisone (starting dose 1 mg/kg).

aggressive therapy for the maintenance of remission (Table 2). As detailed below, cyclophosphamide is the treatment of choice for patients with active WG, but may be substituted by methotrexate in less severe disease. The results of the Non-Renal Wegener's Granulomatosis Treated Alternatively with Methotrexate (NORAM) trial [11**], however, showed that after the withdrawal of treatment at 12 months, relapse rates at 18 months were 70% in the methotrexate limb and 45% in the cyclophosphamide limb, suggesting that continued treatment for the maintenance of remission is advisable. Given the high cumulative toxicity of cyclophosphamide, treatment should be switched to less toxic agents such as methotrexate, azathioprine or mycophenolate mofetil (MMF) as soon as remission is accomplished. In approximately

10% of cases, the administration of cyclophosphamide and corticosteroids alone is insufficient to control disease activity completely. In these cases, additional therapy such as biological agents, plasmapheresis or alternative treatments such as desoxyspergualin may be needed (Table 3) [14,26–28,29**,30**,31,32*,33*].

Cyclophosphamide

Corticosteroids alone are insufficient to control active WG. In historic cohorts, corticosteroid monotherapy prolonged the median survival by only 7.5 months [34] compared with the survival times recorded before the availability of corticosteroids in which WG patients died after a median of 5 months from diagnosis [35]. In contrast, a combination of oral daily cyclophosphamide

Table 2 Recommendations for the maintenance of remission in Wegener's granulomatosis

Protocol	Dose	Category of evidence ^a	Grade of recommendations ^a	References
Azathioprine ^b	2 mg/kg per day p.o.	Ib	A	*Jayne 2003 [5]
Methotrexate ^b	0.3 mg/kg per week i.v./p.o.	Ib	A	de Groot 1996 [15] Langford 1999 [16] Reinhold-Keller 2002 [17] *Metzler 2005 [18**]
Leflunomide ^b	30–40 mg/day	Ib	A	Metzler 2004 [19*] *Metzler 2005 [18**]
Trimethoprim/sulfamethoxazole ^b	2 × 960 mg/day p.o.	Ib	A	*Stegeman 1996 [20] Reinhold-Keller 1996 [12]
Mycophenolate mofetil ^b	2 g/day	IIc	B	Nowack 1999 [21] Haubitz 2002 [22] *Langford 2004 [23*]
Desoxyspergualin	0.5 mg/kg per day	III	C	*Schmitt 2005 [24]

^aBased on the study(ies)^a with the highest level of evidence or grade of recommendations according to definitions by Woolf [14].

^bPrednisone should have been tapered to 7.5 mg/day or less.

Table 3 Recommendations for the treatment of refractory disease in Wegener's granulomatosis

Protocol	Dose	Category of evidence ^a	Grade of recommendations ^a	References
Intravenous immunoglobulin	5 × 400 mg/kg i.v.	Ib	A	*Jayne 2000 [26]
Etanercept ^b	25 mg twice weekly	IIc	B	*Stone 2001 [27]
Infliximab ^b	5 mg/kg twice monthly	IIc	B	Lamprecht 2002 [28] *Booth 2004 [29**]
Rituximab ^b	375 mg/m ² per week for 4 weeks	III	B	*Keogh 2005 [30**]
Desoxyspergualin	0.5 mg/kg per day	IIc	B	*Birck 2003 [31]
Azathioprine (pulse)	1200 mg i.v. monthly, 2 mg/kg in weeks 2 and 3	III	B	*Aries 2004 [32*]
Antithymocyte globulin	5 mg/kg i.v. for 10 days	III	C	*Schmitt 2004 [33*]

^aBased on the study(ies)* with the highest level of evidence or grade of recommendations according to definitions by Woolf [14].

^bPlus standard therapy (cyclophosphamide and prednisone).

at doses of 2 mg/kg together with prednisone at an initial dose of 1 mg/kg per day, as first introduced by Fauci and Wolff in the 1970s, resulted in remission rates of 75–100%, as observed in large cohort studies from the US National Institutes of Health and Germany [2,4]. Therefore, oral daily cyclophosphamide is still the standard of care for patients with severe active generalized WG. The extended use of cyclophosphamide in WG is, however, limited by often serious morbidity, including infections, leukopenia related to bone marrow failure, infertility, haemorrhagic cystitis and a nine to 45-fold increased risk of bladder cancer [2,4,36*].

In view of the fact that the long-term toxicity of cyclophosphamide is correlated with the cumulative doses administered, approaches to limit the total exposure to cyclophosphamide by either shortening the period of oral cyclophosphamide therapy or alternatively by pulse therapy have been studied in the past. The former strategy was the subject of study in the CYCAZAREM trial conducted by the European Vasculitis Study Group (EUVAS) [5]. Patients with a diagnosis of antineutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) ($N = 155$), of whom 61% had WG and who went into remission after treatment with cyclophosphamide 2 mg/kg and prednisone for 3–6 months, were randomly assigned to receive either continued cyclophosphamide therapy for a total of 12 months or azathioprine as a substitute for cyclophosphamide. After 12 months, the cyclophosphamide group was also switched to azathioprine and followed for a further 6 months. Relapse rates during the 18-month period were similar for the long-term (13.7%) compared with the short-term cyclophosphamide group (15.5%). Given the increased risk of toxicity with prolonged cyclophosphamide administration, the results of the CYCAZAREM trial suggest that cyclophosphamide exposure should be limited to phases of active disease, and should be replaced by a less toxic therapy as soon as remission is accomplished.

Another strategy to reduce the cumulative exposure to cyclophosphamide is the intermittent application of intravenous pulses. To date, five prospective trials on the efficacy of pulse cyclophosphamide therapy in WG have been published, of which three had a randomized design [3,7,37]. None of the trials, however, was sufficiently sized in order to enable confident conclusions to be drawn regarding the efficacy of pulse compared with oral cyclophosphamide. Furthermore, the inclusion of patients with microscopic polyangiitis (MPA) and polyarteritis nodosa in two of the three randomized trials represented an important confounding factor for the efficacy analysis, as it has been shown in the CYCAZAREM trial that patients with WG relapsed more frequently than patients with MPA [5]. A meta-analysis of the above-mentioned three randomized trials indicated that compared with daily oral cyclophosphamide, pulse cyclophosphamide appeared to be similarly effective at inducing remission with fewer adverse events [8]. Relapse rates, however, tended to be higher with intermittent pulse therapy. According to the recently presented preliminary survival analysis of a sufficiently large randomized controlled trial (CYCLOPS) including patients with WG and MPA [6], disease-free periods did not differ significantly between patients receiving oral compared with pulse cyclophosphamide therapy. Although these preliminary data sound promising, it seems premature to conclude that oral daily cyclophosphamide can safely be replaced by pulse cyclophosphamide in any patient with WG until a complete data report from CYCLOPS including subgroup analyses for patients with WG only is published.

Methotrexate

Two open-label studies and one randomized trial evaluated the efficacy of methotrexate as a potentially less toxic alternative for induction treatment in WG. In the two prospective open-label studies [9,10] methotrexate was given at doses of approximately 0.3 mg/kg per week combined with corticosteroids to patients with WG who

did not have evidence of life-threatening disease and who had a normal or nearly normal renal function. The successful induction of remission was seen in 10 out of 17 (59%) and 33 out of 42 (79%) patients, respectively [9,10].

In a recently reported prospective unblinded randomized controlled trial (NORAM) [11**] 100 patients with AAV, of whom 89 (94%) had WG and who did not have life or organ-threatening disease were randomly assigned to treatment with either methotrexate at a target dose of 20–25 mg/week or daily oral cyclophosphamide (2 mg/kg). Results of the NORAM trial showed that methotrexate can be as effective as cyclophosphamide, with remission rates of 89.8% for methotrexate and 93.5% for cyclophosphamide, and similar times to remission, thus confirming the results from earlier open-label trials [9,10,11**]. Relapse rates at only 6 months after the complete discontinuation of therapy were, however, high for both methotrexate (69.5%) and cyclophosphamide (46.5%). Another major lesson of the NORAM trial is therefore that some form of immunosuppressive treatment should be continued beyond 12 months for the maintenance of remission. Although severe adverse events did not occur less frequently in the methotrexate limb during the 18-month study period, a beneficial toxicity profile favouring methotrexate is likely to be seen at a later timepoint, as the long-term toxicity of cyclophosphamide (e.g. bladder cancer, myelodysplasia) is often observed only some years after treatment.

The unfavourable relapse rates observed in the NORAM trial highlight the need for maintenance therapy in WG. Two standardized randomized open-label label trials have investigated the efficacy of methotrexate for the maintenance of remission in WG after the successful induction of remission with oral cyclophosphamide [16,17,38]. In a series of 71 patients followed for a mean period of 24 months at our centre, 26 relapses (36%) were seen after a mean time of 19 months [17]. Of note was the fact that an unexpectedly high rate of kidney involvement was seen in 16 out of all 26 relapses (61%) [17]. In a smaller-sized study conducted by Langford and coworkers [38] 22 relapses were seen in 42 patients studied (52%) during a median follow-up period of 32 months. Compared with cyclophosphamide, the incidence of adverse events was low and they were rarely severe in either cohort.

Azathioprine

As outlined above, the results of the CYCAZAREM trial have convincingly demonstrated the potency of azathioprine in preventing relapses in patients with WG [5]. The French vasculitis study group recently presented preliminary data from a prospective multicentre randomized trial comparing azathioprine (2 mg/kg per day) compared with methotrexate (0.3 mg/kg per week) for

the maintenance of remission in 114 patients with WG or MPA after the successful induction of remission with cyclophosphamide pulses, suggesting that both agents are similarly effective drugs for the maintenance of remission [39]. A non-significant trend towards a higher frequency of treatment-related adverse events in the methotrexate limb was, however, reported [39].

Recent data have shown that azathioprine induces the apoptosis of T cells at a molecular level via the modulation of RAC-1 activation upon CD28 stimulation [40]. These experimental data raise interest in whether azathioprine might be a valuable drug, not only for maintenance therapy but also for active WG, in which activated T cells play a central role. Interestingly, recent observations have suggested that the intermittent administration of high doses of azathioprine may be effective for refractory cases of WG. We treated two patients with WG and refractory granulomatous manifestations, particularly retroorbital disease, who had not responded to therapy with cyclophosphamide, infliximab and rituximab, with azathioprine given as intravenous pulses (1200 mg for 24 h) once per month and daily at a dose of 100 mg in weeks 2 and 3 between each pulse [32*]. A regression of granulomatous disease was seen in both patients after the second azathioprine pulse, with further additional improvements [32*]. Benenson and colleagues [41] treated four patients with active WG with a similar regimen of pulse azathioprine (1200–1800 mg/month). The successful induction of remission was reported in two patients, whereas azathioprine had to be withdrawn in the remaining two patients because of persistent disease [41]. Severe adverse events were reported in neither of the two small cohorts.

Leflunomide

Leflunomide inhibits de-novo pyrimidine synthesis and inhibits the responses of activated T and B cells. In a phase II open-label clinical trial [19*], leflunomide (30 mg/day) was given to 20 patients with WG for the maintenance of remission after cyclophosphamide induction therapy. During a median follow-up of 21 months, only one major relapse requiring the reinstatement of cyclophosphamide was recorded [19*]. Eight minor flares were successfully treated by increasing the leflunomide dose to 40 mg a day. In a multicentric randomized controlled clinical trial (LEM) by the German rheumatology network [18**] the potency of leflunomide (30 mg) at preventing relapses in patients with WG after the successful induction of remission with cyclophosphamide was compared with methotrexate (20 mg weekly). The first results of that trial were recently reported [18**], and showed a significantly higher rate of severe relapses in the methotrexate limb (n = 7) compared with the leflunomide limb (n = 1). Adverse events (hypertension, neuropathy, leukopenia), however, necessitated a withdrawal

for maintenance of remission

↓
mg of week 0
phenytoin birth
low birth weight
+ mixed congenital
no evidence of T birth defects

of leflunomide in four out of 26 patients [18**]. These preliminary results suggest that leflunomide is a promising drug for maintenance therapy of WG that warrants further investigation.

Mycophenolate mofetil

Three small open-label clinical trials including five to 14 patients with AAV examined the safety and efficacy of MMF for the maintenance of remission [21,22,23*]. In the study by Nowak *et al.* [21], only one relapse in 11 patients was seen during a follow-up time of 15 months. In contrast, in the study by Langford and coworkers [23*], six out of 14 patients relapsed during a median 18 months of follow-up. The dosage and duration of cyclophosphamide therapy for the induction of remission as well as the MMF dosage (2 g/day) were similar in both studies. Differences in corticosteroid therapy may, however, account for the divergent outcome, because in the study by Langford and colleagues [23*] corticosteroids were completely discontinued after a median of 8 months, whereas in the study by Nowak *et al.* [21] a median dose of 5 mg prednisone was maintained. The tolerability of MMF was reported to be good in both studies. In a small series of five patients with AAV and end-stage renal disease [22], however, MMF doses of more than 1 g were not well tolerated, with anaemia, leukopenia and gastrointestinal symptoms being the most frequently reported adverse events. Overall, data published to date on MMF in AAV are limited. The first results of a recently completed randomized controlled trial by the EUVAS comparing MMF and azathioprine for the maintenance of remission in AAV (IMPROVE) are thus expected with great interest [42].

Tumour necrosis factor blockade

In view of the important role of TNF- α for priming neutrophil granulocytes allowing the subsequent interaction with ANCA and in granuloma formation, several

recent studies have evaluated the efficacy of tumour necrosis factor blockade in AAV. Etanercept, a soluble TNF- α inhibitor consisting of two extracellular p75 TNF- α receptor domains linked to the Fc portion of human IgG1, added to standard treatment (cyclophosphamide, methotrexate, azathioprine, cyclosporine, and steroids) was found to be efficacious in an open-label prospective trial involving patients with persistently active or new flares of WG [27]. On the basis of these positive data, a randomized, placebo-controlled trial (Wegener's Granulomatosis Etanercept Trial; WGET) to evaluate etanercept for the maintenance of remission in 180 WG patients with either severe or non-life-threatening disease activity was conducted [43]. Etanercept was given in addition to standard therapy (cyclophosphamide or methotrexate and steroids), which was tapered and finally discontinued with only etanercept remaining as the sole maintenance therapy [43]. In that trial, the rate of sustained remissions, i.e. the primary endpoint of WGET, was similar in etanercept-treated patients and controls [44**]. Furthermore, the risk of disease flares, the periods of low disease activity (BVAS/WG < 3 for 6 months) and the number of adverse events were similar in both groups [44**]. Given the large number of well defined patients of WG and the strength of the randomized, placebo-controlled design, the results of WGET suggested that etanercept is not effective in the maintenance of remission without concomitant immunosuppressive therapy (see Tables 4 and 5) [42,43].

A note of caution, however, is necessary with respect to drawing rash conclusions from the WGET on the role of TNF- α and the efficacy of different tumour necrosis factor inhibitors in situations other than the maintenance of remission in WG. It has been shown that elevated monocytic TNF- α levels, which correlate with systemic TNF- α levels, are normalized with successful standard

Table 4 Definitions for disease stages used for subclassification of patients with Wegener's granulomatosis in clinical trials [43,44]

Study group	Clinical subgroup	Systemic vasculitis outside ENT tract and lung	Threatened vital organ function	Other definitions	Serum creatinine ($\mu\text{mol/l}$)	Clinical trials using definition
EUVAS	Localized	No	No	No constitutional symptoms, ANCA typically negative	< 120	
	Early systemic	Yes	No	Constitutional symptoms present, ANCA positive or negative	< 120	NORAM
	Generalized	Yes	Yes	ANCA positive	< 500	CYCAZAREM
	Severe	Yes	Organ failure	ANCA positive	> 500	MEPEX
WGET Research Group/VCRC	Refractory	Yes	Yes	Refractory to standard therapy	Any	SOLUTION
	Limited	Allowed	No	No red blood cell casts, nor rise of creatinine > 25% of baseline	≤ 124 , if haematuria, but no red blood cell casts present	WGET
	Severe	Yes	Yes	Any patient not classifiable as limited	Any	WGET

ANCA, Antineutrophil cytoplasm antibody; ENT, ear, nose and throat; EUVAS, European Vasculitis Study Group; VCRC, vasculitis clinical research consortium; WGET, Wegener's Granulomatosis Etanercept Trial.

Table 5 Definitions for disease states used for assessment of outcome in Wegener's granulomatosis [43,44]

Study group	Disease state	Definitions
EUVAS	Complete remission	Absence of any disease activity ^a , BVAS = 0
	Partial remission	Significant decrease of disease activity with persisting low-grade activity believed to regress by continued treatment
	Minor relapse	Recurrent or new disease activity not threatening vital organs that is controllable by an increase of corticosteroid dosage only
	Major relapse	Recurrent or new disease activity threatening vital organs or leading to functional impairment that usually requires reinstitution of cyclophosphamide
WGET Research Group/VCRC	Sustained remission	BVAS/WG of 0 for 6 months
	Low level of disease activity	BVAS/WG < 3 for 6 months
	Flare	Increase of at least one point in BVAS/WG

BVAS, Birmingham Vasculitis Activity Score; VCRC, vasculitis clinical research consortium; WGET, Wegener's Granulomatosis Etanercept Trial.
^aClinical features, serology and imaging.

treatment but not in refractory patients [45]. Therefore, as suggested by these in-vitro data, patients responding to standard treatment would have no further benefit from the addition of a TNF- α blocking agent for the maintenance of remission. In contrast, patients refractory to standard treatment could obtain a benefit from the addition of a tumour necrosis factor inhibitor. The group of patients refractory to standard maintenance therapy and potentially responding to etanercept would, however, have been small and not subject to the addition of etanercept in the WGET. A number of other points such as the tapering of steroids and other immunosuppressants except etanercept make a comparison with other maintenance studies difficult. Moreover, the lack of efficacy of etanercept in maintaining disease remission raises concerns as to its potency similar to previous experiences in Crohn's disease. Therefore, data obtained on the efficacy of etanercept may not be transferred to other tumour necrosis factor blocking agents. Infliximab, a monoclonal chimeric anti-TNF- α antibody was shown to induce remission effectively in Crohn's disease, whereas etanercept was found not to be effective [45]. Although both agents neutralize TNF- α effectively, differences in the potential to lyse macrophages after binding to membrane bound TNF- α , to induce apoptosis and on other immune parameters may account for differences in the efficacy of the two TNF- α -neutralizing drugs in distinct entities [46*,47].

In three open-label clinical trials involving six, eight and 32 patients with AAV who were refractory to standard therapy, infliximab given at doses of 3–5 mg/kg in 2–8-week intervals was found to be effective [28,29**,48]. The occurrence of two deaths and seven serious infections in the largest of the trials [29**] mandate the close monitoring and cautious use of such an intensive immunosuppression. The WGET reported six solid cancers in the etanercept arm. As WG has previously been reported to be associated with renal and urinary bladder cancer [37,49,50], tumour screening before the

start of the trial should be included in such studies. Against this background and as a result of the difficulties in controlling for potential effects of continued concomitant immunosuppressive therapies in open label trials, a well designed randomized controlled clinical trial to evaluate the efficacy of infliximab in patients with WG would be highly desirable.

Rituximab

B cells are a potential target in chronic inflammatory and autoimmune diseases such as WG because they produce autoantibodies, cytokines, interact with antigen-presenting and T cells, and function as (auto)antigen-presenting cells themselves. Rituximab is a chimeric monoclonal antibody directed against the CD20 molecule on the surface of B lymphocytes. The results were recently reported of an open-label study [30**] evaluating the efficacy of rituximab in 11 patients with AAV, of whom 10 had WG and who were all refractory to cyclophosphamide or had contraindications against its use. In all 11 refractory patients the induction of remission was seen after the administration of four weekly doses of rituximab (375 mg/m²) [30**]. This was accompanied by a decrease in ANCA titres and the depletion of peripheral blood B cells [30**]. As all patients received concomitant high-dose corticosteroids and three patients were also treated with plasma exchange, it seems difficult to evaluate to what extent the administration of rituximab contributed to the clinical improvement and the decline in ANCA titres. In three patients with an asymptomatic increase in ANCA titres, a second course of rituximab failed to induce a significant decline in ANCA titres [30**]. It was thus speculated as to whether ANCA production in WG might be restricted to long-lasting plasma cells that do not express CD20, and would thus be unaffected by rituximab therapy despite a decline in B cells [51*]. In a series of eight patients with refractory WG and predominantly granulomatous disease, the administration of rituximab in addition to standard therapy failed to induce a clinical improvement in the majority of

patients (P. Aries, unpublished data). In view of these very limited and partly conflicting data, the results of a currently recruiting randomized controlled trial evaluating rituximab therapy in patients with AAV (RAVE) will be needed in order to define a potential role for this drug in the therapy of WG.

15-Desoxyspergualin

15-Desoxyspergualin is a synthetic analogue of spergualin, a natural product of the bacterium *Bacillus lactosporus*. Although its exact mechanism of action remains obscure, 15-desoxyspergualin has immunosuppressive properties and is licensed in Japan for the treatment of recurrent kidney transplant rejection. In an open-label pilot study [31] up to six cycles of 15-desoxyspergualin were given to 20 patients with AAV of whom 19 had WG and who all were unresponsive or had contraindications against conventional immunosuppressive agents. A clinical response to 15-desoxyspergualin was seen in 70% of patients, with six out of 20 patients attaining a complete remission [31]. In four of these patients and three additional patients with WG, 15-desoxyspergualin was given on a long-term basis for an average of 26 months, and a relapse-free disease course was reported in all seven patients [24]. A larger multicentre phase II trial evaluating the efficacy and safety of 15-desoxyspergualin in refractory WG is currently in progress.

Plasmapheresis

The preliminary results of a multicentre randomized controlled study (MEPEX) indicated that plasmapheresis compared with methylprednisolone pulses may lead to higher rates of renal recovery and dialysis independence in patients with AAV and a creatinine clearance rate of 500 $\mu\text{mol/l}$, who also received cyclophosphamide for the induction of remission [52]. The overall mortality reported in that study, however, was still high, possibly reflecting the severe disease in this patient subgroup with severely impaired renal function. The final results of the MEPEX trial are expected in 2006. A retrospective review of 20 patients with diffuse alveolar haemorrhage who received plasmapheresis as an adjunct to intensive immunosuppressive therapy reported good recovery from alveolar bleeding in all patients [53], which is noteworthy given the usually high mortality rate associated with diffuse alveolar haemorrhage.

Conclusion

Although recently published randomized controlled trials and smaller case series provide evidence for new treatment options and treatment stratifications, there is a continued need for better and at the same time less toxic treatment protocols for the induction of remission and the prevention of relapses. Etanercept is not efficacious for the maintenance of remission, but the role of tumour necrosis factor inhibitors for the induction of

remission and in refractory WG has not been determined under controlled conditions. Other substances such as 15-desoxyspergualin, MMF, leflunomide, and rituximab seem promising candidates for treatment options in different disease stages and activity states.

Differences in trial design are likely to contribute to divergent outcomes in recent major clinical trials in AAV, as has recently been reviewed in this journal [54*]. Therefore, efforts towards a more uniform trial methodology in the field of vasculitis research should be encouraged.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 119–120).

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