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Pharmacological Therapy for Wegener's Granulomatosis

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Abstract

Wegener's granulomatosis (WG) is the most common pulmonary granulomatous vasculitis and was a uniformly fatal disease prior to the identification of efficacious pharmacological regimens. The pathogenesis of WG remains elusive but proteinase 3-specific anti-neutrophil cytoplasmic antibodies may be involved. Histologically, WG is defined by the triad of small vessel necrotising vasculitis, 'geographic' necrosis and granulomatous inflammation. Organ involvement characteristically includes the upper and lower respiratory tracts and kidney, but virtually any organ can be involved. The severity of the disease varies, ranging from asymptomatic disease to fulminant, fatal vasculitis. Similarly, the degree of organ involvement is highly variable; WG may be limited to a single organ (typically the lungs or upper respiratory tract), or may be systemic. Currently, a

regimen consisting of daily cyclophosphamide and corticosteroids, which induces complete remission in the majority of patients, is considered standard therapy. Since approximately 50% of patients experience a relapse following discontinuation of therapy, alternative regimens designed to maintain remissions after using cyclophosphamide and corticosteroids are usually necessary. This 'induction maintenance' approach to treatment has emerged as a central premise in planning therapy for patients with WG.

A number of trials have evaluated the efficacy of less toxic immunosuppressants (e.g. methotrexate, azathioprine, mycophenolate mofetil) and antibacterials (i.e. cotrimoxazole [trimethoprim/sulfamethoxazole]) for treating patients with WG, resulting in the identification of effective alternative regimens to induce or maintain remissions in certain sub-populations of patients. Given the efficacy of methotrexate (for early systemic WG) and cotrimoxazole (in WG limited solely to the upper airways) to induce remissions, and the relatively decreased associated morbidity compared with cyclophosphamide, these alternative regimens are preferred in appropriate patients. Similarly, therapeutic options to maintain disease remission that are less toxic than cyclophosphamide should be offered following induction of remission unless a specific contraindication exists. By following this premise, the development of cyclophosphamide-induced morbidities (e.g. haemorrhagic cystitis, uroepithelial cancers and prolonged myelosuppression) may be minimised. Recent investigation has focussed on other immunomodulatory agents (tumour necrosis factor-α inhibitors [infliximab and etanercept] and anti-CD20 antibodies [rituximab]) for treating patients with WG. However, the current data are conflicting and difficult to interpret. As a result, these newer agents cannot be recommended for routine use until vigorous clinical study confirms their efficacy.

1. Wegener's Granulomatosis (WG)

Wegener's granulomatosis (WG), the most common of the pulmonary granulomatous vasculitides, is characterised by necrotising vasculitis involving small vessels (i.e. arterioles, venules and capillaries), patchy tissue necrosis and granulomatous inflammation.[1-3] It commonly involves both the upper respiratory (e.g. sinuses, ears, nasopharynx, oropharynx and trachea) and lower respiratory tracts (i.e. bronchi and lung), as well as the kidney with varying degrees of disseminated vasculitis.[4-11] The estimated prevalence of WG in the US is 13–30 cases per million persons per 5-year period,[5,12] whereas annual incidence rates of WG (per million) are estimated to be 12 in Norway,[13] 10.3 in England and 4.1 in Spain.[14] The peak incidence is in the fourth to sixth decades of life;[5,7,10,12] children or adolescents are rarely affected, but it can occur at all ages.[15-19] There is no sex predominance.[20]

Clinical manifestations of WG are usually nonspecific; virtually any organ can be involved. Chronic persistent sinusitis, epistaxis, otalgia or otitis media are commonly the presenting and dominant clinical features of WG, but are often mistaken for allergic or infectious aetiologies.[5,20] However, the spectrum of the disease is heterogeneous and is dependent on specific organ involvement. Disease severity can be quite variable, ranging from smouldering disease involving only one site to fulminant, multiorgan vasculitis leading to death. Given that many of the 'classic' features may be lacking *early* in the course, only to evolve months or even years after initial presentation,[5-7,20] the diagnosis is often missed for several months after the initial symptom(s) develop.[10]

Diagnosis of WG requires a heightened clinical suspicion in the appropriate clinical setting. Although firm diagnostic criteria are still lacking, consensus opinion suggests that criteria for diagnosis should include (i) small vessel vasculitis; (ii) nasal or oral inflammation; (iii) abnormalities on chest radiographs; and (iv) abnormal urine sediment. Based on the International Consensus Conference at Chapel Hill in 1993, a requisite feature for the diagnosis of WG is the presence of granulomatous inflammation on biopsy.[21] By contrast, granulomata are absent in microscopic polyangiitis (MPA) or classic polyarteritis nodosa (PAN).[21] A key development in the diagnosis of WG was the recognition that serum antibodies against cytoplasmic components of neutrophils (anti-neutrophil cytoplasmic antibodies; c-ANCA) were present in a majority of patients with WG, and often correlated with active disease.[10,20,22-26] By the late 1990s, an increasing number of cases of WG were diagnosed by clinical criteria and high titres of c-ANCA.[10] However, the specificity of c-ANCA titres alone has been challenged.[26-29] Using enzyme immunoassay, identification of c-ANCA directed against proteinase (PR)-3 (so-called PR3-ANCA) is found in over 80% of patients with WG, although up to 35% of patients with microscopic polyangiitis, rapidly progressive glomerulonephritis and Churg-Strauss syndrome may also develop PR3-ANCA.[26]

Characterising disease severity can be significant when deciding on treatment regimens for patients with WG. For ease of use, we find it helpful to classify disease severity as follows:

- Life-threatening disease. This is defined as (i) acute or chronic renal insufficiency with serum creatinine >2.5 mg/dL; (ii) pulmonary haemorrhage with arterial oxygen partial pressure (pO_2) <70mm Hg; or (iii) new ischaemic symptoms of CNS, heart or intestinal tract. This degree of disease is likely to require the use of cyclophosphamide to induce remission.
- Non-life-threatening disease. This is defined as WG involving one or more organs (excluding those above), where methotrexate can be substituted for cyclophosphamide as a remission-inducing agent.
- Fulminant, life-threatening disease. This is defined as disease that is likely to cause death within days if not treated aggressively.

A more comprehensive review of the clinical features and histopathological manifestations of WG can be found in our recent review.[30]

1.1 Pathogenesis of WG

The exact cause of WG is unknown, but the two key histopathological features of granulomas and vasculitis suggest an exaggerated cellular immune or hypersensitivity response. Similarly, genetic factors may also play a role. Indeed, evidence suggests that constitutive expression of PR3-ANCA on the membranes of resting neutrophils may predispose to the development of WG.[31] Furthermore, retrospective data now demonstrate that c-ANCA titres and PR3-ANCA levels can be prognostic for disease relapse,[32] again indicating that these antibodies are likely to have a role in the development of WG. Still other laboratory investigations have implicated tumour necrosis factor (TNF)-α in the pathogenesis of WG.[33-35] However, it is emphasised that definitive studies implicating B-cell-derived ANCA or TNFα (or other cytokines) in the pathogenesis of WG are lacking.

2. Therapeutic Regimens for Remission Induction

A summary of recommendations regarding appropriate pharmacological therapy to induce remissions in WG is presented in table I and the data to support these recommendations are discussed in detail in this section. Levels of evidence and grades of recommendation (as put forth by the Centre for Evidence-Based Medicine, Oxford, UK)[36] are provided for each intervention, allowing the reader to interpret these recommendations accordingly. As always, therapy for each patient must be individualised, taking into account clinical presentation, comorbid conditions, concomitant medical therapy, and clinician experience and comfort.

Table I. Recommended therapeutic regimens for remission induction in Wegener's granulomatosis, based on extent of disease. Refer to section 2 in the text for further details. This table is not intended to replace the clinician's judgment or expertise. All therapeutic regimens must be individualised to the patient[37]

Extent of disease	Induction therapy	Evidence level and recommendation grade[a]
Non-life-threatening disease	Methotrexate[b] (20–25 mg/week PO) plus prednisone (40–60 mg/day PO with taper)	Level 1b evidence, Grade A recommendation
	When combining methotrexate and prednisone, add cotrimoxazole (1 DS tablet thrice weekly PO)	Level 2b evidence, Grade B recommendation
Isolated upper respiratory tract disease	Cotrimoxazole (1 DS tablet twice daily PO)	Level 2b evidence, Grade B recommendation
Life-threatening disease[c]	Prednisone (40–60 mg/day PO with taper) plus cyclophosphamide (2 mg/kg/day PO) for 3–6 months until remission	Level 1a evidence, Grade A recommendation
	Add cotrimoxazole (1 DS tablet thrice weekly PO)	Level 2b evidence, Grade B recommendation
Fulminant, life-threatening disease	Methylprednisolone (1000mg IV or equivalent daily for 3 days) plus cyclophosphamide (3–4 mg/kg/day IV for 3 days), then follow regimen for generalised disease until remission	Level 5 evidence, Grade D recommendation
	Consider plasmapheresis if available and patient is refractory to above regimen	Level 4 evidence, Grade C recommendation
	Add cotrimoxazole (1 DS tablet thrice weekly PO)	Level 2b evidence, Grade B recommendation

a Based on Phillips et al.[36]

b When prescribing methotrexate, folic acid (1 mg/day orally) is recommended.

c Defined as: (i) acute or chronic renal insufficiency with a serum creatinine >2.5 mg/dL; (ii) pulmonary haemorrhage with an arterial oxygen partial pressure (pO_2) <70mm Hg; or (iii) new ischaemic symptoms of CNS, heart or intestinal tract.

DS = double strength (1 DS tablet of cotrimoxazole is equivalent to trimethoprim 160mg/sulfamethoxazole 800mg); **IV** = intravenous; **PO** = oral.

2.1 Cyclophosphamide and Corticosteroids

Before the introduction of effective therapy, mean survival among patients with untreated active WG was <6 months,[38] with >80% of patients dying within 3 years of onset of symptoms, usually of progressive renal failure.[39] Corticosteroids were initially employed and ameliorated many of the inflammatory manifestations of WG. However, gains in survival were modest, with a mean survival of only 12.5 months.[40] Early experience at the US National Institutes of Health (NIH) affirmed that corticosteroids alone were not adequate to treat severe WG. In an early cohort of patients at that institution, 57 had initially been treated with corticosteroids.[5] Although partial improvement was sometimes cited, none of the 45 patients with renal involvement achieved complete remission with corticosteroids alone.

Initial, influential, studies utilising a regimen of daily cyclophosphamide combined with corticosteroids to induce remissions represented a powerful advance in the treatment of WG,[41] and this regimen remains the 'gold standard' against which all remission-inducing regimens are compared. In the original NIH regimen by Fauci and coworkers,[4,41] patients were treated with oral cyclophosphamide (1–2 mg/kg/day) combined with prednisone (1 mg/kg/day). Among responders, prednisone was gradually tapered to an alternative schedule and discontinued by 6–9 months; cyclophosphamide was continued for a minimum of 12 months past remission, and then ultimately tapered and discontinued. Long-term evaluation of this cohort, spanning 1229 patient-years, revealed that 91% of patients treated with this regimen improved, 75% achieved complete remissions and mortality was only 20%.[5] Importantly, these investigators observed that relapses occurred in 50% of patients and 42% experienced serious morbidity from the adverse effects of treatment. Subsequent studies utilising the cyclophosphamide-plus-corticosteroid regimen confirmed remission rates between 70% and 90%, with early mortality rates of <15%.[7,39,42,43] Consistent

with previous observations, relapses were noted in 30–70% of patients following cessation or tapering of therapy. In this population, reinstitution of therapy was usually efficacious at re-inducing remissions.[7,20,44] Unfortunately, late sequelae of persistent or recurrent vasculitis (e.g. cerebrovascular accidents, myocardial infarction, renal failure, hypertension), or complications of cyclophosphamide therapy (e.g. opportunistic infections, neoplasms), contribute to long-term mortality and morbidity.[5,7,11,44-47] As such, identification of safer and effective therapies associated with acceptable rates of remission and of adverse effects has been of considerable interest.

Use of intermittent high-dose intravenous 'pulse' cyclophosphamide in WG was prompted by the potential for reduced toxicity as well as by favourable experience with this approach in lupus nephritis[48-50] and other autoimmune disorders.[51,52] Although data are limited, rates of remission induction with intermittent intravenous cyclophosphamide are similar to those using daily oral cyclophosphamide, but relapses appear to be more likely following pulse administration.[20,44,45,53-58] While it remains possible that reducing the interval between cycles or extending the number of cycles of intravenous pulse therapy may promote maintenance of remission, this has not been rigorously studied. In adults, most experience exists with daily oral cyclophosphamide and corticosteroids as the preferred regimen; in childhood WG, intravenous pulse cyclophosphamide has been established as a successful induction therapy,[15,16] although direct comparison between intravenous and oral cyclophosphamide in children has not been performed. It is our opinion, therefore, that a regimen containing daily oral cyclophosphamide and corticosteroids is preferred for inducing remissions in generalised, severe WG (Level 1a evidence, Grade A recommendation as put forth by the Centre for Evidence-Based Medicine, Oxford, UK[36]).[7,59-63]

It warrants a mention at this point that optimal corticosteroid dose administration and rates of tapering have never been precisely established in WG or other inflammatory diseases for which corticosteroids are used. Commonly, corticosteroids are started at dosages of prednisone 40–60 mg/day (or equivalent) orally in conjunction with induction agents. In fulminant, life-threatening disease, intravenous pulse corticosteroids are often advocated as initial therapy, followed by oral corticosteroids; again, no prospective data have shown these to be superior to oral corticosteroids alone. In light of this, the role of corticosteroids in relation to induction and maintenance of remissions is unclear. Further elucidation of the precise role of corticosteroids in treating patients with WG is complicated by the multitude of regimens used in combined treatment protocols of large studies. Therefore, it is often difficult to accurately compare results of treatment trials. Given the large number of clinical studies employing corticosteroids for WG, we recommend that corticosteroids be used in all patients undergoing remission induction therapy for WG, and that they be tapered over the course of 6 months after remission is achieved (Level 2a evidence, Grade B recommendation).

2.2 Methotrexate

Methotrexate, a folic acid antagonist that reversibly inhibits dihydrofolate reductase, can be used in conjunction with corticosteroids for inducing remissions in select patients with non-life-threatening WG, and is an acceptable alternative for maintenance of remissions in patients with WG. Given orally or parenterally (i.e. intravenously) on a weekly basis, methotrexate may be used for patients developing serious adverse effects from cyclophosphamide or for non-life-threatening WG.[59,60,64] In the first prospective investigation into the use of methotrexate as a remission-induction agent, 42 patients with non-life-threatening WG (glomerulonephritis in 50%, lung involvement in 52%), oral methotrexate (20–25mg once weekly) combined with oral prednisone (initial dosage 1 mg/kg/day, with gradual taper) was instituted.[64] With this regimen, 71% of patients achieved remissions and overall survival was 93%.[64] As observed for cyclophosphamide-containing regimens, relapses occurred in 11 of 30 patients (37%) following tapering and

discontinuation of the regimen, but reintroduction of methotrexate with corticosteroids led to second remissions in most patients.[64] Toxicity was generally mild, although four patients receiving this regimen developed *Pneumocystis jiroveci* (formerly *carinii*) pneumonia, two of whom died from the complication, presumably because of the lack of prophylaxis, which is commonly used today. Follow-up analysis of the initial 21 patients with glomerulonephritis enrolled in the study demonstrated durable remissions in 20 patients (95%).[60] As reported in the follow-up trial, serum creatinine rose >0.2 mg/dL from baseline in only two patients, suggesting renal-protective effects in patients treated with a methotrexate-containing regimen.[60] In a second open-label, prospective study, 17 patients with severe, non-life-threatening WG were treated with intravenous methotrexate (0.3 mg/kg/week) plus daily oral corticosteroids to determine efficacy in inducing remissions.[59] In this trial, only 59% of patients achieved remissions over a median of 24.5 months, with five of the seven non-responders developing *de novo* glomerulonephritis during the course of the study.[59]

Finally, to determine whether methotrexate was as effective as cyclophosphamide in inducing remissions in patients with early ANCA-associated vasculitis (94% WG, 6% microscopic polyangiitis), De Groot et al.[65] undertook a prospective, randomised, controlled, nonblind study in 100 patients. In this study, 51 patients were randomised to receive oral weekly methotrexate (20–25 mg/week), and 49 to oral daily cyclophosphamide (2 mg/kg/day); both groups received oral prednisolone beginning at 1 mg/kg/day. Immunosuppressants were tapered in a proscribed fashion such that all patients were no longer receiving medications by 12 months. Of the 100 patients randomised, 95 received the intended treatment, and 84 were evaluated through to the end of the trial 18 months later. In this study, methotrexate was as effective as cyclophosphamide in inducing remissions in patients with early ANCA-associated vasculitis (remission rates of 89.8% of methotrexate-treated patients and 93.5% of cyclophosphamide-treated patients within 6 months of therapy initiation). Furthermore, median time to remission was similar between the two groups (3 months [range 1–9 months] for methotrexate and 2 months [range 1–5 months] for cyclophosphamide). Interestingly, the authors also found that time to remission with methotrexate was significantly longer than with cyclophosphamide in a subgroup of patients with more extensive disease (as measured by the Disease Extent Index[66]) or in whom lower respiratory tract involvement was present (nodules, cavities or infiltrates). Together, these data (along with other publications)[59,64,67] suggest that methotrexate, in conjunction with corticosteroids, may be used in place of cyclophosphamide in patients with early disease or in those without lower respiratory tract involvement (Level 1b evidence, Grade A recommendation).

3. Therapeutic Regimens for Maintenance of Remissions

A summary of recommendations regarding appropriate pharmacological therapy to maintain remissions in WG is given in table II. In all instances, the data are reviewed to allow the individual reader to interpret our recommendations.

3.1 Methotrexate

In addition to its role in remission induction in WG, methotrexate has been shown to be efficacious in maintaining disease remissions. To evaluate this, 31 patients with active WG were treated with cyclophosphamide and corticosteroids to induce remissions, followed by transitioning to methotrexate and corticosteroids to maintain remissions in an open-label trial.[9] On this protocol, all patients achieved remissions at a median of 3 months from study entry (range 1–12 months)[9] and were able to be successfully transitioned to oral methotrexate (starting dosage 0.3 mg/kg/week [not to exceed 15 mg/week], increasing by 2.5mg increments to a maximal dosage of 25 mg/week) and corticosteroids. Relapses occurred in only 16% of patients and all occurred >1 year after initiating methotrexate. At the time of relapse, all five patients were taking only methotrexate, having stopped taking corticosteroids

Table II. Recommended therapeutic regimens for maintenance of remissions in Wegener's granulomatosis (WG). This table is not intended to replace the clinician's judgment or expertise. Determination of timing for switch to maintenance therapy is unknown; thus, this is left to the clinician to decide[37]

Extent of disease	Maintenance therapy[a]	Evidence level and recommendation grade[b]
Non-life-threatening disease or Life-threatening disease[c] Fulminant, life-threatening disease	Methotrexate[d] (20–25 mg/week PO) or Azathioprine (2 mg/kg/day PO)	Level 2a evidence, Grade B recommendation or Level 1b/2b evidence, Grade B recommendation
Isolated upper respiratory tract disease	Cotrimoxazole (1 DS tablet twice daily PO)	Level 1b evidence, Grade B recommendation

a Duration of maintenance therapy will be dependent on the individual patient's response to therapy and presence of adverse effects.

b Based on Phillips et al.[36]

c Defined as (i) acute or chronic renal insufficiency with a serum creatinine >2.5 mg/dL; (ii) pulmonary haemorrhage with an arterial oxygen partial pressure (pO_2) <70mm Hg; or (iii) new ischaemic symptoms of CNS, heart, or intestinal tract.

d When prescribing methotrexate, folic acid (1 mg/day orally) is recommended.

DS = double strength (1 DS tablet of cotrimoxazole is equivalent to trimethoprim 160mg/sulfamethoxazole 800mg); **PO** = orally.

a median of 8 months earlier.[9] All five had successful re-induction of remissions. In a similar study, De Groot and colleagues[68] also sought to determine whether methotrexate (with or without corticosteroids) was beneficial in maintaining remissions in patients with WG. Following remission induction with cyclophosphamide (either oral or intravenous) and corticosteroids, patients then received weekly intravenous methotrexate with or without concomitant corticosteroids. In this study, partial or complete remissions were maintained in 19 of 22 patients (86%) who received methotrexate alone and in 10 of 11 patients (91%) receiving methotrexate plus prednisone.[68] These findings were echoed in a separate study of 71 patients who were treated with low-dose (0.3 mg/kg/week) methotrexate following remission induction with cyclophosphamide.[69] However, in this study, the authors also noted that relapses occurred in 26 patients (37%) despite ongoing methotrexate use; further, more than one-half of the relapses occurred in the kidney, highlighting the necessity for ongoing monitoring for relapse occurrence.[69] Similarly, Langford et al.[70] reported a relapse rate of 52% in 42 patients receiving methotrexate and corticosteroids following remission induction with cyclophosphamide and corticosteroids. Again, relapses involving the kidney were observed in a striking 73% of patients.[70] In summary, these data support the use of methotrexate plus prednisone in maintaining remissions in patients with WG, while cautioning that close follow-up to identify relapses is of paramount importance (Level 2a evidence, Grade B recommendation).

3.2 Azathioprine

Azathioprine is a purine analogue which is cleaved *in vivo* to 6-mercaptopurine, and is believed to work by affecting purine nucleotide synthesis and metabolism, thereby altering the synthesis and function of RNA and DNA. Early observational studies reported that maintenance of remission with azathioprine could be achieved in some patients after remission induction with cyclophosphamide and corticosteroids.[4,71] Although azathioprine has a myriad of potential toxicities, serious adverse effects requiring discontinuation of therapy are uncommon (<10%).[47] In contrast to cyclophosphamide, azathioprine lacks bladder toxicity and has low oncogenic potential.[47]

Greater support for the use of azathioprine in maintaining remissions in patients with WG derives from a recent prospective study in which 155 patients with ANCA-associated vasculitis (95 of whom had a confirmed diagnosis of WG; the remainder had microscopic polyangiitis) were treated with cyclophosphamide (2 mg/kg/day orally) and corticosteroids (prednisolone 1 mg/kg/day tapering over 12 weeks to 0.25 mg/kg/day) to induce remissions, followed by randomisation to receive continued cyclophosphamide therapy (1.5 mg/kg/day oral-

ly) or azathioprine therapy (2 mg/kg/day orally) along with prednisolone (10 mg/day) in both groups.[61] At 12 months following enrolment, all patients received azathioprine (1.5 mg/kg/day) and prednisolone (7.5 mg/day) until the conclusion of the study, 18 months following enrolment. In this study, use of azathioprine was as effective as cyclophosphamide at preventing relapses (11/71 [15.5%] versus 10/73 [13.7%], respectively), with a similar rate of adverse events and similar degree of improvement in renal function.[61] Thus, these authors concluded that use of azathioprine for maintaining remissions in ANCA-associated vasculitis could reduce patients' exposure to the potentially oncogenic effects of long-term cyclophosphamide without increasing relapse rates.[61]

However, subsequent experience calls these conclusions into question. Sanders et al.[72] reported their experience with 136 patients with ANCA-associated vasculitis who received either cyclophosphamide alone or azathioprine following 3 months of remission induced by cyclophosphamide. Similarly to the article by Jayne et al.,[61] relapse-free survival at 18 months was 88.6% in the cyclophosphamide group compared with 89.6% in the azathioprine group. However, at 5 years of follow-up, relapse-free survival in the cyclophosphamide group was 57.4%, compared with 42.3% in the azathioprine group ($p = 0.09$),[72] thus challenging the results of Jayne et al.[61] Finally, in a separate report, Slot et al.[73] showed that ANCA titres at the time of switching to azathioprine from cyclophosphamide were predictive of later relapses. In 128 patients with ANCA-associated vasculitis, these authors found that patients in whom ANCA titres were negative at the time of switch from cyclophosphamide to azathioprine had a disease-free survival at 2 and 4 years of 80% and 62%, respectively, similar to the group receiving cyclophosphamide alone. However, patients in whom ANCA was positive at the time of switch had disease-free survivals at 2 and 4 years of 58% and 17%, respectively.[73] These data, in aggregate, therefore suggest that patients with ANCA-associated vasculitis should be in remission for a minimum of 3 months while receiving cyclophosphamide, and have a negative ANCA prior to switching to azathioprine for maintenance (Levels 1b and 2b evidence, Grade B recommendation).

One recent study has attempted to define a role for high-dose, intermittent intravenous azathioprine (1200 mg/month) for four patients with WG intolerant or refractory to prolonged cyclophosphamide therapy.[74] In this study, two patients (50%) achieved remissions after an average six courses of monthly azathioprine, whereas the remaining two patients failed to achieve remission using this regimen. Significantly, one of the two patients failing remission induction experienced disease progression on this regimen.[74] Given the small number of patients used in the trial and the relatively low remission rate (50%) compared with 59% for methotrexate plus corticosteroids,[5,8] or 91% with cyclophosphamide plus corticosteroids,[5] this regimen cannot be endorsed for current use in patients with WG until future, large multicentre trials confirm the results (Level 4 evidence, Grade D recommendation).

3.3 Cotrimoxazole

The mechanism of action of cotrimoxazole (trimethoprim/sulfamethoxazole) is not known, but could reflect antimicrobial or immunomodulatory effects. Relapses of WG are more frequently coincident with respiratory infections or in patients with chronic nasal carriage of *Staphylococcus aureus*.[75] Low-grade bacterial infection may prime neutrophils to express target antigens (e.g. c-ANCA) on the cell surface and may trigger local immune responses.[75] The antimicrobial effect of cotrimoxazole may abrogate these effects, thus limiting neutrophil activation and further tissue damage.

One double-strength tablet of cotrimoxazole (i.e. trimethoprim 160mg/sulphamethoxazole 800mg) twice daily may reduce relapse rates in a minority of patients with WG,[76] but is of limited value as initial therapy for generalised, multi-organ disease.[77] In early, non-randomised studies, DeRemee and colleagues[78,79] reported favourable responses to cotrimoxazole alone or in combination with cy-

clophosphamide plus corticosteroids in patients with indolent or progressive WG. A similar non-randomised study cited favourable responses with cotrimoxazole alone for 10 patients with limited, 'initial phase' WG, but relapses occurred in >50% of patients with generalised disease initially treated with cyclophosphamide plus corticosteroids.[80] A subsequent study treated 72 WG patients with cotrimoxazole for induction or maintenance of remission.[81] Among 19 patients with active WG confined to the respiratory tract, partial or complete remissions were achieved in 11 patients (58%) with cotrimoxazole alone. In contrast, in 53 patients with generalised WG, the addition of cotrimoxazole 1 year after remission was achieved with cyclophosphamide plus corticosteroids did not reduce late relapse rates.[81] A subsequent study of nine WG patients treated with cotrimoxazole (alone or combined with corticosteroids) as initial therapy found that no patient achieved either partial or complete remission.[77] Thus, it is recommended that use of cotrimoxazole to induce remissions in patients with WG be limited to those who, after thorough evaluation, demonstrate disease limited to the upper respiratory tract (Level 2b evidence, Grade B recommendation). Similarly, when disease is identified outside the upper respiratory tract, cotrimoxazole use as a single remission-induction agent cannot be endorsed.

Regarding remission maintenance, studies have shown that cotrimoxazole is less effective than methotrexate following initial treatment with cyclophosphamide plus corticosteroids.[68] Nonetheless, a role for cotrimoxazole in maintaining remissions in WG is plausible. Indeed, one placebo-controlled, randomised trial demonstrated that cotrimoxazole reduced relapse rates in patients with WG who were in remission following a standard cyclophosphamide-plus-corticosteroid regimen.[76] In this study, oral cotrimoxazole 160/800mg or placebo twice daily was initiated as maintenance therapy after remissions were achieved with cyclophosphamide plus corticosteroids. After 24 months of follow-up, relapses had occurred in 18% of 41 patients in the cotrimoxazole cohort compared with 40% in the placebo group.[76] Subgroup analysis revealed that relapse rates were lower only in patients with upper respiratory tract disease, but not in those with renal or lung involvement. Therefore, based on the accumulated data thus far, it appears that use of cotrimoxazole to maintain remissions should be restricted to those patients with WG limited to the upper respiratory tract (Level 1b evidence, Grade B recommendation).

The most important role of cotrimoxazole in WG is to prevent pneumonia caused by *P. jiroveci*, a well known complication of immunosuppressive therapy.[44,82-85] The incidence of *P. jiroveci* pneumonia in patients with WG is 1–20%;[5,44,86] this range is likely to reflect more aggressive immunosuppression in certain studies.[44] Prophylaxis against *P. jiroveci* pneumonia with cotrimoxazole is highly efficacious,[87,88] and should be given to all patients treated with aggressive immunosuppressive therapy (Level 1a evidence from Human Immunodeficiency Virus and Bone Marrow Transplantation literature,[89] Grade A recommendation). Cotrimoxazole 160/800mg thrice weekly is cost effective.[87] Other prophylactic regimens employing dapsone,[90] aerosolised pentamidine (once a month),[87,91] or atovaquone [90] are far more expensive[87] and have less favourable adverse effect profiles. Concomitant use of cotrimoxazole (as therapy for infection; cotrimoxazole 160/800mg twice daily) and methotrexate has been reported to cause significant adverse reactions, such as toxic epidermal necrolysis, significant pancytopenias and even fatal myelosuppression.[92-99] However, when used in prophylactic dosages (160/800mg thrice weekly), cotrimoxazole appears to be well tolerated in patients receiving methotrexate and should be used in this population[9] (Level 2b evidence, Grade B recommendation).

3.4 Adverse Effects of Drugs Used to Induce or Maintain Remissions in WG

A summary of morbidity associated with standard medications used for induction and maintenance of remissions in WG, along with recommendations regarding laboratory monitoring, is provided in table III.

Table III. Morbidity associated with drugs commonly used for induction or maintenance of remissions in Wegener's granulomatosis

Drug	Usual oral dosage	Adverse event (frequency, %)[a]	Recommended routine laboratory monitoring[b]
Corticosteroids	Prednisone 1 mg/kg IBW/day	Serious infection[c] (46) Cataracts (21) Fractures (11) Diabetes mellitus (8) Aseptic necrosis (3)	Blood pressure (each visit) Urine glucose (annually) Bone densitometry (every 1–2 years while remaining on therapy)
Cyclophosphamide	2 mg/kg IBW/day	Amenorrhoea, infertility, biochemical ovarian failure (57) Leukopenia (36–44) Non-glomerular haematuria (12–50) Serious infection[c] (13.6–26) Transient alopecia (17) Bladder cancer (2.8–5) Myelodysplasia (2–8) Increased malignancy risk (2.4-fold)	CBCP (baseline and every 1–2 weeks when dosage changed; every 1–3 months when dosage is stable) Serum creatinine at baseline and every 3–6 months while on therapy Urinalysis (baseline and every 3–6 months while on therapy; every 6–12 months after therapy cessation) Urine cytology (every 6–12 months after therapy cessation)
Methotrexate	0.3 mg/kg IBW/week	Transaminitis (11–24) Mucocutaneous ulcers (2.3) Leukopenia (4.4) Infection (2.3) Hepatic fibrosis (rare) Lung fibrosis (rare)	CBCP (baseline and every 2–8 weeks) LFT, creatinine (baseline and every 2–8 weeks)
Azathioprine	2 mg/kg IBW/day	Leukopenia (29.5) Serious infection (5.6) Drug allergy (7) Anaemia (2.8)	CBCP (baseline and every 1–2 weeks when dosage changed; every 1–3 months when dosage is stable) LFT, creatinine (baseline and every 2–8 weeks)
Cotrimoxazole	1 DS tablet twice daily (therapeutic) 1 DS tablet thrice weekly (prophylaxis)	Anorexia/nausea (9.7) Rash (4.9)	None

a Frequencies collated from various sources.[5,7,9,46,61,65,76,100]

b Adapted from American College of Rheumatology clinical guidelines.[101]

c Defined as one requiring hospitalisation or intravenous antibacterials.

CBCP = complete blood cell count with platelet count; **DS** = double strength (1 DS tablet of cotrimoxazole is equivalent to trimethoprim 160mg/sulfamethoxazole 800mg); **IBW** = ideal bodyweight; **LFT** = liver function tests (including aspartate aminotransferase, alanine aminotransferase and albumin).

4. Therapeutic Options for Typical Local Complications

Although WG is largely a systemic disease, two well-recognised local complications warrant mention. Tracheal (subglottic) and bronchial stenosis occurs in 10–30% of patients, may occur in the absence of disease activity elsewhere,[5,102-104] and is potentially life threatening. Similarly, orbital disease (which is seen in as many as 22% of patients throughout the course of their disease),[5,41,105,106] is a well-recognised and potentially sight-threatening complication that requires aggressive therapy to control. Management of these two local complications are discussed in this section.

4.1 Tracheal (Subglottic) and Bronchial Stenosis

Large airway stenosis is a potentially life-threatening complication of WG. Because of the often progressive nature, medical therapy alone is frequently ineffective in treating endobronchial or tracheal WG.[107] Thus, when large airway stenosis is diagnosed, regional and surgical interventions should be considered. Alternative treatment modalities include laser resection, airway dilatation, intratracheal corticosteroid injections, placement of air-

way stents, tracheostomy, laryngeal-tracheal reconstruction and partial tracheal resection.[102,103,107-111] In these circumstances, individualised, interdisciplinary therapy is often required.[102] When possible, surgical intervention or manipulation of the airways should be minimised during flares of systemic disease activity, because of the theoretical risk of improper or delayed healing.[110]

Analyses of numerous retrospective studies utilising laser resection as part of a therapeutic regimen for subglottic stenosis have reported varying degrees of success but lasting effects are uncommon.[102,103,110] Airway dilatation appears to offer higher rates of long-term airway patency, especially when combined with intralesional corticosteroids. In an initial study, 20 patients with WG and subglottic stenosis treated with intralesional corticosteroids and sequential dilatation were compared with 18 patients who received immunosuppressive medications alone.[107] It is noteworthy that 10 of 18 patients (56%) treated with immunosuppression alone required tracheostomy. Conversely, none of 20 patients receiving intralesional corticosteroids and dilatation required tracheostomy.[107] In a separate study, 21 patients with subglottic stenosis >50% of the tracheal diameter were treated with direct intralesional injection of methylprednisolone (20mg into each of four quadrants) followed by lysis of the stenotic ring and serial dilatation.[112] Follow-up demonstrated that in patients who did not have scarring from previous surgical manipulation, a mean of 2.4 procedures occurring an average 11.6 months apart was required to maintain airway patency. By comparison, patients in whom previous surgical manipulation resulted in airway scarring required an average of 4.1 procedures at an average interval of 6.8 months.[112]

Other treatment modalities for subglottic and bronchial stenosis, including airway stenting, tracheal reconstruction and partial tracheal resections, have reported varying degrees of success.[103,107,110] Airway stents may provide sustained relief of symptoms in some patients, but may be complicated by migration of the stent, granuloma formation, mucus hypersecretion, fungal colonisation or bronchomalacia in the area of the stent.[103] Tracheal reconstruction has been successfully performed in patients with severe tracheal stenosis refractory to medical therapy but is associated with considerable morbidity.[107,110] Thus, these increasingly invasive modalities should only be considered in patients for whom no other therapy has been effective at slowing the progression of disease (Level 5 evidence, Grade D recommendation).

4.2 Orbital Disease

Granulomatous involvement of the orbit from WG may cause blindness, proptosis, pain, swelling, oculomotor palsies, blurred vision, diplopia and reduction of eye mobility.[4,18,105,113,114] Compression or primary involvement of the optic nerve, often the most serious orbital manifestation, may lead to blindness in 2–9% of patients.[4-6,105,106,113,114]

No study has evaluated the optimal medical and/or surgical approach to patients with isolated orbital WG or orbital involvement in generalised WG. However, a retrospective evaluation of 15 patients with isolated orbital WG (n = 12) or with WG involving the orbit and sinonasal structures (n = 3) reported that treatment with cyclophosphamide plus corticosteroids resulted in durable remissions in 9 of 12 patients (75%) available for follow-up a median of 5 (range 1–23) years after the initial diagnosis.[115] Of the 12 initial patients with isolated orbital disease, long-term follow-up was available for eight. Of these patients, 88% (7 of 8) had no further disease or recurrence elsewhere. The final patient experienced multiple recurrences and eventually underwent orbital exenteration.[115] These data suggest that patients with orbital WG, even in the absence of disease elsewhere, should be treated as if they had generalised systemic disease. It can be extrapolated that cyclophosphamide plus corticosteroids for 3–6 months to induce remission followed by maintenance therapy with methotrexate or azathioprine is a reasonable approach (Level 4 evidence, Grade C recommendation). Given the high morbidity, including loss or impairment of vision, adjunctive surgical approaches should be undertaken only if the disease is refractory to medical regimens and if visual com-

promise is present (Level 5 evidence, Grade D recommendation).

5. Therapeutic Options for Fulminant, Life-Threatening Disease

Fulminant, life-threatening disease caused by WG is often defined as: (i) diffuse alveolar haemorrhage with respiratory failure, (ii) rapidly progressive glomerulonephritis; or (iii) CNS vasculitis. In these circumstances, therapy must be initiated immediately to prevent irreversible end-organ damage or death. However, no studies have identified optimal therapeutic regimens. For these patients, the use of methylprednisolone (1000 mg/day intravenously) or its equivalent and cyclophosphamide (3–4 mg/kg/day intravenously) for 3 days, followed by corticosteroid taper and oral cyclophosphamide (2 mg/kg/day) has been reported anecdotally, but has never been studied in rigorous trials. This regimen should be considered only in imminently life-threatening situations, because of the high risk of adverse effects (Level 5 evidence, Grade D recommendation).

Plasmapheresis with plasma exchange (combined with standard medication regimens) has been utilised in the treatment of severe WG, although it has never been studied in a systematic fashion. A number of retrospective reviews, encompassing 27 patients, suggest an improvement in renal function and cessation of pulmonary haemorrhage in patients treated with plasmapheresis.[116-119] However, in the absence of prospective data establishing its efficacy apart from other modalities, plasmapheresis should be reserved only for patients with life-threatening disease refractory to conventional therapies (Level 4 evidence, Grade C recommendation).

6. Emerging Pharmacological Agents for WG

While WG has become a largely treatable disease, relapses remain common. When coupled with the significant toxicities associated with the long-term use of nonspecific immunosuppressant agents, it becomes clear that newer, alternative therapies targeted to a specific pathogenic agent might provide better remission rates with fewer adverse effects. Experimental investigation into ANCA-associated vasculitis has highlighted a potential pathogenic role for both TNFα and B-cell-derived ANCA, and recent clinical investigation provides support for this possibility.

6.1 Tumour Necrosis Factor-α Antagonists

On the basis of a number of studies suggesting a role for TNFα in the pathogenesis of WG,[35,120-125] and on the efficacy of TNFα antagonists in the treatment of other autoimmune disorders,[126,127] investigative interest has recently focused on the use of TNFα antagonists in the treatment of WG. Currently, three TNFα antagonists are marketed worldwide for use in patients: adalimumab (Abbott Laboratories, Abbott Park, IL, USA), etanercept (Amgen, Inc., Thousand Oaks, CA, USA) and infliximab (Centocor, Inc., Horsham, PA, USA), although none currently has an indication for use in WG. Adalimumab has never been studied in patients with WG or other ANCA-associated vasculitides; thus, the potential role of etanercept and infliximab for treatment of WG are only discussed. Etanercept is a soluble, dimeric, recombinant human p75 TNFα receptor fused to the Fc fragment of human immunoglobulin G_1[128] that functions as a 'sink' for circulating TNFα. In contrast, infliximab is a chimeric mouse/human monoclonal antibody directed against TNFα,[129] which inhibits the action of TNFα by binding to both soluble and transmembrane human TNFα, thereby preventing attachment to TNFα receptors.[130]

In the only large-scale randomised trial to assess the efficacy of etanercept in the treatment of WG, investigators from the Wegener's Granulomatosis Etanercept Trial (WGET) randomly assigned 180 patients with documented WG to receive twice weekly subcutaneous injections of etanercept (25 mg/dose; n = 89) or placebo (n = 92) in addition to standard therapy.[131] For the purposes of this study, standard therapy was defined as cyclophosphamide plus corticosteroids for patients with life-threatening disease, and methotrexate plus corticosteroids for patients with non-life-threatening disease. The primary endpoint was sustained disease remission. Pa-

tients receiving cyclophosphamide plus corticosteroids were switched to oral weekly methotrexate (0.25 mg/kg/week, not to exceed 25 mg/week) once remissions were attained, and those in remission with evidence of renal failure (serum creatinine >2.0 mg/dL) were transitioned to receive oral azathioprine (2 mg/kg/day).[131] Corticosteroids were tapered and discontinued within 6 months of randomisation. Patient evaluations occurred at 6 and 12 weeks post-randomisation, and then every 3 months thereafter. Patients were followed until 12 months after randomisation of the last patient.[132] On this protocol, the WGET investigators found no difference in the rate of sustained remissions between the etanercept group (62 of 89 patients [69.7%]) and the placebo group (64 of 85 patients [75.3%]; p = 0.39), nor was there any difference in the number or severity of disease flares or the quality of life (as measured by the Medical Outcomes Study 36-Item Short Form General Health Survey [SF-36]).[131] Of significance, however, was the finding that six patients in the etanercept group, and none in the placebo group, developed solid organ cancers. Comparison with the Surveillance Epidemiology and End Results (SEER) database (in which approximately two solid cancers would have been expected in this group) demonstrated a 3-fold increase in the incidence of solid-organ cancers among patients receiving etanercept. On the basis of results of this study, etanercept does not appear to have a role in the induction or maintenance of remission in WG (Level 1b evidence, Grade B recommendation).

Infliximab has also been studied for the treatment of ANCA-associated vasculitides. To date, only four clinical trials that have included patients with WG have been published,[133-136] comprising a total of 35 patients. With such small numbers of patients, it is difficult to draw firm conclusions regarding the use of infliximab in WG. However, two observations regarding the use of infliximab in this cohort of patients can be made. Firstly, in all studies, the Birmingham Vasculitis Activity Score and mean dose of corticosteroids decreased in patients receiving infliximab, indicating improvement in disease activity. Secondly, the incidence of serious adverse effects was quite variable. Serious infections were absent in one study of 10 patients,[134] whereas 7 of 32 patients (22%) in a separate study developed serious infections.[135] Similarly, of the 35 total patients studied, two (6%) died while receiving infliximab (one from pulmonary haemorrhage and one from pneumonia attributed to cyclophosphamide-induced leukopenia).[135] In aggregate, these data appear to support a possible role for infliximab in the treatment of patients with WG (Level 3a evidence, Grade C recommendation), but larger randomised controlled trials that take into account the extent of disease and previous therapeutic regimens, and that also provide long-term follow-up data, will be necessary prior to recommending infliximab for routine use in this disease.

6.2 Mycophenolate Mofetil

Mycophenolate mofetil (MMF), an inhibitor of purine synthesis, has been used in small, non-randomised trials as both a remission-inducing and remission-maintaining agent for WG. In one study, nine patients with WG were treated with MMF (2 g/day) following induction of remission with cyclophosphamide plus corticosteroids.[62] One patient relapsed during the 15-month study period. In a second prospective study, Langford et al.[63] treated 14 patients with daily cyclophosphamide plus corticosteroids to induce complete remissions, followed by MMF as maintenance therapy. Relapses occurred in 6 patients (43%) at a median of 10 months after achieving complete remissions.[63]

Most recently, Joy et al.[137] evaluated the efficacy of MMF as a remission-inducing agent in 12 patients with ANCA-associated vasculitis (seven of whom had WG). In this trial, ten patients who had received at least two courses of immunosuppression with cyclophosphamide and/or azathioprine and in whom remission was not maintained were administered oral MMF 500mg twice daily (increasing every 2 weeks by 250mg twice daily to a final dosage of 1000mg twice daily) for 6 months. For the ensuing 6 months, all ten patients continued receiving MMF, although three had the dose tapered and

discontinued (one of whom eventually had a flare that was treated with high-dose corticosteroids) and one had a flare while on MMF (and subsequently received etanercept therapy).[137] Despite the varied response, total Birmingham Vasculitis Activity Scores[6,138] significantly improved in each patient both at a 24- and a 52-week timepoint. Thus, MMF may have a role in remission induction in patients refractory to conventional therapeutic regimens but larger studies will be needed to confirm these findings before this treatment can be recommended (Level 4 evidence, Grade C recommendation).

6.3 Rituximab

Rituximab, a chimeric mouse/human monoclonal antibody, directed against the B-cell marker CD20, has potential use in the therapeutic armamentarium against WG. B cells are the primary sources of circulating antibodies and are a primary source of ANCA in WG.[139,140] Since ANCA is believed to contribute to WG pathogenesis,[141,142] eradication of the cellular source of ANCA is an appealing target. Rituximab, by binding CD20 on the surface of B cells, promotes B-cell depletion through a number of mechanisms.[143-145]

In the only published trial to date of rituximab in WG, Keogh et al.[146] performed a prospective, open-label pilot study of ten patients with WG who were resistant to, or intolerant of, cyclophosphamide. In this trial, all patients had previously received cyclophosphamide for their disease but had failed to remain in remission. Patients were treated with a combination of oral prednisone (1 mg/kg/day, not to exceed 80 mg/day) and weekly intravenous infusions of rituximab (375 mg/m^2 body surface area) for a total of four infusions.[146] Prednisone was tapered to complete discontinuation over the course of 5 months. These investigators found that complete clinical remissions were achieved in all ten patients by 3 months following rituximab therapy.[146] B-cell levels were undetectable 1 week following the 4-week rituximab infusion, and were still undetectable 6 months later.[146] In the seven patients who had renal dysfunction prior to treatment, all seven experienced stabilisation of or improvement in serum creatinine levels.[146] Serum ANCA levels dropped in all patients and became negative in six. However, all ten patients had a relapse by 9 months, requiring either a series of 4-weekly rituximab infusions without corticosteroids, or corticosteroids plus rituximab following the initial protocol. All patients again achieved remissions.[146]

On the basis of this preliminary study, whether rituximab will one day have a role in the treatment of WG cannot be predicted. It is possible that rituximab may be effective in inducing remissions in patients with progressive, uncontrolled disease. But this study also clearly highlights that early relapses do occur following rituximab therapy at apparently higher rates than described for cyclophosphamide- or methotrexate-containing regimens. This observation underscores the need to identify which patients might benefit from rituximab use, which patients are likely to relapse following discontinuation, and whether long-term outcomes will be altered by its use. Until these questions are appropriately addressed by prospective investigation, rituximab use in patients with WG should be restricted solely to the setting of clinical trials (Level 4 evidence, Grade C recommendation).

6.4 Other Potential Therapeutic Options

Therapy for WG with cyclosporin,[147-149] gusperimus (15-deoxyspergualin),[150] high-dose intravenous immunoglobulin,[151-156] monoclonal antibodies targeted against T cells,[157-159] Campath-1H (a monoclonal antibody directed against CD52),[160,161] humanised anti-CD4 antibodies,[22] anti-thymocyte globulin[162] and etoposide[163,164] have all been described in case report form. Because data are limited to a few cases in uncontrolled trials, therapy with these agents cannot be endorsed except in the setting of a clinical trial (Level 4 and 5 evidence, Grade D recommendation).

7. Summary and Conclusions

WG is a disease that has gone from being uniformly fatal to one in which complete remissions and long-term survival can be achieved. However,

therapeutic trials for WG, up to now, have been difficult to compare owing to multiple clinical variables (such as disease activity or extent) and to differing therapeutic protocols (such as those related to dose administration of corticosteroids and rate of taper, or timing of discontinuation of immunosuppressants). As a result, no exact conclusions regarding treatment recommendations for WG are possible. Clearly, future studies are needed to identify safer and effective therapies for this group of patients. Additionally, we suggest that new trials also take into consideration risk factors for disease and its recurrence, as well as provide long-term follow-up to assess disease- and treatment-related morbidity and mortality. It is only through this type of prospective investigation that we will be able to better define optimal treatment regimens that will maximise clinical benefit of the therapeutic agents while minimising patient morbidity and mortality.

On the basis of available literature, the combination of cyclophosphamide and corticosteroids remains the treatment of choice to induce remissions in patients with severe, life-threatening disease, while methotrexate plus corticosteroids may be used as an acceptable alternative to induce remissions in patients without life-threatening disease. Methotrexate and azathioprine appear to be efficacious in maintaining remissions, although head-to-head trials have not demonstrated superiority of one agent over another. MMF may be useful as a remission-maintaining agent but larger trials will be necessary to confirm this. Cotrimoxazole clearly has a role in *P. jiroveci* pneumonia prevention, and may have a limited role in maintenance or induction of remissions in isolated upper respiratory tract disease. However, clinicians are cautioned to monitor patients closely for signs of relapse. Study of the TNFα antagonists has yielded conflicting results; etanercept is no more efficacious than 'standard regimens' at maintaining remissions but is associated with increased treatment-related morbidity, whereas infliximab may be useful in treating patients with refractory disease (although larger, randomised trials are needed to confirm this). Rituximab represents a potential new agent for the treatment of patients with Wegener's and other ANCA-associated vasculitides, but confirmation of efficacy in larger, randomised studies will be necessary prior to endorsing it for widespread use.

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