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Induction and maintenance therapy in ANCA-associated systemic vasculitis

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GUIDELINES

Induction therapy

a. Combination treatment with cyclophosphamide plus prednisolone should be used for induction of disease remission when organ function is threatened. Both intravenous (IV) and oral cyclophosphamide show equal clinical efficacy and toxicity. (Level II evidence)

b. Methotrexate is an alternative to cyclophosphamide-based induction therapy in patients with milder, early disease (serum creatinine <150 μmol/L). (Level II evidence)

c. Plasma exchange should be preferred to pulse methylprednisolone as an adjunctive therapy in the initial treatment of severe ANCA-associated systemic vasculitis (AASV) causing necrotising glomerulonephritis and acute kidney failure (creatinine >500 μmol/L). (Level II evidence)

Maintenance therapy

a. Once disease remission has been established, azathioprine in combination with lower doses of prednisolone should be used to prevent disease relapse. (Level II evidence)

b. Although cyclophosphamide (both IV and oral therapy) has been shown to be as effective as azathioprine in the maintenance of disease remission, prolonged use of this agent should be avoided due to its well documented side effects.

c. Methotrexate may be used as maintenance therapy in patients with well preserved kidney function but is less effective than oral cyclophosphamide in preventing disease relapse. (Level II evidence)

d. Prolonged oral co-trimoxazole may decrease the incidence of upper airway disease relapse in patients with Wegener's granulomatosis (WG) but has not been shown to reduce relapse rates in other organs. (Level II evidence)

e. Etanercept is not effective in the maintenance of remission and induces a high level of side-effects. Its use is not recommended. (Level II evidence)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

Maintenance therapy

- **The optimal length of treatment required to minimise relapse has yet to be established. It is recommended that treatment continue for a minimum of 12 months after remission is established, but possibly up to 24 or 36 months for those at highest risk of relapse.**
- **Those at highest risk of disease relapse include patients with WG and those in remission but with ongoing ANCA positivity, particularly PR3-ANCA.**
- **The optimal steroid regimen for the prevention of disease relapse has yet to be established, but it is recommended that steroids be used in combination with a second agent once remission is established, with gradual dose reduction over time.**
- **Mycophenolate mofetil may be useful in the prevention of disease relapse but as prospective evidence is lacking, it should be restricted to those intolerant of other agents.**

Disease relapse

- **The diagnosis of disease relapse should not be based on a change in ANCA titre alone.**
- **No recommendation can be currently made on the optimal treatment of disease relapse in AASV but the reuse of 'induction-like' therapies is suggested.**
- **Evidence from case reports suggests that rituximab is efficacious in the treatment of relapsing or refractory disease.**

BACKGROUND

ANCA-associated systemic vasculitis is an important contributor to end-stage kidney disease (ESKD) in Australia

and New Zealand. The established treatments are associated with considerable toxicity and even mortality in the older age group, in which the diseases – WG and Microscopic Polyangiitis (MPA) – are most common.

Quality randomised controlled trials (RCTs) are somewhat lacking in the area and tend to involve only relatively small patient numbers. Some treatment regimens are based largely on historical precedents and case series, dating back to the late 1980s/early 1990s when dramatic improvements in the outcome of the diseases were seen, mainly due to cyclophosphamide (CYC) treatment. It became evident however, that the toxicity of such treatment was substantial and was contributing to mortality. Follow-up studies of patients treated with prolonged courses of oral CYC therapy revealed an incidence of bladder cancer as high as 5% at 8 years.[1] Other side effects linked to long term CYC use include haemorrhagic cystitis, infertility and haematological malignancies.[2]

Since then, shorter durations of induction treatment with conversion to less toxic alternatives for maintenance treatment (azathioprine, methotrexate) have been the focus of most trials.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for vasculitis were combined with MeSH terms and text words for antineutrophil cytoplasmic antibodies and combined with MeSH terms and text words for steroids, cyclophosphamide, rituximab, infliximab, methotrexate, plasma exchange, etanercept, mycophenolate mofetil, leflunomide, anti-TNF-alpha antibody and IVIG. The search was carried out in Medline (1966 – August Week 3, 2006).
Date of searches: 25 August 2006.

WHAT IS THE EVIDENCE?

Induction therapy

Cyclophosphamide and prednisolone

Original protocols from the National Institutes of Health for induction and maintenance therapy in WG included a prolonged course of oral prednisolone and CYC.[2] The dose of prednisolone was weaned from 60 mg per day to a tapering dose of alternate daily prednisolone based upon clinical response, such that most patients were on a dose of 20 mg alternate daily by 6–12 months. Cyclophosphamide was continued at a dose of 2 mg/kg until the disease had been in remission for 1 year and then was weaned by 25 mg every 3 months. This protocol, which was based on retrospective evidence only and resulted in a relapse rate of approximately 50%, but was found to be associated with unacceptable toxicities, as mentioned.

In an effort to minimise the toxicity of prolonged CYC exposure, several trials have examined the use of pulse CYC versus continuous oral therapy. By using pulse IV CYC the total dose of CYC administered can be reduced. This is assumed to represent lower drug exposure for the individual patient, however, differences in drug absorption and metabolism based on the two routes of administration are rarely considered. As well as this, while it may be possible to demonstrate beneficial short term effects of lower total drug exposure, as discussed, long term follow-up data is really required to demonstrate the superiority of one route of administration over another.

The first trial[3] compared pulse IV then intermittent oral CYC and prednisolone (PCYP) with continuous oral CYC and prednisolone with conversion to azathioprine (AZA) after a median 3 months of treatment (CYCAZP) in 54 patients. The study included WG, MPA and classic polyarteritis nodosa patients who were randomised and stratified by renal function based on serum creatinine concentration (<250, 251–500 and >500 µmol/L).

Methodological concerns included the allowance of dose escalation of steroid therapy, and also the use of plasma exchange (PE) and intravenous immunoglobulin (IVIG) in both groups in the event of severe or life-threatening disease, (31 patients in total) which may have contaminated the results. Although a power calculation was performed, the study did not have sufficient numbers to show a difference of the magnitude proposed.

The results showed no significant difference in toxicity, either as infectious complications or leukopenia and no significant difference in patient or renal survival. The discussion of the results fails to answer the study question in any real detail, other than to say both therapies seemed equivalent, albeit contaminated by other immune suppression in over half (31/56) of the cases.

The second trial[4] compared the efficacy and toxicity of intravenous monthly 'pulse' CYC with daily oral CYC therapy in 47 patients, combined with intravenous and then oral steroids. Methodological concerns include the randomisation process, with 56 patients being randomised but only 47 included in the analysis (i.e. not intention-to-treat analysis) because of prior treatment with CYC or dialysis therapy prior to being included in the study. The primary endpoints were 1) progression of disease in spite of immunosuppressive therapy; 2) lack of complete remission after 12 months of treatment; 3) relapse during or up to 1 year after the end of CYC therapy after a complete remission had been achieved; and 4) severe adverse effects of treatment, including severe opportunistic infections, intractable thrombocytopenia or leukopenia. The *a priori* endpoint was not stated in terms of stopping criteria or power calculations but the study was terminated after 5 years when significant differences were found in the two groups. There was no mention of how many interim analyses were performed.

The results showed no difference in mortality, remission (although numerically less in the daily oral group), renal function, or relapses. There was no difference in terms of primary disease either (WG or MPA). With regard to toxicity, the IV CYC treatment had significantly less leukopenia (60% vs 18%), although 4 patients did not have their white cell count (WCC) monitored (group not stated). Similarly, thrombocytopenia was seen in 3 patients on daily

oral therapy but none on IV CYC. There was borderline significant difference between infections (depending on the statistical test used) of 10 infections in the daily oral group versus 3 in the IV CYC group ($P < 0.056$, < 0.044, depending on the test).

A French group[5] similarly performed a trial examining the potential benefits of IV versus oral CYC. Fifty patients with newly-diagnosed WG were randomised to either oral or pulse IV CYC after initial induction therapy that included IV then oral steroids and a single pulse of IV CYC. Treatment was continued for 1 year after remission was achieved. Steroid doses were tapered in both groups according to the same protocol. Once again, IV CYC therapy resulted in significantly lower drug exposure compared to oral therapy. As in the trial by Haubitz *et al.*,[4] there were fewer infectious complications in patients treated with pulse IV therapy but this did not equate to significantly better patient survival. Unlike in Haubitz's trial however, the relapse rate for patients treated with IV CYC therapy was significantly greater than for those treated with oral therapy (59% versus 13%, $P = 0.02$). Again, no long term follow up data was available.

Meta-analysis of these three trials comparing IV and oral CYC therapy for AASV[6] concluded that IV therapy was more likely to induce remission than oral therapy and was associated with a lower risk of infection. There was an increased incidence of disease relapse in patients treated with IV CYC compared to oral, but this failed to reach statistical significance. The incidence of death and ESKD was no different between the two treatment modalities. The authors concluded that based on current evidence, pulse IV CYC is less toxic than continuous oral CYC and as potent an inducer of remission, possibly at the expense of a higher relapse rate. The total number of patients included in the analysis was only 143, prompting the authors to suggest that a large prospective randomised trial was needed to address the issue better.

The most recent RCT to address this issue (in print) was performed by the European Vasculitis Study Group (EUVAS) in 160 patients with newly diagnosed AASV and renal involvement (but serum creatinine <500 µmol/L). Patients were treated with prednisolone and randomised to daily oral CYC 2 mg/kg/day or pulse IV CYC 15 mg/kg (with a 2 week interval between the first 2 pulses, then at three-weekly intervals). Azathioprine was given at 3 months after remission was achieved in both groups and patients were followed for 18 months. The first primary endpoint was disease-free period between remission and relapse. Results revealed that there was no difference in time to remission and first relapse, suggesting that oral and pulse IV CYC were equally effective. Drug toxicities were similar for both routes of administration. The authors concluded that either induction regimen can be used, depending on local circumstances.

Methotrexate

In an attempt to minimise the toxicity of CYC treatment, the EUVAS conducted an RCT designed to answer the question of whether methotrexate (MTX) could replace CYC in the treatment of AASV.[7] The trial was not blinded and recruited 100 patients from across Europe. It was limited however, to patients without critical organ manifestations of disease (all patients had serum creatinine concentration of <150 µmol/L) and thus, a very different spectrum of disease to the former studies.

This was a better quality study with patients receiving the same steroid regimen in each group and no adjunctive immune suppression being given. Patients were treated with either CYC/Pred or MTX/Pred for 12 months, and followed up for 18 months. Prospective power calculations suggested 92 patients would be required to show non-inferiority of MTX/Pred, accepting a difference of 15% in the 2 treatments, with 80% power. Randomisation was stratified by site and diagnosis (WG or MPA). The primary endpoint was remission by 6 months and analysed as a non-inferiority test by intention to treat.

The results showed non-inferiority of MTX in inducing remission (89.8% in MTX/Pred group vs 93.5% in CYC/Pred group, $P = 0.241$), but time to remission was longer. With respect to relapse rates, CYC was shown to be superior to MTX in maintaining remission with a significantly lower relapse rate of 47% versus 70% as well as a greater time to relapse in the CYC group. Infectious complications were the same for both groups. The effects of ANCA type and titre on disease relapse rates were not studied. Most relapses occurred on withdrawal of the drugs at 12 months, prompting the authors to suggest that maintenance therapy, particularly with MTX, should be continued for more than 12 months. This is yet to be tested in a prospective trial.

Plasma exchange

Plasma exchange (PE) aims to deplete circulating pathogenic autoantibodies; other effects, such as the removal of cytokines, complement, and coagulation factors, and less well-defined immunoregulatory phenomena may also contribute to its therapeutic effect.[8]

Four RCTs failed to demonstrate a generalised benefit of PE in the treatment of non anti-GBM antibody mediated rapidly progressive glomerulonephritis.[9–12] The number of patients included in these trials was small and inclusion criteria and immunosuppressive regimen varied. Included in these trials were cases of histologically-proven crescentic/focal-necrotising glomerulonephritis of non anti-GBM antibody type. The ANCA testing was variable. Nonetheless, in all these studies, subset analysis reveals that PE was found to be beneficial for those patients presenting with severe disease or dialysis dependency.

The recently reported MEPEX trial by the EUVAS has revealed an increased rate of renal recovery with PE compared to IV pulse methylprednisolone (ivMeP) in AASV patients presenting with moderate to severe renal failure.[13] One hundred and thirty-seven patients with a new diagnosis of AASV confirmed by renal biopsy and serum creatinine above 500 µmol/L were randomised to receive seven PEs ($N = 70$) or 3000 mg of ivMeP ($N = 67$). Both groups

received oral CYC and oral prednisolone. The primary endpoint was dialysis independence at 3 months. Secondary endpoints included renal and patient survival at 1 year and severe adverse event rates. Randomisation was stratified for dialysis requirement/oliguria. Mean age was 66 years. The most common diagnosis was MPA followed by WG and renal-limited vasculitis. The proportion of each disease subtype did not differ in the PE and ivMeP groups. At 3 months, the renal outcome was significantly better in the PE group, with 69% of patients alive and off dialysis compared to 49% treated with ivMeP ($P = 0.02$). Twelve-month patient survival and adverse events were similar in both groups.

Maintenance therapy

Once remission is established in AASV, there is a need for ongoing maintenance therapy to minimise the chance of disease relapse. Based on available historical data, it is difficult to quantify the incidence of disease relapse in AASV without the use of maintenance therapy, however, early studies suggested that relapse was almost universal in patients treated with steroids alone.[14]

The point of transition from induction therapy to maintenance therapy in AASV relies on a strict definition of disease remission. Once the criteria for disease remission have been met, ongoing therapy can be considered maintenance until disease cure or relapse. While several scoring systems have been devised to define disease remission, the mostly widely accepted and validated system is the Birmingham Vasculitis Activity Score (BVAS).[15] This scoring system grades systemic and organ specific activity of disease from 0 to 63, based on newly present or worsening symptoms. Remission is defined by a stable or improved BVAS and is independent of serum ANCA status.

Drugs used for maintenance therapy should be chosen based on their effectiveness in preventing disease relapse and allowing steroid minimisation, while also considering short and long term toxicities.

Cyclophosphamide and prednisolone

Trials that examine the role of CYC in combination with steroids as therapy for AASV have already been discussed. While a short course of CYC, either oral or IV, remains the cornerstone of induction treatment, maintenance therapy with CYC should be avoided due to the well-documented severe side effects associated with prolonged drug exposure.

Azathioprine

Although not specifically designed to examine the role of AZA as maintenance therapy in AASV, the randomised trial by Adu *et al.*[3] was the first trial to use AZA for this purpose. While it is not possible to draw firm conclusions from this study as to the benefit of any single agent, the trial at least gave some support to the notion that AZA could be used in AASV to prevent disease relapse.

A large, prospective, randomised trial was performed by the EUVAS[16] to specifically address the issue of AZA versus CYC maintenance therapy in AASV. One hundred and forty-four patients with AASV in remission were randomly assigned to 12 months of maintenance therapy with either AZA (2 mg/kg) or CYC (1.5 mg/kg). After 12 months of maintenance therapy, those treated with CYC were switched to AZA (1.5 mg/kg) for a further 6 months while those in the AZA group remained on the drug at a lower dose (1.5 mg/kg) for the remaining 6 months of the trial. In both groups, steroids were continued at a dose of 10 mg/day for 12 months and then reduced to 7.5 mg/day for 6 months. All patients enrolled received the same induction therapy of oral CYC and prednisolone.

The results confirmed that AZA was as effective as CYC in the maintenance of remission of AASV, with relapse rates similar in both groups. In those treated with AZA, 15.5% relapsed over the course of the trial compared with 13.7% in those treated with CYC. Of note, relapse rates were higher in patients with WG compared to those with MPA. It was somewhat disappointing that adverse events and patient survival were also the same in both groups, although as discussed, the effects of prolonged CYC exposure are often delayed by many years. Overall, 21% of patients suffered a serious adverse event during treatment. The authors concluded that patients with AASV in remission could be safely converted to AZA maintenance therapy, thus avoiding prolonged exposure to CYC.

One group[17] warned against the blanket substitution of AZA for CYC as maintenance therapy in AASV, based on a retrospective analysis performed on their cohort of patients. Eighty-four patients with AASV treated with CYC for 18 months were compared with 44 patients who were switched to AZA after remission. Although relapse rates were similar in the two groups, sub-analysis suggested that those patients who were PR3-ANCA positive at the time of commencement of AZA therapy had a higher rate of relapse than those who were PR3-ANCA positive and were maintained on CYC. Given the retrospective nature of the study and the data presented, it is not clear whether these concerns are valid. However, there is certainly some evidence to suggest that patients with ongoing ANCA positivity during maintenance therapy are at a higher risk of disease relapse than those who become ANCA negative during treatment.[18] This subgroup of patients may need to be considered for more aggressive therapy.

Methotrexate

As discussed, the trial by de Groot *et al.*[7] concluded that 12 months of treatment with MTX was less effective than CYC in maintaining disease remission in AASV. The authors suggested that extending the length of treatment with MTX beyond 12 months may reduce relapse rates further. Several authors have reported non-controlled, open label cohorts of patients treated with longer courses of MTX.[19,20] When compared with historical controls treated with CYC, prolonged therapy with MTX seems to be as effective in the maintenance of disease remission.

Etanercept

A single RCT has been performed examining the use of etanercept as induction and maintenance therapy for WG.[21] It demonstrated that there was no advantage to its use in combination with standard treatment as far as induction of remission or maintenance of remission, when compared with standard treatment alone. One hundred and eighty-one patients with newly-diagnosed WG or relapsed disease were randomised to standard treatment combined with etanercept 25 mg subcutaneously twice weekly or placebo. Standard treatment included CYC and prednisolone for patients with severe disease and MTX and prednisolone for patients with limited disease. On induction of remission, AZA was substituted for CYC in patients with severe disease and MTX was continued in patients with limited disease. Randomisation was stratified by severity of disease (limited or severe). The primary outcome was sustained disease remission defined as BVAS score of 0 for at least 6 months.

There was no significant difference observed between the groups for the primary outcome measure. In the etanercept arm, sustained remission was achieved in 70% of patients and in the placebo group, in 75% of patients. There was also no difference detected between the groups in terms of the relative risk of disease flare. The only detectable difference in outcome was the occurrence of six solid cancers in the etanercept group versus no cancers in the control group ($P = 0.01$). All patients who developed cancer had also been treated with CYC, prompting the authors to suggest that the combination of etanercept with CYC may particularly predispose patients to an increased incidence of malignancy.

Bactrim

Observational studies have suggested that infection, particularly of the upper respiratory tract, may predispose to disease relapse in WG.[22] A prospective RCT was performed to specifically examine the role of co-trimoxazole in combination with conventional immunosuppression for the prevention of disease relapse in WG.[23] This multi-centre trial recruited 81 patients with WG in remission and randomised patients to receive co-trimoxazole twice daily for 2 years or placebo. Patients with severe renal impairment (GFR < 30 mL/min) were excluded. Other immunosuppression included prednisolone and CYC and was adjusted according to protocol.

Although 20% of patients could not tolerate co-trimoxazole treatment, on an intention-to-treat analysis, there were still significantly fewer relapses in the co-trimoxazole–treated group, at 17% compared with 40% in the placebo group (RR relapse 0.40, 95% CI 0.17, 0.98). Most of this difference was accounted for by significantly more upper airway and nasal lesions in the placebo-treated group compared with the co-trimoxazole–treated group ($P < 0.04$). The relapse rate for other organ involvement was not significantly different between the two groups. The study also demonstrated a lower rate of respiratory and non-respiratory infections in the co-trimaxazole–treated group compared with placebo. This prompted the authors to conclude that prolonged treatment with co-trimoxazole was beneficial only in the prevention of upper airway relapse in WG, possibly as a result of a lower infection rate.

Relapse Therapy

It is clear that despite aggressive induction therapy and ongoing maintenance therapy, there is still a significant incidence of disease relapse in AASV. Reported rates of relapse vary between 25%–35% in patients with MPA,[24] and up to 50% in patients with WG.[2] As already discussed, there is some evidence to suggest that those with ongoing PR3-ANCA positivity while in remission are at greater risk of relapse than those patients rendered ANCA negative with induction therapy.

There have been many studies performed that examine the role of serial ANCA measurement in predicting disease relapse in AASV. For example, in one series,[25] 100 patients with AASV were followed prospectively with changes in ANCA titre correlated with disease relapse. Over the 2 years of the study, 71% of patients with a rising PR3-ANCA titre and 100% of patients with a rising MPO-ANCA titre (as detected by ELISA) went on to develop disease relapse. Others[26] did not observe such a strong association between rising ANCA titres and disease relapse and advise against its use as a marker of impending disease recurrence. In an effort to clarify this issue, a meta-analysis was performed[27] of more than 22 studies including 950 patients that examined the relationship between serial ANCA measurement and disease relapse. Unfortunately, as a result of the considerable methodological heterogeneity between studies, firm conclusions could not be drawn from the analysis. Based on the conflicting evidence, it would seem reasonable to suggest that a diagnosis of disease relapse in AASV should not be based on a rise in ANCA titre alone and treatment should be reserved for those with other clinical manifestations of disease.

A rise in other inflammatory markers such as ESR or CRP that may suggest disease relapse, have been found to be of limited prognostic value in the studies performed.[28]

Unfortunately, there are no RCTs that specifically address the issue of treatment of disease relapse in AASV. Most studies use 'induction-like' therapies including high-dose steroids and CYC with variable results. The subgroup of patients with frequent disease relapse despite adequate maintenance therapy may benefit from newer agents such as rituximab, based on recent case reports.[29]

Alternative agents

Mycophenolate mofetil

To date, no RCTs have been published that examine the use of mycophenolate mofetil (MMF) for induction or maintenance therapy in AASV. In a recent study,[30] MMF was successfully used as induction therapy in 32 patients with AASV who were unable to be treated with CYC, with high

rates of complete remission (78%) and partial remission (19%) obtained. Patients were treated with MMF 1 g twice daily in combination with oral steroids for 12 months. After 1 year of treatment, the dose of MMF was weaned by 500 mg every 3 months. Unfortunately, 19 of the 31 patients (61%) who initially responded to MMF therapy had a disease relapse. Median relapse-free survival was 16 months.

Several pilot studies involving small cohorts of patients have suggested the drug may be of benefit as maintenance therapy in AASV. For example, in one small study,[31] MMF was used to treat 14 patients with WG in remission. Remission was induced with standard CYC and steroid therapy and then patients were switched to maintenance therapy with MMF for 2 years. Forty-three per cent of the patients treated with MMF had a disease relapse. This rate of relapse is considerably higher than that observed in patients treated with AZA or CYC in other trials. The drug was well tolerated in the patient group, with no infective or gastrointestinal complications. Another small study[32] observed a much lower relapse rate of 10% in 11 patients with AASV in remission treated with MMF. A larger, more recent retrospective study of MMF in AASV,[33] involved 51 patients treated in a single centre over a period of 4 years. Mycophenolate mofetil was used as induction therapy in 43% of patients and as maintenance therapy in 57% of patients. Overall response rates to treatment were high but again, a high incidence of disease relapse was noted (up to 50% at 2 years) as well as a high incidence of treatment-related side effects, observed in up to 71% of patients.

Cyclosporin

Several case reports have been published suggesting cyclosporin may be of benefit in maintenance of disease remission in AASV. This agent may be most attractive in patients with already established ESKD where nephrotoxicity is less of a concern.[34] A single series of 7 patients with WG has been published, suggesting a role for cyclosporin in the maintenance of disease remission.[35] After induction therapy with steroids and CYC, cyclosporin was administered for 18 months with no reported relapses of disease. The cyclosporin was however, administered in combination with CYC for the first 6 months of maintenance therapy, likely contaminating results.

Leflunomide

Following on from an open-labelled trial that suggested a role for leflunomide (LEF) in the maintenance of remission in WG,[36] an RCT was performed comparing LEF with MTX in 54 patients with WG in remission.[37] After the induction of remission with combination CYC and prednisolone, 26 patients were randomised to receive daily oral LEF for 24 months and 28 patients to receive weekly oral MTX therapy. The trial had to be stopped prematurely due to a high rate of relapse in the MTX arm of the study, with 13 of 28 patients suffering relapse within 6 months of commencing treatment. Of the 13 relapses, 7 were considered severe. In the LEF arm, 6 of 26 patients suffered a relapse, of which only 1 was considered severe. Adverse events were significantly more common in the LEF-treated group, with 4 patients having to cease LEF therapy due to severe side effects. Although inconclusive, the trial suggests a possible role for LEF in maintenance therapy for WG.

Intravenous immunoglobulin

A single RCT has been performed with intravenous immunoglobulin (IVIG) in patients with refractory AASV.[38] In this trial, 34 patients with active vasculitis despite at least 2 months of standard treatment were randomised to receive a single course of IVIG at a total dose of 0.4 g/kg/day for 5 days or placebo. Of the 17 patients who received the IVIG, 14 showed a treatment response versus 6/17 in the placebo arm ($P = 0.015$). However the benefit of IVIG was not maintained beyond 3 months, suggesting a possible role for repeat courses of IVIG in selected patients. Minor side effects from IVIG were frequent, including a transient rise in serum creatinine in 4 patients.

A more recent study has examined the role of IVIG as induction therapy for AASV.[39] Twelve patients with new onset or relapsed AASV were treated with a single course of IVIG over 5 consecutive days without any other concomitant immunosuppressive therapy. Immediately following IVIG therapy, there was a significant reduction in vasculitis activity as measured by the BVAS. Without a control arm, it is difficult to draw firm conclusions from this trial but further studies of the role of IVIG in AASV seem warranted.

Infliximab

There are no RCTs that examine the role of the TNF-α inhibitor – infliximab – in the treatment of AASV. There is very little data even in the form of case series supporting the use of infliximab in renal vasculitis.

The largest study performed to date[40] was divided into two parts. Study 1 included 16 patients undergoing induction treatment in non-life threatening new disease or relapse disease. They were treated with standard therapy with CYC and prednisolone with the addition of infliximab. Study 2 included patients with evidence of persistent disease activity on immunosuppression. These were treated with the addition of infliximab to their continuing immunosuppression. There were no control arms to the study. Both studies showed a remission rate of 88% with a relapse rate of 20%. Severe infections were seen in 21% of patients treated with infliximab. Without a control arm, it is difficult to draw firm conclusions from this study, but as the authors suggest, it does provide support for a larger clinical trial.

Side effects of treatment are a significant issue in TNF-α inhibition and these are not well documented in some series. One particular prospective study using infliximab therapy for refractory vasculitis[41] was abandoned due to a lack of clinical efficacy and side effects. This included 9 patients who suffered multiple adverse effects (including one death) with no detectable benefit on disease activity.

Rituximab

There are currently no RCTs that examine the role of rituximab in the treatment of AASV. Several larger case series[42–46] include a total of 48 patients treated with rituximab, of which 40 entered disease remission. The dose of rituximab varied somewhat between the series but most investigators used 375 mg/m^2 in four, weekly doses. The outcome was overwhelmingly positive in the view of most authors. The only detractor[44] treated 8 patients with rituximab with only 2 patients entering remission. The author subsequently treated these patients with AZA with more success than with rituximab. The dose interval for rituximab used in this series was 4 weeks rather than weekly or fortnightly. Considering that the effect of rituximab lasts for many months, it is difficult to see how this would affect disease response. Nevertheless, currently it would seem appropriate to avoid this particular dosing regimen.

Some authors have used rituximab in refractory or recurrent disease with success. In one series,[43] 11 patients who had failed CYC therapy and were all PR3-ANCA positive were treated with rituximab 375 mg/m^2 weekly for 4 weeks. All patients received high-dose corticosteroids concurrently. Eight had 3 days of ivMeP and three underwent PE prior to the rituximab infusion. All patients achieved remission. In a second series,[45] 10 patients with previously diagnosed WG and contraindications to further CYC treatment were treated with the same dose of rituximab. Again, all patients went into remission. B cells were undetectable in peripheral blood for approximately 9 months, in these studies.

Based on the lack of clinical trials involving rituximab use of this drug should be reserved for patients who have failed or are intolerant of other treatments.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

1. RCT – Mycophenolate vs CYC for primary induction therapy. Rationale: there is increasing anecdotal experience of the benefit of MMF in AASV, in patient groups intolerant of or resistant to CYC, or young patients in whom there are fertility concerns with the use of CYC. There are a number of reports or small case series of patients successfully treated with MMF after failure of CYC, suggesting efficacy even in resistant disease. An RCT of MMF versus CYC could investigate whether MMF is as efficacious as CYC but with a better side effect profile in terms of leukopenia, infections and infertility.
2. RCT – Rituximab vs CYC for primary induction therapy. Rationale: as there is increasing evidence for the pathogenicity of ANCA, B-cell depleting treatments such as rituximab have been appealing, and reports of successful treatment (mostly in severe or refractory disease) are increasing. The role of rituximab as primary treatment is yet to be investigated.

There are several ongoing prospective studies currently being performed by the EUVAS. The REMAIN trial is examining prolonged low dose maintenance therapy of 4 years duration compared to 2 years of treatment. The IMPROVE trial is comparing MMF with AZA as maintenance therapy for patients with AASV in remission. The MUPIBAC trial is examining the role of nasal mupirocin for the prevention of ENT disease relapse in WG.

Unfortunately, due to the low incidence of the disease and the prolonged follow-up required for these trials, it may be some time before the results are available.

CONFLICT OF INTEREST

All of the authors have no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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APPENDICES

Table 1. Characteristics of included studies

Study ID	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Main conclusions
Adu *et al.*, 1997[3]	54	Randomised controlled clinical trial	UK	Patients with Wegener's granulomatosis, polyarteritis nodosa and microscopic polyangiitis	Pulse cyclophosphamide	Continuous cyclophosphamide	35–42 months	Increased toxicity was found with continuous cyclophosphamide.
Guillevin *et al.*,1997[5]	50	Randomised controlled clinical trial	Multicentre, France	Patients with Wegener's granulomatosis	Pulse cyclophosphamide	Continuous cyclophosphamide	24–30 months	Pulse and oral cyclophosphamide are effective in achieving initial remission of Wegener's granulomatosis and associated with less side effects and lower mortality. Long-term treatment pulse cyclo-phosphamide does not maintain remission or prevent relapses as well as oral cyclophosphamide.
Haubitz *et al.*, 1998[4]	47	Randomised controlled clinical trial	5 nephrology centres, Germany	Patients with Wegener's granulomatosis	Pulse cyclophosphamide	Continuous cyclophosphamide	37–43 months	IV cyclophosphamide is an effective treatment with low toxicity.

De Groot *et al.*, 2005[7]	100	Randomised controlled clinical trial	26 centres, Europe	Patients with antineutrophil cytoplasmic antibody-associated systemic vasculitis	Methotrexate	Oral cyclophosphamide	18 months	For initial treatment of early AASV, methotrexate can replace cyclophosphamide. Immunosuppressive treatment should be continued for more than 12 months.
Glockner *et al.*, 1988[10]	26	Randomised controlled clinical trial	2 nephrology centres, Germany	Histologically-confirmed rapidly progressive crescentic glomerulonephritis	Plasma exchange and immuno-suppressants	Immuno-suppressants alone	6 months	Kidney function could be improved with immunosuppressive treatment, no advantage of plasma exchange was found.
Cole *et al.*, 1992[9]	32	Randomised controlled clinical trial	University Hospitals, Canada	Patients with crescentic glomerulonephritis	Plasma exchange and drug therapy	Drug therapy only	12 months	No additional benefit was found with plasma exchange in non-dialysis patients with rapidly progressive glomerulonephritis.
Pusey *et al.*, 1991[12]	48	Randomised controlled clinical trial	UK	Patients with Wegener's granulomatosis, microscopic polyangiitis, rapidly progressive glomerulonephritis	Plasma exchange, prednisolone, cyclophosphamide, azathioprine	Drug therapy only		Plasma exchange provides benefit to dialysis-dependent patients. Patients responded well to early immunosuppressive treatment.

Table 1. *Continued*

Study ID	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Main conclusions
Metzler *et al.*, 2007[37]	54	Randomised controlled clinical trial	5 rheumatological centres, Germany	Patients with generalised Wegener's granulomatosis	Daily oral leflunomide	Weekly oral methotrexate	21 months	Leflunomide (30 mg/day) might be effective for preventing relapse in WG, but is associated with adverse events.
Jayne *et al.*, 2007[13]	137	Randomised controlled clinical trial	28 centres in 9 European countries	Patients with a new diagnosis of ANCA-associated systemic vasculitis	Plasma exchange	IV methyl prednisolone	12 months	Plasma exchange increased the rate of renal recovery.
Jayne *et al.*, 2003[16]	144		Multicentre, Europe/UK	Patients with Wegener's granulomatosis, microscopic polyangiitis and renal-limited vasculitis in remission	Azathioprine	Oral cyclophosphamide	18 months	Azathioprine is as effective as cyclophosphamide in maintaining disease remission with similar rates of adverse events.
Jayne *et al.*, 2000[38]	34	Randomised controlled clinical trial	5 hospitals, UK	Patients with Wegener's granulomatosis or microscopic polyangiitis	IV immunoglobulin	Placebo	12 months	After standard therapy, IV immunoglobulin is an alternative treatment for ANCA-associated systemic vasculitis with persistent disease activity.
Stegeman *et al.*, 1996[23]	81	Randomised controlled clinical trial	Multicentre	Patients with Wegener's granulomatosis	Co-trimoxazole	Placebo	24 months	Treatment with co-trimoxazole reduces the incidence of relapses in patients with Wegener's granulomatosis in remission.

Table 2. Quality of randomised trials

Study ID	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Adu *et al.*, 1997[3]	Computer- generated, sealed envelopes	No	No	Not stated	Not stated	0.0
Cole *et al.*, 1992[9]	Computer- generated random numbers	No	No	Yes	No	0.0
De Groot *et al.*, 2005[7]	Central, in blocks of 4 by country	No	No	No	Yes	3.0
Glockner *et al.*, 1988[10]	Telephone consultation with statistician	No	No	Not stated	Not stated	3.8
Guillevin et al., 1997[5]	Not specified	No	No	Not stated	No	20.0
Haubitz *et al.*, 1998[4]	Not specified	No	No	Not stated	No	16.1
Jayne *et al.*, 2007[13]	Central	No	No	Not stated	Yes	25.5
Jayne *et al.*, 2003[16]	Central, in blocks of four by country	No	No	No	Yes	2.1
Jayne *et al.*, 2000[38]	Central	Yes	Yes	Yes	No	5.9
Metzler *et al.*, 2007[37]	Central, permuted blocks of 4	No	No	Not stated	No	14.9
Pusey *et al.*, 1991[12]	Random numbers	No	No	Not stated	No	7.1
Stegeman *et al.*, 1996[23]	Not specified	Yes	Yes	Yes	Not stated	7.4

Table 3. Results for dichotomous outcomes

Study ID	Outcomes	Intervention group (number of patients with events/ number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Adu *et al.*, 1997[3]	Complete remission	8/24	7/30	1.43 (95%CI: 0.60, 3.38)	0.10 (95%CI: −0.1[illegible], 0.34)
	Mortality	5/24	4/30	1.56 (95%CI: 0.47, 5.19)	0.08 (95%CI: −0.13, 0.28)
	Leukopenia	7/24	13/30	0.67 (95%CI: 0.32, 1.42)	−0.14 (95%CI: −0.40, 0.11)
	Relapse	7/24	8/30	1.09 (95%CI: 0.46, 2.59)	0.03 (95%CI: −0.22, 0.27)
Cole *et al.*, 1992[9]	Serious infection	4/16	2/16	2.00 (95%CI: 0.42, 9.42)	0.13 (95%CI: −0.14, 0.39)
	Gastrointestinal bleeding	1/16	1/16	1.00 (95%CI: 0.07, 14.64)	0.00 (95%CI: −0.17, 0.17)
	Mortality	2/16	0/16	5.00 (95%CI: 0.26, 96.50)	0.13 (95%CI: −0.06, 0.31)
De Groot *et al.*, 2005[7]	Remission at 6 months	46/51	55/59	0.97 (95%CI: 0.86, 1.09)	−0.03 (95%CI: −0.13, 0.07)
	Mortality	2/51	2/49	0.96 (95%CI: 0.14, 6.56)	0.00 (95%CI: −0.08, 0.08)
	Remission	44/47	43/44	0.96 (95%CI: 0.88, 1.05)	−0.04 (95%CI: −0.12, 0.04)
	Relapse	32/46	20/43	1.50 (95%CI: 1.03, 2.17)	0.23 (95%CI: 0.03, 0.43)
	Leukopenia	3/51	14/49	0.21 (95%CI: 0.06, 0.67)	−0.23 (95%CI: −0.37, −0.08)
Glockner *et al.*, 1988[10]	Mortality	1/14	1/12	0.86 (95%CI: 0.06, 12.28)	−0.01 (95%CI: −0.22, 0.19)
	Severe complications	3/14	2/12	1.29 (95%CI: 0.26, 6.46)	0.05 (95%CI: −0.25, 0.35)
	Recompensation of renal function	10/14	9/12	0.95 (95%CI: 0.60, 1.52)	−0.04 (95%CI: −0.38, 0.30)
Guillevin *et al.*, 1997[5]	Sustained remission	11/23	12/17	0.68 (95%CI: 0.40, 1.15)	−0.23 (95%CI: −0.53, 0.07)
	Relapse	12/23	3/17	2.96 (95%CI: 0.99, 8.87)	0.35 (95%CI: 0.07, 0.62)
	Mortality	5/23	4/17	0.92 (95%CI: 0.29, 2.93)	−0.02 (95%CI: −0.28, 0.24)
Haubitz *et al.*, 1998[4]	Mortality	0/22	3/25	0.16 (95%CI: 0.01, 2.96)	−0.12 (95%CI: −0.26, 0.02)
	Complete remission	22/22	21/25	1.19 (95%CI: 1.00, 1.41)	0.16 (95%CI: 0.00, 0.32)
	Improved renal function	13/22	16/25	0.92 (95%CI: 0.59, 1.46)	−0.05 (95%CI: −0.33, 0.23)
	Leukopenia	4/22	15/25	0.30 (95%CI: 0.12, 0.78)	−0.42 (95%CI: −0.67, −0.17)
Jayne *et al.*, 2007[13]	Mortality at 1 yr	19/70	16/67	1.14 (95%CI: 0.64, 2.02)	0.03 (95%CI: −0.11, 0.18)
	Adverse events at 1 year	35/70	32/67	1.05 (95%CI: 0.74, 1.48)	0.02 (95%CI: −0.15, 0.19)
	Renal recovery at 3 months	48/70	33/67	1.39 (95%CI: 1.04, 1.86)	0.19 (95%CI: 0.03, 0.35)
Jayne *et al.*, 2000[38]	50% reduction in BVAS at 3 months	14/17	6/17	2.33 (95%CI: 1.18, 4.61)	0.47 (95%CI: 0.18, 0.76)
	Mortality at 3 months	0/17	2/17	0.20 (95%CI: 0.01, 3.88)	−0.12 (95%CI: −0.29, 0.06)
	Adverse effects	12/17	4/17	3.00 (95%CI: 1.21, 7.45)	0.47 (95%CI: 0.17, 0.77)
Metzler *et al.*, 2007[37]	Leucopenia	1/26	0/28	3.22 (95%CI: 0.14, 75.75)	0.04 (95%CI: −0.06, 0.14)
	Relapse	6/26	13/26	0.46 (95%CI: 0.21, 1.03)	−0.27 (95%CI: −0.52, −0.02)
	Severe side effects/ withdrawals	5/26	0/26	11.00 (95%CI: 0.64, 189.31)	0.19 (95%CI: 0.03, 0.35)
Pusey *et al.*, 1991[12]	Mortality at 1 year	3/25	6/23	0.46 (95%CI: 0.13, 1.63)	−0.14 (95%CI: −0.36, 0.08)
Stegeman *et al.*, 1996[23]	Remained in remission	34/41	24/40	1.38 (95%CI: 1.04, 1.84)	0.23 (95%CI: 0.04, 0.42)