

## Review

# Treatment of ANCA-associated systemic vasculitis

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### ABSTRACT

The treatment of systemic vasculitis has undergone important changes in recent years. Cyclophosphamide still plays a crucial role in the induction of remission in severe forms, reducing the mortality. However, its use entails a significant long-term toxicity and the accumulation of damage resulting from a sub-optimal control of the process. Strategies have been developed to limit exposure to the drug and minimize its toxicity, such as using intravenous pulses as an alternative to oral administration and a sequential strategy. Both induce remission in less severe cases and work also for the maintenance of remission; the use of alternative immunosuppressants, such as methotrexate, azathioprine or leflunomide has been advocated. In life-threatening situations, options such as plasmapheresis or intravenous immunoglobulins are available. Biologic therapies are a promising alternative, but their use must be limited for now to refractory cases.

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### Tratamiento de las vasculitis sistémicas asociadas a ANCA

#### RESUMEN

El tratamiento de las vasculitis sistémicas ha experimentado cambios sustanciales en los últimos años. La ciclofosfamida sigue teniendo un papel crucial en la inducción de remisión en formas severas, reduciendo considerablemente la mortalidad. Sin embargo, su empleo conlleva una importante toxicidad a largo plazo y el acúmulo de morbilidad derivada de un control subóptimo del proceso. Se han desarrollado estrategias para limitar la exposición al fármaco y minimizar su toxicidad, como son el uso de pulsos endovenosos como alternativa a la vía oral y la estrategia secuencial. Tanto para inducir remisión en casos no severos como para el mantenimiento de remisión se preconiza el empleo de inmunosupresores alternativos, como son el metotrexate, la azatioprina o la leflunomide. En determinadas situaciones con compromiso vital puede recurrirse a opciones como la plasmaféresis o las inmunoglobulinas endovenosas. Las terapias biológicas suponen una alternativa prometedora, si bien su empleo actual debe restringirse a los casos refractarios.

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### Introduction

Systemic necrotizing vasculitis are a heterogeneous group of processes that are defined by inflammation and necrosis of the vascular wall with or without inflammatory infiltrates in the surrounding tissues. Vasculitis associated to antineutrophil cytoplasmic antibodies (ANCA), (AAV) are quantitatively the most important subgroup, characterized by small vessel involvement and the presence of autoantibodies directed against cytoplasmic antigens in neutrophils (the so-called ANCA) with specificity against myeloperoxidase (MPO) or proteinase 3 (PR3).<sup>1</sup>

Although not common diseases, they are not to be regarded as exceptional.<sup>2</sup> Thus, in a well-defined area of northwestern Spain, the annual incidence was 2.95/10<sup>6</sup> for Wegener's granulomatosis (WG) and 7.91/10<sup>6</sup> for microscopic polyangiitis (MPA).<sup>3</sup> Despite the fact that mortality has improved substantially, even exceeding that of the general population,<sup>4</sup> it ranges from 0 to 27.4% in different randomized clinical trials conducted to date.

In this article, which is not intended as a systematic review, we focus primarily on AAV, the most common being systemic necrotizing vasculitis and because it is the group in which most recent clinical trials have been concentrated. While it is true that almost all of them have been performed in WG, it is also true that most therapeutic principles are applicable to all AAV, particularly in the setting of severe multisystem disease.

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## Classic treatment

Conventional treatment of these pathologies, consisting of the combined use of cyclophosphamide (CFM) and glucocorticoids (GC), has been in force for more than thirty years. This is a remarkably effective treatment introduced in the 70s by Wolfe and Fauci, leading to the transformation of these diseases, which before were uniformly chronic, recurrent and lethal processes.<sup>5</sup>

This treatment protocol, which we refer to here as the classical regime, consists of the administration of oral CFM (CFMo) at a dose of 2 mg/kg (which can be used in 3 to 5 mg/kg the first days in particularly severe cases), maintaining doses until one year after remission is achieved, then proceeding to the tapering the drugs (progressive reduction of dose) until their suspension about 6 months later (Figure 1). The initial response usually occurs after 2–4 weeks and remission in 2–3 months, although it may take up to six months. If the answer is deemed unsatisfactory, the dose of CFM can be increased in 25 mg increments up to 200 mg, the limiting factor being leukopenia (an event that should be avoided, rather than it being a goal). CFM is accompanied by GC (1 mg/kg prednisone or equivalent), which is maintained for a month (a window period of CFM), proceeding to tapering in about 6–12 months, using an early conversion to alternative days. With this therapy, remission is achieved in more than 80% of cases.

## Contribution of cyclophosphamide: reviewing the evidence

The real contribution of Wolfe and Fauci at the NIH (National Institutes of Health) was the use of chemotherapy for non-neoplastic diseases, initially in WG and then in the rest of the systemic vasculitis. In spite of being standard therapy, the level of evidence supporting the effectiveness of the CFM in these processes is limited and has been established by observational studies. The initial work of the NIH showed that if CFM was added, the mortality of patients with GW descended, compared with historical cohorts, 20% to 50%. These results are extended to MPA and other severe systemic vasculitides. Thus, in a study of MPA, the relative risk (RR) of death was 5 if only GC had been used.<sup>6</sup> This same group concluded, in another study, that the RR of resistance to treatment is lower (0.43 according to their data) when CFM is used in addition to GC.<sup>7</sup> Moreover, the use of CFM to induce remission reduces the likelihood of organ damage, so that the longer the patient uses CFM

in the first six months of treatment, the lower the probability of irreversible damage being caused.<sup>8</sup>

So we can conclude that the use of a highly toxic alkylating agent seems fully justified in a substantial proportion of patients with severe necrotizing systemic vasculitis, for which CFM is still the standard treatment, as currently recommended in the guidelines of the European League Against Rheumatism (EULAR).<sup>9</sup>

## Limitations of classical the approach

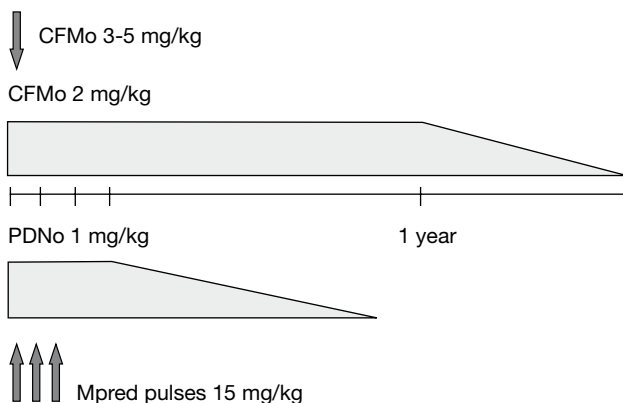
However, it soon became clear that the long-term joint use of CFM and GC entailed a significant accumulation of morbidity, arising both from the toxicity of drugs and the damage associated with suboptimal control of the disease. Despite treatment, the accumulated damage is frequent, occurs early and may affect up to between 66 and 89% of patients one year after diagnosis.<sup>10–12</sup> The toxicity associated with the classical treatment is clear if we analyze the results of two single center cohorts of GW, more or less contemporary and of similar severity, which have published their long-term follow-up. The cohort group of the NIH, paradigm of the classical therapeutic regime (at least one year of CFM after remission), with a proportion of CFM use of 92%, reports a proportion of morbidity attributable to treatment of 42%.<sup>13</sup> On the other hand, the group of Wolfgaang Gross, the German Vasculitis Center, has conducted a treatment protocol tailored to the level of activity and extension, switching to other immunosuppressive maintenance once remission with CFMo is obtained. In total, 89% of patients were treated with CFMo.<sup>14</sup> Both cohorts coincide in a high percentage of late occurring infections as well as tumors (Table 1). It is clear that patients treated with CFMo double their risk of neoplasia, the most feared late complication of this therapy. This is more evident in the particularly marked increase in the RR of bladder cancer (between 9 and 45) and lymphoma (11), with obvious dose-response relationships. In this sense, a cumulative dose of less than 35 g CFM seems safe.<sup>15–17</sup>

Hoffman wondered in an editorial in *Arthritis and Rheumatism*,<sup>18</sup> more than a decade ago, if it was time to change the standard treatment, and perhaps now is. And since then, different strategies to improve the classical protocol have been developed, improvements that have enabled us to optimize the control of activity while minimizing toxicity resulting from treatment. In parallel, we have conducted a considerable number of randomized clinical trials, many of them promoted by the EUVAS (European Vasculitis Study Group) that, as a cooperative multinational group, has launched a systematic plan of study designs aimed at meeting the great questions raised in the therapy of systemic vasculitis, several of them already successfully completed, others still in progress.<sup>19,20</sup> The improvements that have been imposed in recent years include optimizing the dosage of CFM, the adequacy of treatment of severity, the successful use of prophylaxis against adverse effects and the development of the sequential strategy. The critical discussion of these issues will occupy the bulk of this review.

**Table 1**  
Toxicity of oral cyclophosphamide\*

	Groos 2000	NIH 1992
Patients	155	158
Follow up	7 years	8 years
Myelodysplasia	8%	2%
Solid tumors	4.5%	2.8%
Severe infection	26%	46%
Mortality	14%	20%

NIH indicates National Institutes of Health.  
\*Comparing two long term follow up cohorts.



**Figure 1.** Classic treatment. After a year of induction with oral cyclophosphamide (CFMo) tapering takes place. Prednisone is administered for 4 weeks at a full dose and then tapered. In severe cases, the initial treatment is intensified: CFMo (3–5/mg/day) 2–5 days and three pulses of methylprednisolone (15 mg/kg). CFMo indicates oral cyclophosphamide; Mpred, methylprednisolone; PDNo, prednisone.

### Optimizing the dose of cyclophosphamide

#### Pulse CFM versus oral CFM

The use of pulse CFM (CFMp) basically aims to achieve an induction of remission accumulating less cytotoxicity, always in comparison to daily CFMo. An induction regimen with CFMp rarely exceeds 20 g and represents 50% of the dose usually needed when using CFMo with the same purpose. This means a total amount of CFM well below the cancer risk 'threshold' identified to date. But what is the evidence that supports this therapy? In the controlled studies that have compared the two methods there has not been any appreciated differences between CFMo and CFMp in the percentage of remission, although several of them found fewer recurrences with CFMo.<sup>21-24</sup> These studies, conducted over the past decade, suffer from important methodological limitations, either because of the heterogeneity of the vasculitides or due to the small number of patients included in each of them (Table 2). Despite the variability in the CFMp administration regimen and the insufficient sample size, De Groot et al attempted to perform a meta-analysis and concluded that CFMp is equal to or better than CFMo and is consistently less toxic.<sup>25</sup>

It is unclear if these results are transferable to severe vasculitis, as these have been excluded in several of the studies cited. In some centers, highly specialized in the management of these patients, CFMp has not obtained such favorable results, particularly in extended WG.<sup>26,27</sup> In an attempt to give a more definitive answer to this question, the EUVAS CYCLOPS study was undertaken. This test was designed with the purpose of comparing CFMo against CFMp as induction therapy in systemic vasculitis with involvement of a vital organ. It excluded, yes, the critically ill, that is, alveolar hemorrhage or creatinine >500 µm/l. The calculation of the sample size was

adequate, with 140 patients in total. In the preliminary results at one year (reported in abstract form at the last international AAV workshop) no differences in mean time to remission or in any side effects, although there was a strong trend towards lower mortality in the group treated with CFMp.<sup>28</sup> In any case, at least until the publication of more definitive results, we are before a still unanswered question.

There is little comparative data between CFMp and long term CFMo. The best comes from a study published recently by Guillevin, where they completed an average of six years of follow up a group of patients who had participated in a comparative study of CFMo against CFMp. Unlike the CYCLOPS preliminary data, it was found that the mode of administration of CFM had no influence on mortality, although it must be emphasized that the study size was small and there were changes to the oral route in case of unsatisfactory responses.<sup>29</sup>

As for the pattern to follow, there are essentially two protocols on which we have extensive information (Figure 2). The protocol most employed by the French multicenter group uses CFM adjusted to body surface area at a rate of 0.6 g/m<sup>2</sup>, with initial administration of three pulses every 15 days and then monthly. The scheme proposed in the guidelines of the British Society for Rheumatology suggested adjusting the dose to body weight at a rate of 15 mg/kg, then administering pulses every three weeks after the 3 biweekly doses.<sup>30</sup> To our knowledge, there are no studies comparing the two dosing regimens, and the guidelines seem quite similar to us.

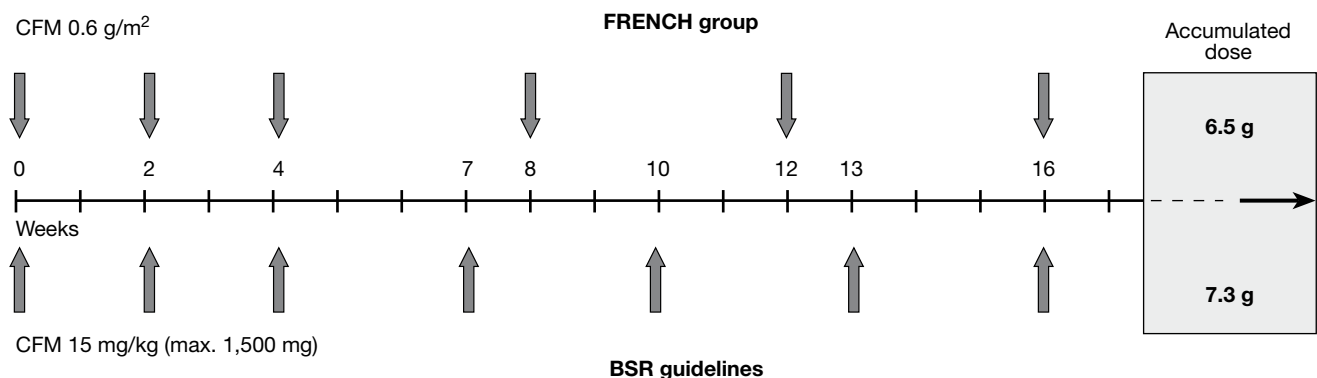
#### Adjusting for age and sex

For the correct dosage adjustment it is necessary to consider the age / renal failure relationship.<sup>30</sup> Contrary to popular belief, there is

**Table 2**  
Oral vs pulse cyclophosphamide: controlled studies

	n	Dose		Remission, %	Relapse, %	
		Pulse/oral	CFMp			Vasculitis
Hautbitz	22/25		0.75/m <sup>2</sup> /4 weeks	WG/MPA	100/84	40/28
Adu	24/30		15 mg/kg/3 weeks	WG/MPA/cPAN	83/86.6	29.6/26.6
Garayaud	12/13		0.6 g/m <sup>2</sup> /month	cPAN/Churg-Strauss	76/75	15/16
Guillevin	27/23		0.75/m <sup>2</sup> /3 weeks	WG	78.3/88.9	59.2/13

CFMo indicates oral cyclophosphamide; CFMp, pulse cyclophosphamide; cPAN, classic panarteritis nodosa; MPA, Microscopic polyangiitis; WG, Wegener's granulomatosis.



**Figure 2.** Cyclophosphamide administration protocols. Cumulative dose after induction (week 16), calculated in an example of a patient weighing 70 kg and 170 cm tall, results very similar. BSR indicates British Society for Rheumatology; CFM, cyclophosphamide.

**Table 3**  
Pulse cyclophosphamide: adjusting to age and renal function

Age	Creatinine 150-300 $\mu\text{mol/l}$	Creatinine 300-500 $\mu\text{mol/l}$
<60 years	15 mg/kg	12.5 mg/kg
>60 and <70 years	12.5 mg/kg	10 mg/kg
>70 years	10 mg/kg	7.5 mg/kg

more evidence for dose adjustment for age than for renal function (Table 3).

### Adapting treatment to severity

Another strategy aimed at saving CFM is to adapt treatment to severity, using alternative immunosuppressive drugs in less severe or localized disease.

It seems clear that the mortality of a systemic necrotizing vasculitis depends more on the extent and severity of the disease than on the type of vasculitis. Studies carried out by the French multicenter group prove it. Thus, for example, a prospective observational study with long-term follow-up (88 months on average), which included 278 patients with classical polyarteritis nodosa (CPAN), MPA and Churg-Strauss concludes that the level of activity and visceral affection score are the determinants of mortality.<sup>31</sup>

Reliably stratifying patients according to the severity and/or the extent of disease is obviously an unavoidable step needed to adapt treatment to the severity of the case. EUVAS once proposed a classification of severity,<sup>32</sup> which has been used in various clinical trials, although not uniformly (Table 4). On the other hand, the French working group has developed a validated instrument, the FFS (*five factor score*), a scale derived from the prospective study of a large number of cases which has been shown to predict mortality (Figure 3).<sup>33</sup>

The strategy of adapting treatment to the severity often proved successful, as seen in different retrospective studies. The experience of the Cleveland Vasculitis Clinic is particularly informative in this regard.<sup>34</sup> In a large recent study of this group, performed in 82 patients with WG, no differences in remission induction were seen when comparing CFMo to methotrexate (MTX), using the latter only in severe cases. Overall survival of the group was striking: 96.3% of patients were alive after 4 years of mean follow-up. The incidence of infection was lower than reported in the NIH cohort (0.076/patient-year compared to 0.11/patient-year).<sup>13</sup> However, the two cohorts are not comparable, as the study of Cleveland excluded patients with creatinine of >2 mg/dl after the induction of remission. The recurrence rate, 66% at two years was quite high in this study, although not substantially different from that seen in controlled trials which have used MTX for the maintenance of remission.

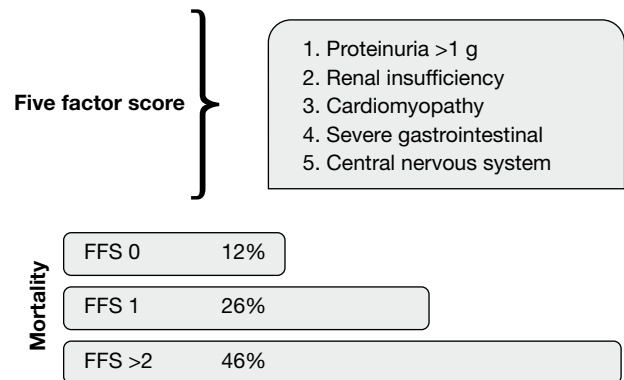
NORAM data, a controlled study sponsored by the EUVAS, also supports this strategy. In this trial CFMo was compared with MTX for the induction of remission in limited WG, showing no differences in efficacy. Interestingly, and probably because of limited follow-up (18 months), there were no differences in the incidence of infection, although a higher percentage of leukopenia in the group receiving CFMo was detected.<sup>35</sup>

A recent retrospective analysis of 595 patients conducted by the French multicenter group concluded that mortality during the first year of disease is greatest in patients treated only with GC only when the FFS is greater than or equal to 2.<sup>36</sup> Based on this and other previous studies by the same group, they propose to use the FFS to adapt treatment to severity, so that patients with FFS of 0

**Table 4**  
EULAR severity subclassification

Clinical subgroup	Constitutional symptoms	ANCA	Vital organ	Serum creatinine, $\mu\text{mol/l}$
Localized	No	+/-	No	<120
Systemic from onset	Yes	+/-	No	<120
Generalized	Yes	+	Yes	<500
Renal severe	Yes	+	Yes	>500
Resistant	Yes	+/-	Yes	Any

ANCA indicates anti-neutrophil cytoplasmic antibodies.



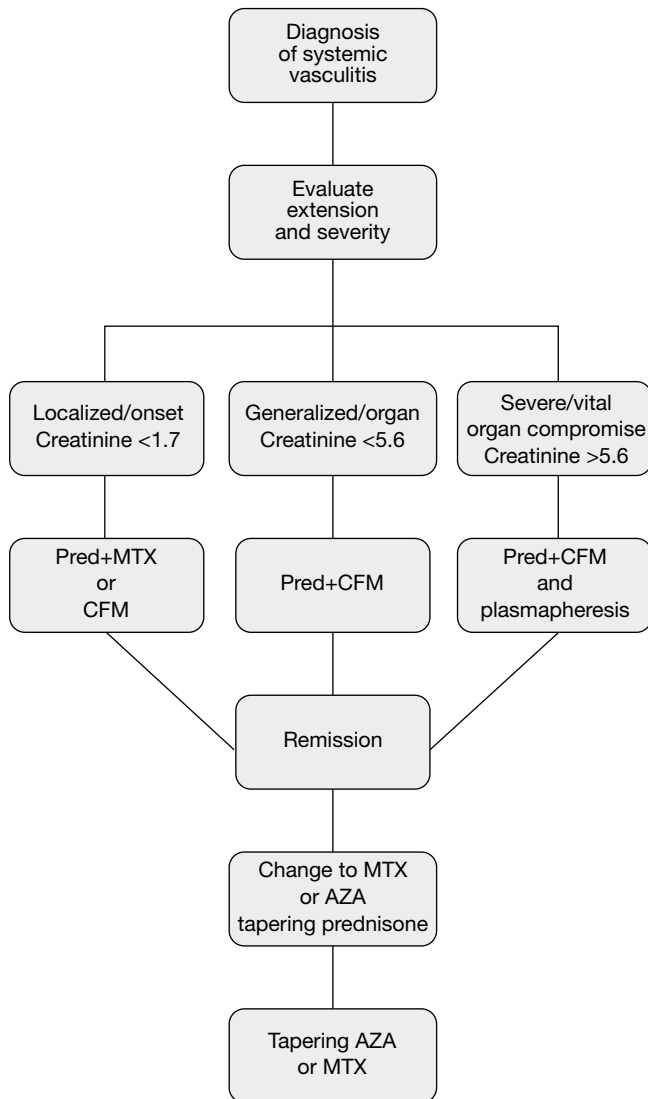
**Figure 3.** FFS (*five factor score*): 0 to 5 points. Mortality increases with each point.

could be treated only with GC, adding an immunosuppressant if a satisfactory response is not obtained.<sup>37</sup> The British Society of Rheumatology suggests a management algorithm also based on an adaptation strategy to the extent and severity of the process (Figure 4).<sup>38</sup>

### Alternatives to the CFM in severe cases

Mycophenolate mofetil (MMF) is the only alternative that has been compared directly with CFM for induction of remission in severe cases. It is a potent immunosuppressant that inhibits inosine monophosphate dehydrogenase, limiting the synthesis of guanosine nucleotides. Beyond its immunosuppressive nature, MMF shows various potentially beneficial effects on endothelial cells.<sup>38</sup> These features, along with the good results obtained in other systemic autoimmune diseases, position MMF as a promising alternative. In fact, MMF has already been successfully used in vasculitis patients resistant or intolerant to CFM.<sup>39,40</sup> In a recent controlled, unblinded trial, Hu et al found MMF superior to CFM in the induction of remission in a small group of patients with AAV, all with renal impairment (creatinine <500  $\mu\text{mol/l}$ ). What was surprising in this study was the small number of patients who achieved complete remission with CFM (47.1 compared to 77.8% with MMF), a figure lower than commonly described in the medical literature.<sup>41</sup>

It is obvious that appropriate tests are needed and with a longer-term design to define the role of MMF induction of remission in the AAV.



**Figure 4.** Treatment algorithm for systemic vasculitis proposed by the British Rheumatology Society (Lapraik et al, Rheumatology 2007). Creatinine in mg/dl. AZA indicates azathioprina; CFM, cyclophosphamide; MTX, methotrexate; Pred, prednisone.

### Options for severe disease that compromises the life of the patient

In addition to the measures outlined above, including the use of megadoses of pulse GC, there are two therapeutic resources that can help achieve a more rapid and complete control of the disease in particularly serious situations: plasmapheresis (PF) and the infusion of high-dose intravenous immunoglobulin (IVIG). So far, none of the two methods has been shown to favorably modify survival, but there is some evidence that supports its use.

#### Plasmapheresis

The controversy about the possible role of PF in systemic vasculitis has dragged on for over 20 years. Pathogenically, PF appears to be a tempting therapeutic procedure for AAV. Through

PF we not only withdraw ANCA and proinflammatory cytokines such as TNF- $\alpha$  and IL-6, capable of priming the neutrophils making them susceptible to activation by ANCA from circulation, but also complement proteins and proteases that are harmful to the vascular endothelium.<sup>42</sup>

In a meta-analysis by Guillevin, performed on two randomized studies it was concluded that PF did not contribute at all to conventional immunosuppressive therapy in the presence of glomerulonephritis.<sup>43</sup> However, two decades before, Pusey et al suggested, in a small controlled study, that PF was effective only in a situation of dialysis.<sup>44</sup> These results have recently been confirmed by a controlled multicenter study, carried out by EUVAS: the MEPEX study. This study compared the use of pulse methylprednisolone (PMP) with PF, performed early (within two weeks after the start of dialysis). In the analysis conducted after one year of follow-up, PF was superior than PPM in terms of dialysis free survival, although there was no difference in mortality. Nor were there any differences in adverse effects. Perhaps the limited follow up time partly explains these results. In any case, the primary endpoint was the independence of dialysis at 3 months.<sup>45</sup> A post hoc analysis shows that even with histopathologically ominous signs, such as extensive glomerular lesions and tubular atrophy, the probability of renal recovery exceeds the risk of death when the patient receives adjuvant PF.<sup>46</sup> Regarding capillaritis with alveolar hemorrhage, no controlled trial has been performed, but the observational study by Klemmer et al deserves comment.<sup>47</sup> In this study, survival of all of the 20 patients treated with PF (several of them with acute severe disease, requiring mechanical ventilation) is striking, given the high mortality of this process, usually above 50%. We believe these results reaffirm, until better evidence is available, the use of PF in the management of rapidly progressive glomerulonephritis and pulmonary capillaritis with an origin in a AAV. The same conclusion is drawn from the recent systematic review of evidence from the Cochrane Collaboration.<sup>48</sup>

#### Immunoglobulins

IVIG has been shown to be effective as adjuvant therapy in small series of patients with severe vasculitis and also in a controlled study.<sup>49-52</sup> In the latter, IVIG were added to conventional immunosuppressive therapy.<sup>52</sup> In spite of the small number of patients included, the study had sufficient power to detect differences with placebo. The beneficial effects were of limited duration (three months on average) and some patients experienced a transient deterioration of renal function. Moreover, the use of IVIG is a treatment with a good safety profile,<sup>53</sup> which may benefit patients with severe vasculitis, particularly in a situation of rapidly progressive glomerulonephritis.<sup>50,51</sup> And it can also be a convenient option if superimposed infection is suspected. Its mechanism of action is not well understood. Possibly the restoration of the anti-idiotypic network against ANCA is the most important but not the only one. It also seems to be relevant in the modulation of the B cell repertoire and the downregulation of proinflammatory cytokines, among other mechanisms.<sup>54</sup>

#### Reducing risks associated with high-intensity immunosuppression

Given the undeniable toxicity of conventional treatment of systemic vasculitis, we propose the use of preventive measures that help minimize it. Although the available evidence is limited (Table 5) and some of these measures have been extrapolated from nonsuperimposable situations of immunosuppression, their use has become more widespread and is recommended by most experts.<sup>9</sup>

**Table 5**  
High intensity immunosuppression: prophylactic measures

Problem	Measure	LE
Hemorrhagic cystitis	Mesna and hidration	C
Infertility	LH-RH analogues (leuprorelin)	A Ib (C?)
Cancer	Screening (bladder, cervix, etc.), photoprotection, tobacco	C
Osteoporosis	Biphosphonates, vitamin D, teriparatide	A
<i>Pneumocystis jiroveci</i>	Prophylaxis cotrimoxazole/pentamidine	B
Pneumonia	Antipneumococcal vaccine and cotrimoxazole	C
Tuberculosis	Chemoprophylaxis if there is latent tuberculosis	C

LE indicates level of evidence; LH-RH, lutenizing hormone releasing hormone.

Cotrimoxazole (CTX) adds to its ability to prevent *Pneumocystis jiroveci* infection the fact that it can reduce the incidence of pneumonia, according to studies in HIV-infected patients. There is retrospective data suggesting its efficacy for *P. jiroveci* prophylaxis in systemic vasculitis, such as that provided by observational studies published by the Vasculitis Center at the Cleveland Clinic. The incidence of pneumonia by *P. jiroveci* disappeared in the current cohort of the center after the introduction of CTX (11 cases in 180 patients in 1992, 0 cases of 82 patients in 2007).<sup>34</sup> Furthermore, in contrast to pentamidine, it is a therapy with a good cost/effectiveness ratio in this context, increasing the life expectancy of patients undergoing immunosuppressive therapy for WG.<sup>55</sup> Its use is advisable in case of global lymphopenia under 400 cells/ $\mu$ l. Although the recommended dose for the prevention of infection is low, this does not rule out an immunomodulatory effect on the underlying disease.

Polyvalent pneumococcal vaccination is indicated in all patients who will be subjected to immunosuppression, reducing the risk of bacteremia and death associated with infection by *Streptococcus pneumoniae*.<sup>56</sup>

For chemoprophylaxis of *Mycobacterium tuberculosis* infection, the measures applicable to all patients who are predicted to receive high doses of corticosteroids GC apply.<sup>57</sup>

### Maintenance therapy

The main current challenge for management of AAV is not so much the induction of remission as maintenance, while minimizing treatment toxicity. Up to 50% of vasculitis (60%-80% in the case of WG) recur and often do so when immunosuppressive therapy is reduced or withdrawn. This scenario does not seem to have changed substantially over the past decade. Although few studies have addressed the consequences of repeated outbreaks, available information suggests that the recurrences involve accumulation of damage, which can be severe. Thus, in a recent large study group by the Chapel Hill group, renal recurrences had an RR for ESRD of 4.7.<sup>7</sup>

### Strategies for maintaining remission

In recent years, mimicking the oncological strategies, treatment is advocated in two phases: the first phase of remission induction and, given the recurrent nature of the AAV, a second maintenance phase. The maintenance concept should encompass not only the avoidance of outbreaks of disease and minimize the accumulation of damage, but also implement measures to control concurrent processes, such as atherosclerosis and the risk of deep vein thrombosis, progression to end stage renal disease, etc. As has happened in other

chronic inflammatory diseases mediated by immune mechanisms, accumulating data suggests an increased cardiovascular risk for patients with systemic vasculitis.<sup>58</sup> Also, at least in regard to the WG, there also appears to be an increase of risk for venous thrombosis.<sup>59</sup> So, until more studies are available, it seems reasonable to propose aggressive management of traditional cardiovascular risk factors in these patients. Moreover, it has been recently suggested that statins may have a favorable effect on the activity of vasculitis.<sup>60</sup>

### Defining disease status

Adequate discrimination between an outbreak of disease and the presence of irreversible damage, a key aspect in the long-term management of these processes is not always easy. Sometimes the clinician has to resort to a biopsy to rule out the presence of active vasculitis in the affected tissue, as biomarkers of inflammation or activity are not as reliable as they should be in this sense. The definitions recommended by EULAR for use in clinical trials can be useful in guiding the clinician (Table 6).<sup>61</sup>

### Evidence supporting the sequential strategy

The only study to date that supports the sequential strategy is CYCAZAREM.<sup>62</sup> This study was sponsored by EUVAS for the purpose of comparing the classical treatment: induction and maintenance with CFMo, and then: induction with CFMo and maintenance with azathioprine (AZA). An adequate number of patients with severe AAV were included, with a clear predominance of MPA. It was able to show that sequential therapy was equivalent in efficacy to monotherapy with CFMo. Both the cumulative damage index and mortality were similar at 18 months. The recurrence rate was also similar, extremely low, however, in both groups (15.5 in the AZA group compared to 13.7% for CFM). We do not know whether these results could be replicated with the use of CFMp instead of CFMo to induce remission. On the other hand, the study has a long enough follow-up to conclude whether or not there are differences in both cumulative damage and in cancer incidence between the two treatment modalities. In any case, the impact that this study had on daily clinical practice seems to have been high, leading to widespread use of the sequential strategy since its publication.

The retrospective study of the Cleveland Vasculitis Clinic, as cited previously, permits modulation of this strategy.<sup>34</sup> In this study, which

**Table 6**  
EULAR definitions of disease status

Status	Definition
Remission	Absence of activity that merits maintaining treatment IS
Response	50% of reduction in an activity score and absence of new manifestations
Relapse	Recurrence or debut of a manifestation attributable to active disease
• Major	With vital or organ compromise
• Minor	Without vital or organ compromise
Resistance	Stable or increasing activity in spite of 4 weeks of standard treatment
• Lack of response	<50% of reduction of an activity score after 6 weeks of therapy
• Persistent disease	Presence of $\geq$ one major item or 3 minor ones (BVAS or BVAS/WG) after 12 weeks of treatment
Low activity	Persistence of minor symptoms that improve with discrete increases in GC

BVAS, Birmingham Vasculitis Activity Score; BVAS/WG, Birmingham Vasculitis Activity Score for Wegener Granulomatosis; GC, glucocorticoids; IS, immunosuppressant.

outbreaks lymphopenia during the study. This finding is interesting because, if confirmed in prospective studies, maintenance of lymphopenia below 500 cel/μl could become a therapeutic target. In short, it appears that monotherapy with MTX may be sufficient in cases of localized WG.

### Choice of immunosuppressant

If we are inclined to use a sequential therapy, we must overcome a new hurdle: choosing the most appropriate immunosuppressant in order to maintain remission. Ideally, the choice should be individualized. We have comparative data from controlled studies (Table 7) which, although not definitive, can facilitate the task. We have already commented on the efficacy of AZA as an alternative to CFM<sub>o</sub> in maintaining remission in patients with severe vasculitis, as seen in the CYCAZAREM trial. CTX received attention for a time in the medical literature, but due to the high recurrence rates of up to 100% on a comparative study with MTX, this agent has been relegated to marginal use. MTX is a good alternative, although, except in the case of CTX,<sup>63</sup> its use has been associated with a higher recurrence rate than for all other drugs to which it has been compared. In a recent study, Metzler et al faced leflunomide (LFN) with MTX and conclude that LFN is superior as a maintainer of remission, with no renal relapses to its credit.<sup>64</sup> The study is not without its weaknesses, such as the high percentage of withdrawals due to adverse effects LFN and the fact that the strategy implemented with MTX was too conservative, both in the dose escalation as the route used, which was oral. An ongoing study, IMPROVE, proposes to compare MFM with AZA but, to our knowledge, has not yet released any results.

Unfortunately, there are no long-term controlled trials, a cardinal aspect to consider when planning maintenance therapy. Retrospective studies suggest a higher rate of relapse with AZA vs CFM after years of follow up, especially in patients with positive ANCA PR3, but also point to a greater mortality with CFM.<sup>65,66</sup> These studies do not provide conclusive data because, in addition to bias common in retrospective studies, the treatments under comparison were performed at different historical moments.

As expected, long-term monitoring studies with MTX have shown high rates of relapse and recurrence, often renal.<sup>67,68</sup> In the prospective study of the German group of Lübeck, which used intravenous MTX

after induction with CFM, one third of patients had relapsed after a mean of 25 months. Of the 26 outbreaks recorded, 15 were renal.<sup>68</sup> In this study, the level of remission as measured by DEI Score (an extent of disease index specific to WG) was a powerful risk factor for recurrence.

The WEGENT study results have been recently published. This trial directly compared AZA and MTX in the maintenance of remission after induction with CFMp. At 29 months, there was no difference in survival between the two arms. Although not statistically significant, there was a strong trend towards more adverse effects in the group treated with MTX.<sup>69</sup> This fact could be explained by the high percentage of patients with renal failure, a known risk factor for toxicity associated with use of MTX.

### Role of GC in the maintenance of remission

Part of the variability in results between different clinical trials of maintenance therapy can be attributed to the heterogeneity in the use of GC. Walsh et al performed a metaanalysis of all studies where the pattern of GC was sufficiently specified, and concluded that its continued use appears to be associated with lower risk of recurrence.<sup>70</sup> While there is no clinical trial designed with this purpose in AAV, it is also true that the long-term use of low-dose GC, common in many inflammatory rheumatic diseases, has an acceptable safety profile and until better evidence, represents a reasonable move. It remains to be established whether the prevention of cumulative damage that results from repeated outbreaks compensates for the deleterious effects of continued use of GC.

### Duration of treatment

Once the immunosuppressant is selected, the duration of treatment must be set. Once again we encounter uncertainty, highlighting the lack of a uniform and standardized definition of relapse. Recurrences, whatever definition is used, are more frequent in the first two years, particularly in the six months after the initial withdrawal of immunosuppressive treatment, so early suspension does not seem advisable.

In vasculitis with involvement of vital organs, we know that maintaining 10 months of treatment is better than four months, at least using CFMp. We know this from two multicenter controlled

**Table 7**

Maintenance therapy: controlled studies controlados

	Study	Year	Dose	Relapses, %	Toxicity	Suggested by
AZA	CYCAZAREM	2003	2 mg/kg	AZA vs CFM 13.7 vs 15.5 18 m	≈	Severe disease
CTX	De Groot et al	1996	800/160 mg/12 h	CTX vs MTX 100 vs 9 14 m	20% suspended with CTX	Localized?
MTX	NORAM	2005	20-25 mg	MTX vs CFM  69 vs 45 18 m	≈	Disease not severe, without IR
MFM	IMPROVE	2007	2 g	MFM vs AZA	?	?
LFN	Metzler et al	2007	30 mg	LFN vs MTX 23 vs 46 21 m	>% suspended LFN	IR?

AZA, azathioprine; CFM, cyclophosphamide; CTX, cotrimoxazole; IR, renal failure; LFN, leflunomide; m, months; MFM, mycophenolate mofetil; MTX, methotrexate.

studies done by the French group: one conducted in the cPAN and MPA, and one in Churg-Strauss. In the first, the recurrence rate was 66% with 6 monthly pulses compared to 22% when a total of 12 pulses were used (after induction with weekly pulses). Moreover, the difference in bouts of disease increased with time, at least until 36 months of follow-up after discontinuing immunosuppressive therapy. There were no differences in survival nor in incidence of tumors, which was low. At 3 years, the percentage of survivors without bouts of disease was higher than 70%, a figure which suggests that it is enough to maintain 10 months of CFMp.<sup>71</sup> In the study done with Churg-Strauss patients, similar in design, the results were very similar: the rate of disease-free survival was clearly favorable to the arm which received 12 pulses. Here again there were no differences in serious adverse effects.<sup>72</sup> A retrospective 18-24 month study strengthens these results, finding a low recurrence rate (21%) using long term CFMp. CFM was well tolerated, with a cumulative rate of infection of 18.9%.<sup>73</sup>

But is one year of treatment enough? If we compare, as proposed by Hoffman in a recent editorial,<sup>74</sup> the NORAM trials conclusions and those of CYCAZAREM, both already mentioned, it is clear that stopping treatment after 12 months in NORAM led to a significant increase in the number of relapses which were not seen in CYCAZAREM, where treatment was continued until the end of the study. However, it is worth considering that NORAM patients were less severe, with a predominance of limited forms of WG, which tend to have more recurrence.

In order to provide evidence on this issue, EUVAS has launched the REMAIN study, comparing two periods of remission after treatment with CFM: immunosuppression with AZA and low dose prednisone for two years versus four years.

### Maintenance therapy for all patients?

It is known that a considerable subset of patients achieved long periods of remission after a single course of induction with CFM and GC, reaching one third of the cases according to data from the NIH cohort.<sup>75</sup> The problem is that we have no reliable tool to identify them in advance. Although a number of factors associated with recurrence have been described,<sup>76,76</sup> in the absence of a weighted index that integrates them, it is often difficult and inaccurate to classify patients in this way. In any case, the factors endorsed in the medical literature are presented in Table 8. The reduction or withdrawal of immunosuppressive therapy is without a doubt the most robust.

When making decisions, one should consider that there is little evidence to support an adaptation of the duration of treatment to the risk of recurrence. Supporters of a long-term maintenance treatment for all patients, which is the position that appears to enjoy greater success among experts, claim that the number of bouts of disease after stopping is high, that recurrences are unpredictable and independent of the severity and current maintenance therapies are not as toxic. In other words, that the toxicity risks are compensated by avoiding outbreaks, thereby reducing damage accumulation.

### Monitoring

EULAR recommends a structured clinical assessment using validated instruments, both to establish the extent as well as the degree of activity, although the level of evidence of this approach does not pass evidence level C 9. Prospective studies are needed to help define the more cost-effective monitoring strategies.

The BVAS (Birmingham Vasculitis Activity Score), with its version for WG, is a multiitem tool that measures activity and has been widely validated and used,<sup>77</sup> but not designed for its application in the individual patient.

**Table 8**  
Relapse risk factors

Reduction or suspension of immunosuppressive therapy
Early suspension of steroids
Use of low dose CFM in induction
Respiratory tract affection
Prior couts
URT infection ( <i>Staphylococcus aureus</i> )
ANCA positive at the momento of IS switch
Wegener or anti-PR3 positive persistent
• Especially localized forms?

ANCA, anti neutrophil cytoplasm antibodies; CFM, cyclophosphamide; IS, immunosuppressant; PR3, proteinase 3; URT, upper respiratory tract.

The particularly detailed guidelines of the British Society of Rheumatology, include a consensus of European authorities in this field. Close monitoring of the CBC is a standout point, because they suggests doing it weekly during the first month and biweekly for the next two months.<sup>30</sup>

Regarding the utility of ANCA, we know that their positivity, both at the onset as well as at the time of remission, increases the risk of recurrence exponentially with increments of 4 or more times, in MPO or PR3, over the baseline. However, ANCA showed a weak association with activity. Only half of the elevation of ANCA end in relapse and relapses are preceded by elevation of ANCA in about the same proportion.<sup>78,79</sup> A systematic review of the evidence, which includes 22 studies, concluded that the data is sufficiently heterogeneous as to prevent the conduction of a meta-analysis, and cannot confirm that the serial measurement of ANCA is useful in order to monitor activity.<sup>80</sup> For all these reasons, it does not seem sensible to make treatment decisions based solely on the level of MPO or PR3 in the individual patient. This does not mean that close clinical monitoring of all patients who present a significant rise in ANCA is not merited.

### Refractory vasculitis: biological therapies and other options

Around 15%-20% of patients with AAV are refractory to conventional treatment with GC and CFM, but figures vary according to the criteria used to define refractoriness, and the greater or lesser amount of seriously ill patients in a given cohort.<sup>81</sup> Before labeling a patient as refractory, certainly an unusual situation in everyday clinical practice, one must ensure that this really is the case and not a delayed response, infection, toxicity due to therapy or simply irreversible damage without activity. It is also imperative to ascertain whether the conventional treatment has been carried out or not optimized. If CFMp have been tested and remission has not achieved, this may be achieved with the oral route, as recommended by Guillevin,<sup>82</sup> a strategy for which there is some evidence that was classified as level B 30. There are other options, all of them requiring permission today in our country, which could be beneficial, including biological therapies.

### Biological therapies

Increased awareness of the immunopathogenic mechanisms operating in AAV is facilitating the rapid development of alternative therapies aimed at more specific targets: the so-called biological therapies.<sup>83</sup>

#### Rituximab

B cells are one of the potential targets in various inflammatory diseases mediated by autoantibodies, including AAV because, as well as producing ANCA and cytokines, these cells interact with



T cells and can act as efficient antigen-presenting cells. Ablative therapy with rituximab (RTX), the more widely available anti-CD20, have shown encouraging results in small series of patients with refractory or recurrent AAV, with percentages of responders over 90%.<sup>84,85</sup> Although recurrences are common, retreatment is usually successful.<sup>86</sup> Almost invariably, RTX has been used along with conventional immunosuppressive drugs and their effectiveness appears to be independent of the ANCA status. However, the limited information available shows that the efficiency is not uniform, being more predictable in the presence of widespread vasculitis than in localized forms, where many failures have been reported. One possible explanation for its variable efficacy in limited WG, forms usually more “granulomatous”, is the formation of pseudo-lymphoid organ formation within the granuloma, where B cells, housed in protected niches, could escape the effects of anti-CD20. However, small case series reported a late response in this subgroup of patients, in other words, the time criterion to define failure of RTX has not been established and probably differs depending on the type of manifestation.<sup>87,88</sup>

Randomized trials are needed to clarify both the potential effectiveness of ablative therapy with this monoclonal antibody and its place in the treatment sequence, as well as the ideal drug with which it should be combined. We hope the RAVE (Rituximab for ANCA-Associated Vasculitis) study, still ongoing, can provide some answers.

#### *Anti-TNF therapy*

The information available does not seem to justify usual treatment with anti-TNF therapy for patients with refractory AAV. Despite the results of *in vitro* studies showing the *in situ* production of TNF in ANCA-associated glomerulonephritis and the benefit of TNF blockade in several experimental models, clinical use does not appear to have fulfilled the expectations. Some pilot studies have suggested the possible efficacy of infliximab (IFX), including long-term follow-up.<sup>89-91</sup> On the other hand, a French multicenter study, which has not been published in full, has directly compared RTX and IFX in a small number of patients, without appreciating differences between biological therapies.<sup>92</sup> However, studies with negative results and adverse effects of consideration have also published. In the largest cohort to date,<sup>93</sup> which included 32 cases of AAV treated with IFX, 21% of the patients suffered a severe infection that required hospitalization, percentages that are high and that would be attributable in part to the concomitant use of conventional immunosuppressants.

Worse luck seems to have suffered by the most widely used anti-TNF soluble receptor, etanercept (ETZ). In the WEGET study, a controlled study in which ETZ was added to conventional immunosuppressive therapy, it failed to surpass placebo with regard to the rate of recurrence. In addition there was a higher number of tumors in the group receiving ETZ, associated with the concomitant use of CFM.<sup>94</sup> With these data in mind and given the failure of ETZ in other granulomatous processes, such as Crohn's disease, we conclude that it might not be the most suitable TNF blocker, at least in the WG. It should be noted, however, that randomization of the WEGET study was not optimal as there were significant differences in terms of visceral involvement, unfavorable for the group treated with ETZ. To further complicate things, there are cases of AAV in connection with the use of anti-TNF in patients with rheumatoid arthritis, although the pathogenic mechanism is probably different.<sup>95</sup>

#### **Rescued therapy**

In cases of truly refractory vasculitis or with sufficient persistent activity, especially if it compromises vital organs, there are some

options of an experimental character, whose potential benefit is based on anecdotal cases or small series of patients. The use of experimental biologic therapies, costly and potentially toxic, should assume that the clinician has some experience with the drug to be used and, of course, expertise in the assessment of response in this complex group of disorders. Otherwise, it would not hurt to consider the patient's transfer to a referral center. In addition, at least ideally, it should also raise participation in protocols or multicenter registries, due to the rareness of these diseases, resulting in difficulty to the gathering of experience regarding the use of new therapies. In this section we discuss therapies with potential effectiveness but that have less documented experience in autoimmune inflammatory diseases.

They include the Alemtuzumab (previously known as Campath-1H), an Ig k-1 anti-CD52 humanized monoclonal antibody, which can cause a marked lymphocytic depletion, used as third-line therapy in chronic lymphocytic leukemia. It has considerable hematological toxicity but has been associated with very favorable results in a monocentric series of 71 patients with severe vasculitis refractory to CFM. Remission was achieved in no less than 85% of cases, but recurrences were common.<sup>96</sup>

Something similar happened with antithymocyte globulin, an official but rudimentary “biological”, which also acts as ablative therapy, in this case the target being activated T cells. In a small open study it achieved a high percentage of remissions in refractory WG. Again, toxicity appears here as a limiting factor to consider.<sup>97</sup>

Gusperimos or deoxypergualine is an immunosuppressant derivative of spargualine that has antiproliferative effects predominantly on naive CD4 + T cells. The mechanism of action is not yet known in detail, but available data suggests that it works by blocking the nuclear factor kB transcription. Dramatic responses after failing standard therapy have been reported.<sup>98</sup> A European multicenter study also recently completed has shown a response rate above 90% in patients refractory to CFM or MTX. Adverse effects were common but rarely led to drug discontinuation.<sup>99</sup> Based on these data, the European Union has allocated orphan drug status to gusperimos for the treatment of WG.

#### *Autologous bone marrow transplantation*

As has happened with other autoimmune diseases, bone marrow transplantation (BMT) has been tried in individual patients, with varying results.<sup>100</sup> The mixed cooperative group European League Against Rheumatism and the European Group for Blood and Marrow Transplantation (EULAR / EBMT) have recently reviewed the experience with this procedure in a heterogeneous group of systemic vasculitis, concluding that the BMT is a feasible treatment, with manageable mortality, for AAV, considering relevant the performance of controlled trials.<sup>101</sup>

#### **EULAR Guidelines**

In a serious and barely prevalent disease, that often requires aggressive immunosuppression, guidelines written by groups of experts are particularly welcome. Recently, EULAR has promoted the development of two important documents in this area. The first of these, recommendations for the management of primary of small and medium-caliber vessel vasculitis, was developed by a multidisciplinary group of European and American experts, using a modified Delphi method in accordance with the EULAR standard operating procedures, conducting a systematic review of the literature 9. They issued a set of 15 recommendations, classifying the evidence for each of them, as well as the experts' “vote”; recommendations are shown in Table 9. The second EULAR document, guidelines for clinical trials in vasculitis, was made following a similar methodology, including a review of evaluation systems and biomarkers, as well as

recommendations for defining the status of activity, which can also be very useful for daily clinical practice.<sup>61</sup>

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**Table 9**

EULAR recommendations for the management of small vessel systemic vasculitis

Recommendation	LE	Vote
1. Management in collaboration with expert centers	3	D
2. ANCA tested in an adequate clinical context	1A	A
3. Pathological basis for diagnosis	3	C
4. Structured clinical evaluation	3	C
5. Classification according to severity	2B	B
6. CFM+GC to induce remission in generalized vasculitis	1A/1B	A
7. MTX+GC in forms without vital organ compromise	1B	B
8. High dose GC to induce remission	3	C
9. Plasmapheresis if GN is rapidly progressive	1B	B
10. Maintain remission with low dose GC and AZA, MTX or LFN	1B/2B	A/B
11. Alternative immunomodulation if failure to achieve remission or relapse at maximum dose of standard therapy	3	C
12. Immunosuppression in essential cryoglobulinemic vasculitis	4	D
13. Antivirals for cryoglobulinemic vasculitis associated to hepatitis C	1B	B
14. Antivirals+plasmapheresis+GC in hepatitis B associated vasculitis	3	C
15. Investigate unexplained persistent hematuria in all patients receiving CFM	2B	C

ANCA indicates anti neutrophil cytoplasm antibodies; AZA, azathioprina; CFM, cyclophosphamide; GC, glucocorticoids; GN, glomerulonephritis; LFN, leflunomide; LE, level of evidence; MTX, methotrexate.

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