Treatment of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis
A Systematic Review

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Systemic vasculitis with positivity for antineutrophil cytoplasmic antibodies (ANCA) constitutes a subgroup of disorders affecting small- to medium-sized vessels and includes Wegener granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome. The incidences of these life-threatening conditions vary from 2.4 cases per million for Churg-Strauss syndrome to 3.6 for microscopic polyangiitis to 10 cases for Wegener granulomatosis.

Among other manifestations, pauci-immune necrotizing and crescentic glomerulonephritis and pulmonary capillaritis are common features of Wegener granulomatosis and microscopic polyangiitis; however, patients with Wegener granulomatosis and Churg-Strauss syndrome exhibit granulomatous inflammation of the respiratory tract, which is rich in eosinophils in the latter syndrome. Furthermore, patients with Churg-Strauss syndrome present with asthma and peripheral eosinophilia and the heart may be involved, mostly as rapid-onset heart failure. However, vasculitic damage is usually less severe than in microvascular.

Context Immunosuppressive therapies for antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis have greatly advanced patient survival but have turned ANCA-associated vasculitis (AAV) into chronic, relapsing disorders. Long-term treatment and disease-related morbidity are major threats. The last decade has seen a collaborative international effort to determine effective treatment.

Objective To analyze the reported evidence on AAV therapy in order to provide physicians with a rational approach for dealing with various clinical scenarios.

Data Sources We searched English-language articles on the medical treatment of AAV published between 1966 and March 2007 using MEDLINE. Articles from the reference lists of the most relevant articles retrieved were also analyzed.

Study Selection Studies of current available drug treatments or medical interventions for patients with AAV were included. Duplicate publications, case reports, and uncontrolled trials and series including fewer than 10 patients were excluded.

Data Synthesis We included 2 meta-analyses, 20 randomized controlled prospective trials, and 62 uncontrolled trials with more than 10 patients or observational studies. Outcome measures and treatment protocols were heterogeneous across trials. Cotrimoxazole can be used alone or in combination with corticosteroids to induce and maintain remission in cases of isolated upper respiratory tract involvement. To induce remission, methotrexate plus corticosteroids can be used instead of cyclophosphamide for patients with generalized, non–organ-threatening disease. When methotrexate is used as maintenance therapy, the likelihood of relapse is high and rigorous monitoring is mandatory. Pulse cyclophosphamide can be used to induce remission in patients with generalized organ-threatening disease. The combination of azathioprine and daily prednisone is effective in maintaining remission. Plasma exchange is at present the best complement to immunosuppressants in advanced renal disease. In Churg-Strauss syndrome, treatment can be started with high doses of corticosteroids, tapering them when the clinical situation improves. In patients with a high risk of death, cyclophosphamide should be introduced.

Conclusions Although AAV therapies should be tailored to the patient’s specific clinical situation, evidence for treatment of several disease states is lacking. There is a need for safer and more effective drugs.
scopic polyangiitis and Wegener granulomatosis.\textsuperscript{1,2} Compelling evidence on the pathogenic role of ANCA in vasculitis comes from in vitro and murine studies. However, the influence of ANCA in granulomatous lesions seems negligible (FIGURE 1 and FIGURE 2).

Over the last 10 years, collaborative international research efforts have sought to determine the most effective AAV therapy, including several randomized controlled trials and numerous ongoing trials, some probing exciting alternatives to nonideal immunosuppressants.\textsuperscript{4} It is accepted that studies should be designed according to different disease states to obtain therapies tailored to patients’ needs.\textsuperscript{4} This activity is boosted by continuing discoveries in AAV pathogenesis. The objective of this article is to analyze the reported evidence on AAV therapy to provide physicians with a rational clinical approach for different scenarios.

**EVIDENCE ACQUISITION**

We systematically searched MEDLINE for English-language articles published between 1966 and March 2007 for studies in humans using the terms (singly and in combination) ANCA-associated vasculitis, microscopic polyarteritis, microscopic polyangiitis, necrotizing glomerulonephritis, and necrotising glomerulonephritis and the Medical Subject Heading terms Wegener Granulomatosis, Churg-Strauss Syndrome and Antibodies, Antineutrophil Cytoplasmic. We also manually searched the reference list of relevant articles retrieved (mostly review articles; FIGURE 3) and identified 4174 references.

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**Figure 1.** Model of Pathogenesis of Granulomatous Inflammation in Wegener Granulomatosis and Therapeutic Immune Response Targets

Immune response therapies and targets are indicated in blue boldface text.


Two authors (A.G. and G.E.) read the titles and abstracts (if available) looking for articles on current available drug therapy or medical interventions for any AAV (inclusion criterion). Articles considered by both authors to meet this criterion were fully reviewed. Duplicate publications, case reports, and uncontrolled trials and series with fewer than 10 patients were excluded. Two meta-analyses, 20 randomized controlled prospective trials, and 62 uncontrolled trials with more than 10 patients or observational studies were finally analyzed.

**EVIDENCE SYNTHESIS**

**Rationale for the Current Approach**

When the natural history of Wegener granulomatosis was described in 1958, it was usually a fatal disease without effective treatment and patient survival after diagnosis averaged 5 months. The introduction in the 1960s of corticosteroids only extended average survival by 8 months. This changed radically when Fauci and Wolff pioneered the use of cyclophosphamide in the early 1970s. The administration of daily oral cyclophosphamide (1-2 mg/kg) and prednisone (1 mg/kg) resulted in a dramatic clinical benefit. Prednisone was tapered and discontinued within 6 to 9 months, while cyclophosphamide was maintained at least for a year once remission was achieved.

A long-term evaluation of 158 patients with Wegener granulomatosis who had undergone this schedule showed that 75% achieved complete remission with an 87% survival rate. However, 42% of patients had permanent treatment-related morbidity. Adverse events included cyclophosphamide-cystitis (43%), infertility (57% [16 of 28] fertile women analyzed), infections (0.11 infections per patient-year, including 6 episodes of *Pneumocystis jiroveci* pneumonia and 34...
therapy.13 At this point, research on the duration of maintenance being adopted in 1994.14 Due to the granulomatosis, with a consensual de-
\[\text{quandary.}\]

pathogenic-oriented therapies may pro-
\[\text{duce} \]

pharmacodynamics induction therapy can be
\[\text{switched to less toxic azathioprine as}
\]
maintenance therapy.9 Furthermore, pa-
\[\text{tients with less severe disease can achieve}
\]
remission with methotrexate with a suc-
\[\text{cess rate similar to that of cyclophos-
}\]
phamide.10

Although these schedules minimize the devastating adverse effects of cyclophosphamide, refractory cases exist (10%)11 and relapses are fairly common even in treated patients. Due to repeated bouts of disease activity and long-
\[\text{term treatment-related morbidity, accumu-
}\]
lative organ damage is a major threat.12 Moreover, there is no agreement on the duration of maintenance therapy.13 At this point, research on pathogenic-oriented therapies may provide better answers to the AAV treatment quandary.

Data on AAV treatment stem mainly from studies of patients with Wegener granulomatosis, a consensus description of microscopic polyangiitis being adopted in 1994.14 Due to the overlap between Wegener granulomatosis and microscopic polyangiitis, some patients classified as having Wegener granulomatosis probably had microscopic polyangiitis.15 This, together with the similar response to therapy (and their low incidence), has meant that the 2 conditions are considered together for therapeutic investigation.

Given the shortage of randomized trials, it is not easy to propose a guideline for AAV treatment. The methods used in these studies is heterogeneous with different definitions for remis-
\[\text{sion, relapse, and disease states.11 Fur-
}\]
thermore, both the initial dose of glucocorticoids and immunosuppressants and the tapering schemes vary.

The most logical strategy is to design the treatment according to the clinical situation.16 Jayne et al17 for the European Vasculitis Study (EUVAS) group defined several subgroups of patients covering the spectrum of AAV severity. To aid understanding, we have slightly modified the clinical characteristics of EUVAS subgroups to allow the inclusion of patients from other studies with similar but not identical features.

**Localized Disease**

The EUVAS definition refers to patients with symptoms restricted to the upper and/or lower airways, without constitut-
\[\text{tional symptoms or systemic vasculitis.}
\]

**Remission Induction.** In the 1980s, DeRemee and colleagues18,19 reported favorable responses to cotrimoxazole alone or in combination with cyclophosphamide plus corticosteroids in 11 of 12 patients with Wegener granulomatosis. Seven patients fulfilled criteria of localized Wegener granulomatosis. A positive result was also seen in a subsequent study,20 with 11 of 19 pa-
\[\text{tients with localized Wegener granulo-
}\]
motasis responding to cotrimoxazole with complete (n = 6) or partial (n = 5) remission lasting a median of 43 months.20

**Remission Maintenance.** In the only randomized study of cotrimoxazole as remission maintenance in localized dis-
\[\text{ease, cotrimoxazole, or placebo twice}
\]
daily was initiated after remission was achieved with cyclophosphamide plus corticosteroids.21 Eight patients with localized Wegener granulomatosis were included in the cotrimoxazole group and 7 received placebo. Half were treated with corticosteroids. After 24 months, re-
\[\text{lapses were less frequent in the cotri-
}\]

moxazole group (18% vs 40%).21 Relapse rates were significantly lower in patients with upper respiratory tract disease but not in those with renal or lung involvement.

**Recommendation.** Owing to its fa-
\[\text{vorable response rates and the favor-
}\]
able adverse-effect profile, cotrimoxa-
\[\text{zole, in our opinion, can be used alone}
\]
or in combination with corticosteroids to induce and maintain remission when disease is limited to the upper respiratory tract (See levels of evidence for recommendations in Table 1).

**Generalized Non–Organ-Threatening Disease**

(Early Systemic Disease)

EUVAS defined early systemic disease as patients with localized Wegener granulomatosis with constitutional symptoms or with multifocal Wegener granulomatosis or microscopic polyangiitis without threatened organ function. Serum creatinine levels must be lower than 1.7 mg/dL.17 There may be lung involvement, but the partial pressure of oxygen must be higher than 70 mm Hg and the diffusing lung capacity of carbon monoxide must be more than 70%.

**Remission Induction.** Studies have analyzed the effectiveness and safety of immunosuppressants less aggressive than cyclophosphamide, with methotrexate being the most tested10,21–28 (Table 2), including 4 prospective, uncontrolled studies.23,26 Remission rates ranged from 35% to 74%.23 The lower rate of treatment success achieved in 1 trial26 may be explained by the different
doses of concomitant corticosteroids. The EUVAS’ Non-Renal Wegener’s Granulomatosis Treated Alternatively With Methotrexate (NORAM) study by de Groot et al\textsuperscript{10} is the only trial to compare the effectiveness and safety of methotrexate plus corticosteroids with oral cyclophosphamide plus corticosteroids for induction of remission. Six months after initiation of therapy, the remission rate in the methotrexate group (89.8\%) was not significantly lower than in the cyclophosphamide group (93.5\%). Of note, remission was delayed among patients in the methotrexate group who had more extensive disease or pulmonary involvement.

Etanercept is a tumor necrosis factor α (TNF-α)–blocking fusion protein that contains the ligand-binding domain of the human TNF-α receptor 2. The rationale for the use of TNF-α blockers in AAV stems from (1) a positive correlation between TNF-α serum levels and disease activity; (2) the presence of TNF-α in vasculitic lesions; (3) in vitro evidence for a role of TNF-α in neutrophil priming (Figure 2); (4) the efficacy of TNF-α blockade in suppressing vasculitis in an animal model\textsuperscript{31}; and (5) the predominance of T-helper cells with a T-helper type 1 cytokine repertoire including TNF-α in Wegener granulomatosis granulomata (Figure 1).\textsuperscript{32}

The Wegener’s Granulomatosis Etanercept Trial (WGET)\textsuperscript{27,28} assessed the efficacy of etanercept in the treatment of Wegener granulomatosis. One hundred eight patients were randomly assigned to receive etanercept or placebo in addition to standard therapy (corticosteroids plus cyclophosphamide for patients with severe disease and corticosteroids plus methotrexate for patients with limited disease).\textsuperscript{27} No differences were found in remission rates with the addition of etanercept or placebo to methotrexate and corticosteroids. Of note, 6 patients in the etanercept group, and none in the placebo group, developed solid cancers, although all patients were treated with cyclophosphamide. It is possible that the combination of TNF-α inhibitors and cyclophosphamide increases the risk of cancer beyond that observed with cyclophosphamide alone.

### Table 1. Treatment for Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

<table>
<thead>
<tr>
<th>Disease State</th>
<th>Treatment Induction</th>
<th>Remission Maintenance&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Localized disease</strong></td>
<td>Cotrimoxazole ± corticosteroids&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2b/B</td>
<td>When methotrexate is used for maintenance therapy, monitor closely for relapse.</td>
</tr>
<tr>
<td><strong>Generalized non-organ-threatening disease</strong></td>
<td>Methotrexate + corticosteroids</td>
<td>1b/A</td>
<td>For refractory disease, see Table 4.</td>
</tr>
<tr>
<td><strong>Generalized organ-threatening disease</strong></td>
<td>Pulse cyclophosphamide + corticosteroids</td>
<td>1a/A</td>
<td>For patients who test positive for proteinase-3 ANCA at the time of switching to azathioprine, monitor closely for relapse. For patients with contraindications or intolerance to azathioprine, consider alternative therapy with leflunomide (1b/A), methotrexate (1b/A), or mycophenolate mofetil (4/C).</td>
</tr>
<tr>
<td><strong>Severe renal vasculitis</strong></td>
<td>Cyclophosphamide + corticosteroids + plasma exchange</td>
<td>1b/A</td>
<td>For refractory disease, see Table 4.</td>
</tr>
<tr>
<td><strong>Diffuse pulmonary hemorrhage</strong></td>
<td>High-dose cyclophosphamide + pulse methylprednisolone</td>
<td>5/D</td>
<td>For refractory disease, see Table 4.</td>
</tr>
<tr>
<td><strong>Churg-Strauss Syndrome</strong></td>
<td>Cyclophosphamide + corticosteroids</td>
<td>1a/A</td>
<td>Less toxic immunosuppressant</td>
</tr>
<tr>
<td><strong>FFS=0</strong></td>
<td>Corticosteroids</td>
<td>1a/A</td>
<td>Low-dose corticosteroids if persistent asthma</td>
</tr>
</tbody>
</table>

<sup>a</sup> In cases of minor relapse (recurrence or new onset of non-organ- and non-life-threatening disease activity) consider adjusting immunosuppressants and/or corticosteroids.

<sup>b</sup> Level of evidence and grade of recommendation follow the Oxford Centre for Evidence-Based Medicine definitions.\textsuperscript{22}

<sup>c</sup> Add cotrimoxazole to prevent infection by Pneumocystis jiroveci when using immunosuppressants.

<sup>d</sup> Maintain immunosuppressants and taper corticosteroids for at least 12 to 18 months.
### Table 2. Studies on Methotrexate for Remission Induction and/or Maintenance in Patients With Generalized Non–Organ-Threatening Disease

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Type of study</td>
<td>Prospective uncontrolled</td>
<td>Prospective uncontrolled</td>
<td>Prospective uncontrolled</td>
<td>Randomized controlled trial</td>
<td>Randomized controlled trial</td>
<td>Prospective uncontrolled</td>
<td>Prospective uncontrolled</td>
</tr>
<tr>
<td>Phase of treatment</td>
<td>Induction and maintenance</td>
<td>Induction and maintenance</td>
<td>Induction and maintenance</td>
<td>Induction and maintenance</td>
<td>Induction and maintenance</td>
<td>Maintenance</td>
<td>Maintenance</td>
</tr>
<tr>
<td>No. of patients</td>
<td>42</td>
<td>17</td>
<td>19</td>
<td>95</td>
<td>52</td>
<td>22</td>
<td>71</td>
</tr>
<tr>
<td>Definitions of complete remission</td>
<td>Absence of active disease, pulmonary infiltrates, systemic inflammatory disease, and stabilization or improvement of renal features</td>
<td>Absence of abnormalities in clinical, radiological, and immunological data</td>
<td>Absence of active disease in any organ for at least 1 mo without treatment</td>
<td>Absence of new or worse disease activity (BVAS 1) but allowed persistent activity (BVAS 2) in 1 item scoring &lt;2 points</td>
<td>Sustained remission, BVAS 0 for at least 6 mo; Remission, BVAS 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete remission, %</td>
<td>71</td>
<td>35</td>
<td>74</td>
<td>89.8 Methotrexate; 93.5 Cyclophosphamide</td>
<td>67.3 Methotrexate; 74.6 Cyclophosphamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to remission, mean (wk)</td>
<td>4.2</td>
<td>NS</td>
<td>NS</td>
<td>3 Methotrexate; 2 Cyclophosphamide</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definitions of relapse</td>
<td>Return of the categories of disease after remission</td>
<td>Reemergence of symptoms after remission</td>
<td>Recurrence of Wegener granulomatosis after remission</td>
<td>Remission or new onset of vasculitis activity (clinical manifestations) after remission</td>
<td>Increase of at least 1 point in the BVAS</td>
<td>Return of the categories of disease after remission</td>
<td>Reemergence of symptoms after complete or partial remission (at least 3 mo)</td>
</tr>
<tr>
<td>Relapses, %</td>
<td>37</td>
<td>40</td>
<td>57</td>
<td>69.5 Methotrexate; 46.5 Cyclophosphamide</td>
<td>NS</td>
<td>73</td>
<td>37</td>
</tr>
<tr>
<td>Time to relapse, mean (wk)</td>
<td>29</td>
<td>NS</td>
<td>10</td>
<td>13 Methotrexate; 15 Cyclophosphamide</td>
<td>NS</td>
<td>15</td>
<td>19.4</td>
</tr>
<tr>
<td>Toxic effects, %</td>
<td>50</td>
<td>12</td>
<td>42</td>
<td>38 Adverse events in 46 patients</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>10</td>
<td>0</td>
<td>6</td>
<td>7</td>
<td>NS</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>4</td>
<td>0</td>
<td>9</td>
<td>NS</td>
<td>NS</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>NS</td>
<td>NS</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>NS</td>
<td>NS</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Mucositis</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Gastrointestinal event</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: BVAS, Birmingham Vasculitis Activity Score; MPA, microscopic polyangiitis; NS, not specified; WGET, Wegener’s Granulomatosis Etanercept Trial.

Maximum serum creatinine level (to convert creatinine from mg/dL to mmol/L, multiply by 88.4).

Methotrexate was administered by intravenous route.

Results are expressed in months. In DeGroot et al,19 and WGET, Wegener’s Granulomatosis Etanercept Trial.

Mean serum creatinine level (to convert creatinine from mg/dL to mmol/L, multiply by 88.4).

Mean serum creatinine level (to convert creatinine from mg/dL to mmol/L, multiply by 88.4).

Percentages are referred as sustained remission.

Statistically significant.
Remission Maintenance. Most data on the role of methotrexate in remission maintenance in generalized non–organ-threatening disease comes from nonrandomized studies (TABLE 3),24-28,28-30,41-43 with relapse rates varying between 37% and 73%. In general, these patients were taking only methotrexate at the time of relapse.20,30,41 The high number of renal relapses (66%) is noteworthy.30 De Groot et al13 demonstrated that low-dose methotrexate (0.3 mg/kg once weekly) was superior to cotrimoxazole for remission maintenance (91% vs 58%) in 65 patients with generalized non–organ-threatening Wegener granulomatosis, results similar to those previously reported by Reinhold-Keller et al20 who showed that neither cyclofosfamide alone nor cyclofiosfamide plus low-dose prednisone sustained remission in non–organ-threatening Wegener granulomatosis. The NORAM10 trial (n=100) was devised as a remission induction and not as a remission maintenance trial. Relapse rates at 18 months were unexpectedly high (70% in the methotrexate group and 47% in the cyclophosphamide group), with 45% of the methotrexate group and 30% in the cyclophosphamide group experiencing a relapse before maintenance therapy was discontinued. The authors con-

<p>| Table 3. Studies on Remission Maintenance in Patients With Generalized Organ-Threatening Disease |
|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|</p>
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Azathioprine</th>
<th>Mycophenolate Mofetil</th>
<th>Leflunomide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jayne et al,9 2003</td>
<td>71 Azathioprine</td>
<td>Azathioprine</td>
<td>2 g/d</td>
</tr>
<tr>
<td>2005</td>
<td>73 Cyclophosphamide</td>
<td>Methotrexate</td>
<td>20 mg/d</td>
</tr>
<tr>
<td>Sanders et al,24 2005</td>
<td>76 Azathioprine</td>
<td>Azathioprine, 2 mg/kg per d</td>
<td>Leflunomide, 30 mg/d; Methotrexate, 20 mg/wk</td>
</tr>
<tr>
<td>Slot et al,35 2004</td>
<td>44 Azathioprine</td>
<td>Cyclophosphamide, 1.5 mg/kg per d</td>
<td></td>
</tr>
<tr>
<td>Nowack et al,36 1999</td>
<td>11 Azathioprine</td>
<td>Azathioprine, 2 mg/kg per d</td>
<td></td>
</tr>
<tr>
<td>Langford et al,37 2004</td>
<td>14 Azathioprine</td>
<td>Methotrexate, 0.3 mg/kg per wk</td>
<td></td>
</tr>
<tr>
<td>Koukoulaki and Jayne,38 2006</td>
<td>29 Azathioprine</td>
<td>Azathioprine, 1.5-2 mg/kg per d</td>
<td></td>
</tr>
<tr>
<td>Metzler et al,39 2004</td>
<td>20 Azathioprine</td>
<td>Cyclophosphamide, 2 mg/kg per d</td>
<td></td>
</tr>
<tr>
<td>Metzler et al,40 2005</td>
<td>26 Azathioprine</td>
<td>Azathioprine, 2 mg/kg per d</td>
<td></td>
</tr>
<tr>
<td>Type of study</td>
<td>Randomized controlled trial</td>
<td>Prospective uncontrolled</td>
<td>Prospective uncontrolled</td>
</tr>
<tr>
<td>No. of patients</td>
<td>71</td>
<td>55</td>
<td>76</td>
</tr>
<tr>
<td>Time to initiate treatment</td>
<td>After at least 3 mo of remission taking cyclophosphamide</td>
<td>After 3 mo of remission taking cyclophosphamide</td>
<td>When remission was achieved with cyclophosphamide (mean 14 wk)</td>
</tr>
<tr>
<td>Initial dose</td>
<td>Azathioprine, 2 mg/kg per d</td>
<td>Azathioprine, 2 mg/kg per d</td>
<td>Azathioprine, 2 mg/kg per d</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide, 1.5 mg/kg per d</td>
<td>Methotrexate, 0.3 mg/kg per wk</td>
<td>Methotrexate, 2 mg/kg per d</td>
</tr>
<tr>
<td>Time of treatment, mean, mo</td>
<td>12</td>
<td>21</td>
<td>36</td>
</tr>
<tr>
<td>Follow-up, mean</td>
<td>18 mo</td>
<td>5.3 y</td>
<td>5 y</td>
</tr>
<tr>
<td>Definition of relapse</td>
<td>Major: recurrence or first appearance of at least 1 BVAS item indicative of vital organ threatening; Minor: recurrence or first appearance of at least 3 other BVAS items</td>
<td>Signs of activity + biopsy-proven vasculitis or lung nodules after exclusion of other disorders</td>
<td>BVAS&gt;0</td>
</tr>
<tr>
<td>Relapses, %</td>
<td>15.5 Azathioprine; 13.7 Cyclophosphamide</td>
<td>At 18 mo, 13 Azathioprine; 10 Methotrexate</td>
<td>At 2 y, 24 Azathioprine; 24 Cyclophosphamide</td>
</tr>
<tr>
<td></td>
<td>At 36 mo, 41 Azathioprine</td>
<td>At 4 y, 49 Azathioprine; 35 Cyclophosphamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>37 Methotrexate</td>
<td>43 At 18 mo after remission</td>
<td>48</td>
</tr>
<tr>
<td>Abbreviations: BVAS, Birmingham Vasculitis Activity Score; NS, not specified.</td>
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cluded that although maintenance of immunosuppression beyond 12 months was advisable, continued treatment with methotrexate or cyclophosphamide does not guarantee the absence of relapses. The WGET trial revealed no differences between etanercept and placebo groups in rates of sustained remission in non–organ-threatening disease.

**Recommendation.** To induce remission, methotrexate plus corticosteroids can be used instead of cyclophosphamide in patients with generalized, non–organ-threatening disease. However, when methotrexate is used as maintenance therapy, the likelihood of relapses is high so we recommend rigorous monitoring for early detection. Currently, there is no evidence for the cessation of methotrexate maintenance treatment at 12 months.

**Generalized Organ-Threatening Disease (Generalized Disease)**

The EUVAS group defined generalized disease as patients with Wegener granulomatosis or microscopic polyangiitis with constitutional symptoms, threatened organ function, and serum creatinine levels lower than 5.7 mg/dL. Others have labeled this subgroup as having **life or organ-threatening disease**. To aid joint analysis of different studies, we have defined **generalized organ-threatening disease** as renal insufficiency, serum creatinine levels lower than 5.7 mg/dL, threat to other organs including vital organs, or both.

**Remission Induction.** Daily oral cyclophosphamide plus corticosteroids substantially advanced the treatment of generalized Wegener granulomatosis and remains the gold standard therapy. Studies have found remission rates between 70% and 100% and early mortality rates of less than 20%, with increased treatment-related morbidity. Therefore, research centered on searching for equally effective but safer treatments, including changing the route of administration and dosage of cyclophosphamide and testing a monthly intravenous regimen.

Ten nonrandomized studies demonstrated similar rates of remission induction with intermittent intravenous cyclophosphamide as those using the daily oral drug. The advantage of the intravenous route is the smaller cumulative dosage and, therefore, fewer adverse events. Three randomized trials have compared the effectiveness and security profile of pulsed cyclophosphamide with daily oral administration for remission induction. A meta-analysis that summarized the results from these trials concluded that pulsed cyclophosphamide is as effective as daily oral cyclophosphamide with much less severe toxic effects, yet possibly with a higher relapse rate.

To clarify this controversy, the EUVAS group devised a randomized trial comparing the efficacy of oral cyclophosphamide (2 mg/kg per day) with intravenous pulsed cyclophosphamide (15 mg/kg every 2 weeks for the first 3 pulses and every 3 weeks thereafter) with the same corticosteroids regimen in both groups. Two studies that compared the efficacy of oral cyclophosphamide with pulse cyclophosphamide and 71 switched to azathioprine after remission was achieved with cyclophosphamide and corticosteroids. No difference was found in the relapse rate between the 2 groups at 18 months (15.5% vs 13.7%). Simililar relapse rates for those taking azathioprine after remission were reported by a French group in a randomized trial comparing azathioprine with methotrexate in remission maintenance, with no differences being detected in relapse rates.

**Remission Maintenance.** Treatment with pulse cyclophosphamide has been found to be less effective in preventing relapses than oral cyclophosphamide, although other reports disagree. The discrepancies may be due to differences in doses and, mainly, pulse administration intervals between studies. Two studies that prolonged cyclophosphamide pulses for another 18 months found lower rates of relapses.

Another way to reduce cyclophosphamide morbidity is to switch this drug with less toxic immunosuppressants, such as azathioprine, mycophenolate mofetil, or leflunomide (Table 3). The efficacy of azathioprine in remission maintenance was initially reported in nonrandomized trials with relapse rates between 11% and 46%. The first randomized, prospective study of azathioprine in remission maintenance was the CYCAZAREM (Randomized Trial of Cyclophosphamide vs Azathioprine During Remission in ANCA-Positive Systemic Vasculitis) study by Jayne et al.

A total of 100 patients with generalized AAV and vital organ manifestations were enrolled in the CYCAZAREM (Randomized Trial of Cyclophosphamide vs Azathioprine During Remission in ANCA-Positive Systemic Vasculitis) study by Jayne et al.

The study included 160 patients with generalized AAV and vital organ manifestations. Preliminary results show that pulsed cyclophosphamide is more effective in patients treated with pulse cyclophosphamide, with a higher relapse rate. With regard to biological therapies, the addition of etanercept to cyclophosphamide in the WGET trial had no beneficial effect on remission induction. Infliximab—a chimeric IgG1 monoclonal antibody—is another TNF-α blocker that has been used as adjuvant therapy in remission induction. In a prospective uncontrolled study of 16 patients, the addition of infliximab shortened the prior-to-remission period by a mean of 6.4 weeks and allowed early tapering of prednisolone, with a 40% reduction in the cumulative dose compared with standard regimens.
indicate that relapses occur predominantly after therapy discontinuation and that patients with generalized AAV with a higher cumulative exposure to cyclophosphamide may have a lower rate of relapse. Finally, in patients with positive proteinase 3-ANCA at the time they switched to azathioprine, disease-free survival at 2 and 4 years was shorter than for patients with negative proteinase 3-ANCA.39

In an open-label trial enrolling 11 patients with AAV who had achieved remission under cyclophosphamide and corticosteroids, mycophenolate mofetil (2 g/d) maintained remission for 15 months in all but 1 patient.36 Conversely, Langford et al37 detected relapses in 6 of 14 patients with Wegener granulomatosis. The differences may be attributed to 2 factors: concomitant steroids were withdrawn after a median of 8 months in the former study but were maintained at low doses in the latter and the trial only involved patients with Wegener granulomatosis, which is known to intrinsically reoccur at a higher rate than microscopic polyangiitis.9 In a retrospective study,38 14 of 29 patients taking mycophenolate mofetil experienced a relapse in a mean of 14 months. These limited, controversial findings may be clarified when the results are available from the International Mycophenolate Mofetil Protocol to Reduce Outbreaks of Vasculitis (IMPROVE) trial, an ongoing randomized trial comparing mycophenolate mofetil with azathioprine for maintenance therapy.11

In a phase 2, open-label trial, oral leflunomide (30-40 mg/d) plus low-dose prednisolone was administered as a maintenance agent to 20 patients with Wegener granulomatosis. During a follow-up of 21 months, 1 major flare was recorded. Eight minor relapses were successfully treated by increasing the leflunomide dose.39 These results led to a multicenter randomized trial comparing 30-mg daily leflunomide with 20-mg weekly methotrexate in 54 patients with AAV. The trial was interrupted after an unexpectedly high number of severe relapses occurred in the methotrexate group (13 vs 4). Four patients treated with leflunomide were withdrawn due to serious adverse effects (hypertension, neuropathy, and leukopenia). The WGET trial found no differences between etanercept and placebo in rates of sustained remission in patients with organ threatening disease.27

**Recommendation.** Pulse cyclophosphamide with oral corticosteroids can be used to induce remission in patients with generalized organ-threatening disease. Patients should be started with 1 mg/kg per day of oral prednisone plus 0.6 to 0.7 g/m² (15 mg/kg; maximal dose: 1 g/m²) intravenous pulse cyclophosphamide (every 3 weeks for 6 months). Prednisone should be tapered to 10 mg by 6 months and maintained at this dose until month 15, when it should be tapered to 7.5 mg and maintained for at least 3 more months followed by local practice. Cyclophosphamide doses should be adjusted by age, renal function, and leukocyte count. The combination of azathioprine and daily prednisone effectively maintains remission. Patients who test negative for ANCA may benefit most with this regimen while patients positive for proteinase 3-ANCA should be closely monitored because they have a higher probability of relapse. Two milligrams per kilogram of azathioprine should be started when cyclophosphamide is discontinued. At 6 months it should be reduced to 1.5 mg/kg per day and maintained for at least 6 more months. In our opinion, leflunomide, methotrexate, and mycophenolate mofetil may be useful alternative therapies to maintain remission.

**Severe Renal Vasculitis and Immediately Life-Threatening Disease**

Because of a worse prognosis, patients with rapidly progressive renal failure with and without diffuse alveolar hemorrhage have traditionally received a greater immunosuppressive load such as daily pulses of methylprednisolone (1 g) and intravenous cyclophosphamide (3-4 mg/kg per day) over brief periods. However, the evidence supporting this practice is scarce.74

Despite use of immunosuppressants, only 50% of patients presenting with advanced renal failure maintain independent renal function at 1 year.72,73 Retrospective studies have suggested that plasma exchange may be beneficial for patients with severe renal disease and pulmonary hemorrhage.76-80 Plasma exchange is supposedly effective because it removes ANCs. In a randomized controlled trial that compared 25 patients with necrotizing glomerulonephritis treated with immunosuppressants plus plasma exchange with 23 patients receiving immunosuppressants alone, Pusey et al81 found that patients receiving plasma exchange who were initially dialysis-dependent had a greater likelihood of recovering renal function. In a recent multicenter trial,4 in which 137 patients with severe renal vasculitis (serum creatinine > 5.7 mg/dL) were randomly assigned to undergo plasma exchange or receive pulsed methylprednisolone. Two-thirds of these patients were dialysis-dependent on presentation. All patients were treated with the standard remission induction regimen. Preliminary results show that recovery of independent renal function at 3 months was significantly higher in the plasma exchange group (69% vs 49%). Mortality was 25% with no differences between groups. Therefore, plasma exchange is, at present, the best complement to immunosuppressants in advanced renal disease. Nevertheless, the potential of combining plasma exchange and methylprednisolone in these patients and the use of plasma exchange for less severe renal disease and pulmonary hemorrhage remains unclear.

**Refractory Disease**

Numerous experimental therapies have recently been used for patients not achieving remission with the gold standard treatment or those with contraindications (TABLE 4). However, there is a lack of randomized trials analyzing the best therapy for these patients and the definition of refractory disease varies widely.
Intravenous Immunoglobulin
Intravenous immunoglobulin may be effective by interfering with ANCA binding to their antigens (due to antiidiotype antibodies) and by inhibiting ANCA-mediated neutrophil activation. A retrospective study first revealed a beneficial effect of pooled intravenous immunoglobulin in 1993. In a randomized, placebo-controlled, double-blind trial published in 2000, adding a single course of intravenous immunoglobulin (2 g/kg) to immunosuppressants was significantly effective. The primary end point was the number of pa-

Table 4. Treatments for Patients With Refractory Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

<table>
<thead>
<tr>
<th>Source</th>
<th>No of Patients</th>
<th>Study Type</th>
<th>Definition of Refractory</th>
<th>Primary End Point</th>
<th>Length of Treatment</th>
<th>Responders, %</th>
<th>Definition of Remission</th>
<th>Relapse Rate, %</th>
<th>Mean BVAS at Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jayne et al.82 2000</td>
<td>24/10</td>
<td>Double-blind, randomized controlled trial</td>
<td>Active vasculitis needing more therapy and at least 2 mo of treatment with prednisone and cyclophosphamide or azathioprine</td>
<td>NS</td>
<td>Reduction in BVAS by &gt;50% after 3 mo</td>
<td>83</td>
<td>Intravenous Ig; 35 Placebo</td>
<td>NS</td>
<td>31 Intravenous Ig; 27 Placebo</td>
</tr>
<tr>
<td>Richter et al.83 1995</td>
<td>14/1b</td>
<td>Prospective uncontrolled</td>
<td>Poor responders or intolerant to conventional therapy</td>
<td>7</td>
<td>Clinical and/or radiological improvement after 4 wk</td>
<td>1 Course, 10 patients; 2 Courses, 2 patients; 3 Courses, 3 patients</td>
<td>0 Complete remission; 40 Partial remission</td>
<td>0 Complete remission; absence of any clinical and/or radiological features of active vasculitis; Partial remission; any improvement</td>
<td>NS</td>
</tr>
<tr>
<td>Jayne et al.84 1993</td>
<td>14/11</td>
<td>Retrospective series</td>
<td>Resistant to conventional therapy</td>
<td>16</td>
<td>Remission rate</td>
<td>1 Course of 5 d</td>
<td>50 Complete remission at 8 wk</td>
<td>NS</td>
<td>24 NS</td>
</tr>
<tr>
<td>Stassen et al.85 2007</td>
<td>29/3</td>
<td>Prospective uncontrolled</td>
<td>Cyclophosphamide contraindication</td>
<td>0</td>
<td>Remission rate</td>
<td>19 mo (1.9-58 mo)</td>
<td>78 Complete remission at 5 mo; 19 Partial remission at 5 mo</td>
<td>Complete remission; BVAS of 0 plus PCR &lt;10 mg/L; Partial remission; &quot;clinically relevant&quot; improvement of BVAS</td>
<td>59 14</td>
</tr>
<tr>
<td>Birck et al.86 2003</td>
<td>19/1</td>
<td>Prospective uncontrolled</td>
<td>Intractable course, severe adverse effects, frequent relapses, constant low-grade disease under immunosuppressants, or denied to be treated with cytostatics</td>
<td>9</td>
<td>Remission rate after 6 cycles of 15-deoxyspergualin</td>
<td>NS</td>
<td>30 Complete remission; 40 Partial remission</td>
<td>Complete remission; absolute absence of clinical signs of disease activity; Partial remission; absence of acute or never clinical activity</td>
<td>25 5.8</td>
</tr>
<tr>
<td>Schmitt et al.87 2004</td>
<td>15/0</td>
<td>Prospective uncontrolled</td>
<td>Unresponsive to at least 6 wk of standard treatment; Intolerant of standard treatment; Low-grade disease after reduction or omission of immunosuppressants</td>
<td>7</td>
<td>Induction of partial or complete remission for at least 1 mo</td>
<td>2.2 Infusions (1-5) during a 10-d regimen</td>
<td>27 Complete remission; 60 Partial remission</td>
<td>Complete remission; no abnormal clinical and radiological vasculitis findings; Partial remission; partial regression of activity</td>
<td>54 NS</td>
</tr>
</tbody>
</table>

(continued)
patients with decreased Birmingham Vasculitis Activity Score (BVAS) of at least 50% at 3 months. However, there were no significant differences in either the score beyond 3 months or the exposure to immunosuppressants following intravenous immunoglobulin.

**Mycophenolate Mofetil**

Stassen et al.\(^6\) recently reported the results of a study in which 32 patients were initially treated with mycophenolate mofetil (2 g/d) plus prednisolone (1 mg/kg per day). After 2.2 months, 78% of patients achieved complete remission. Maintenance therapy with mycophenolate mofetil yielded a 59% rate of relapse within a median of 12 months. Sixteen infectious episodes were seen in 12 patients while taking mycophenolate mofetil. Thus, mycophenolate mofetil seems to be able to suppress activity in acute disease.

**15-Deoxyspergualin**

In an open-label trial, Birck et al.\(^8\) found that 6 cycles of subcutaneous or intravenous 15-deoxyspergualin (0.5 mg/kg per day) for 6 months led to clinical improvement in 70% of cases. The favorable adverse effect profile with no renal and liver toxicity and with reversible bone marrow suppression suggests that 15-deoxyspergualin is a promising therapy.

**Antithymocyte Globulin**

Because activated CD4 T cells producing T-helper type 1 cytokines seem to play a crucial role in AAV,\(^3\) there exists a rationale for the use of T-lymphocyte blocking therapies (Figure 1). The infusion of antithymocyte globulin causes rapid, deep depletion of T lymphocytes. In a prospective, uncontrolled trial,\(^8\) a 10-day regimen of antithymocyte globulin–induced remission in 13 of 15 patients with Wegener granulomatosis. Remission was seen in 6 of 7 patients with persistent activity despite cyclophosphamide, and in 7 of 8 patients in whom cyclophosphamide was contraindicated. Due to the potential adverse effects of antithymocyte globulin, including pulmonary edema, the authors recommended avoiding the drug in cases of infection and balancing its risk against possible benefits in cases of pulmonary hemorrhage.

**Rituximab**

Rituximab is a chimeric monoclonal anti-CD20 IgG1 antibody that induces apoptosis of B lineage cells, with the exception of plasma cells and pre-B cells. Infusion of rituximab causes a 6-month depletion of circulating B cells.
Besides non-Hodgkin B-cell lymphoma, rituximab is effective against several autoimmune diseases including rheumatoid arthritis and systemic lupus erythematosus. In AAV, the depletion of B cells, the immediate precursors of plasma cells, might halt the replacement of true ANCA-producing cells (ie, CD20 negative plasma cells; Figure 1) leading to the disappearance of pathogenic antibodies and the resolution of vasculitic lesions. This hypothesis is supported by the assumption that ANCA-producing plasma cells have a short lifespan.

The best evidence for the treatment of refractory AAV with rituximab emerges from a small retrospective series and a prospective study. The maximum tolerated dose of cyclophosphamide failed to control disease activity in 11 of 21 individuals. Immunosuppressive agents were removed at initiation of rituximab (4 weekly doses of 375 mg/m²); the treatment protocol included initial high-dose prednisone (1 mg/kg per day) and, in some patients, a 3-day cycle of methotrexate (1 mg/kg per week). The maximum tolerated dose of cyclophosphamide failed, cyclophosphamide should be introduced to induce remission, which may be maintained with another less toxic drug.

**Churg-Strauss Syndrome**

Most studies of Churg-Strauss syndrome treatment have been performed by the French Vasculitis Study Group, which proposed the 5-factors score as a predictor of death in Churg-Strauss syndrome: (1) renal insufficiency (creatinine level > 1.58 mg/dL); (2) proteinuria higher than 1 g/dL; (3) gastrointestinal bleeding, perforation, infarction, or pancreatitis; (4) central nervous system involvement; and (5) cardiomyopathy. The presence of each factor is given 1 point. Three classes of scores are defined as 0 when no factor is noted; 1 when 1 factor is present, and 2 when 2 or more factors are present. The score is associated with a higher risk of mortality when it is 1 or higher.

This score is useful in deciding the first-line of treatment. In one study, early deaths of patients with a 5-factors score of 2 were more frequent when steroids were prescribed alone. A meta-analysis of the French Vasculitis Study Group trials showed improved outcomes after early administration of oral cyclophosphamide in patients with severe manifestations (score, ≥1) at onset. This group also demonstrated that the addition of plasma exchange to the combined treatment of corticosteroids and pulse cyclophosphamide did not enhance the 5-year cumulative survival rates in patients with severe (score, ≥1) Churg-Strauss syndrome. More than 80% of survivors in long-term remission had persistent asthma requiring permanent low doses of oral or inhaled corticosteroids. The duration of the immunosuppressive treatment is also controversial in Churg-Strauss syndrome. Preliminary prospective data suggest that patients receiving 6 pulses of cyclophosphamide had more relapses than those receiving 12 pulses (94% vs 41%).

**Recommendation.** Treatment can be started with high doses of corticosteroids (1 mg/kg per day), tapering them when the patient improves. In patients with a 5-factors score equal to or greater than 1 or when corticosteroids fail, cyclophosphamide should be introduced to induce remission, which may be maintained with another less toxic drug.

**Controversies and Uncertainties**

How long should immunosuppression be maintained? Unfortunately, reported studies cannot answer this question. Although indirect data from randomized trials indicate that maintenance treatment of at least 12 to 18 months would be necessary for generalized AAV, recent data indicate that relapses occur predominantly after therapy discontinuation. We believe that it is reasonable to consider discontinuing methotrexate or azathioprine in the total absence of clinical signs of vasculitis activity and especially in the cases of patients who test negative for ANCA and patients without previous relapses. However, rigorous monitoring is mandatory for early detection of relapses. This question may be answered by the Randomized Trial of Prolonged Remission-Maintenance Therapy in Systemic Vasculitis (REMAIN), an ongoing trial in which 2 years vs 4 years of azathioprine and prednisolone are being compared in patients with renal vasculitis.

**Biologic Therapy for AAV**

The dramatic results for rituximab should be interpreted with caution. It is difficult to determine the true efficacy of rituximab in AAV in reported studies due to the simultaneous administration of high-dose glucocorticoids, which may contribute to ANCA negativization and the remission rates observed. Furthermore, the intrinsic ability of rituximab to reduce autoantibody levels remains unproven because ANCA may persist after infusion despite B cell depletion. This may be because ANCA can be continuously produced by long-lived plasma cells. It is possible that rituximab acts through immunological mechanisms other than the suppression of ANCA production (eg, by inhibiting B cell-dependent T cell functions). This uncertainty may be clarified by an
ongoing randomized, placebo-controlled trial exploring the potential role of rituximab plus corticosteroids (vs cyclophosphamide plus corticosteroids for induction and azathioprine plus corticosteroids for remission) in both induction and maintenance phases.

The apparently positive data on infliximab, added to laboratory research suggesting a fundamental role for TNF-α in AAV, justify the design of a randomized trial to determine whether this molecule, unlike etanercept, could become a therapeutic mainstay in AAV. Due to its molecular structure, infliximab-induced soluble TNF-α blockade is more complete and sustained. In addition, infliximab can bind membrane-bound TNF-α and activate apoptosis of T cells. This binding to surface TNF-α also induces cell lysis via complement fixation. Infliximab has also been found to down regulate T-cell cytokine response (TNF-α and interferon γ) after specific and nonspecific in vitro stimuli, whereas etanercept up regulated this response. These differences may explain why infliximab but not etanercept has succeeded in treating Crohn disease, otherwise a granulomatous disorder.

FUTURE DIRECTIONS AND CONCLUSIONS

The agents that have accumulated the highest evidence are not as effective and safe as would be desirable. Therefore, research should focus on clarifying and consolidating the evidence for new immunosuppressants and those biological agents that have been initially successful (rituximab and infliximab). These agents may reduce the rate of relapses and increase safety, challenging the status quo of immunosuppressive therapy in AAV. High-quality, comparable evidence requires studies following homogeneous guidelines. Definitions of disease activity (eg, remission, relapse), disease states (eg, localized, early systemic), and treatment protocols (eg, same regimen of corticosteroids tapering) should be systematic and consistent. The European League Against Rheumatism has recently issued evidence-based and expert-opinion-based recommendations for AAV trials. A new set of biological molecules is under consideration. A series of sophisticated agents directed against key pathogenic points, with proven efficacy in some autoimmune conditions, may well deserve clinical investigation for AAV. A reasonable strategy to suppress the autoimmune cellular response might be the blockade of co-stimulating molecules that intervene in the antigen presenting cell-dependent T cell activation (eg, by using abatacept). Figure 1 is thought to be the initial step in Wegener granulomatosis granuloma formation. At the vasculitic pole of the spectrum, monoclonal antibodies and fusion proteins aimed at inhibiting ANCA, suppressing neutrophil priming and endothelial activation, and interfering in the neutrophil-endothelium adhesion cascade or neutrophil degranulation might also prove fundamental in healing vasculitic damage (Figure 2).

The success of novel agents requires trials designed according to pathogenic knowledge. Patients might not only benefit from therapies tailored to disease severity but also may be treated according to clinical manifestations and biological markers reflecting the susceptible-to-block pathogenic pathway. As long as safety concerns are overcome, this strategy might even involve the combined use of agents in overlapping situations (eg, simultaneous presence of orbital granuloma and necrotizing alveolar capillaritis).

Author Contributions: Dr Bosch had full access to all the data in the study and takes responsibility for the integrity and the accuracy of the data analysis. Study concept and design: Bosch, Guilabert, Espinosa, Mirapeix. Acquisition of data: Bosch, Guilabert, Espinosa, Mirapeix. Analysis and interpretation of data: Bosch, Guilabert, Espinosa, Mirapeix. Drafting of the manuscript: Bosch, Guilabert, Espinosa, Mirapeix. Critical revision of the manuscript for important intellectual content: Bosch, Guilabert, Espinosa, Mirapeix. Statistical analysis: Bosch. Administrative, technical, or material support: Bosch, Guilabert, Espinosa, Mirapeix.

Study supervision: Bosch, Guilabert, Espinosa, Mirapeix. Financial Disclosures: None reported. Additional Contribution: We thank Mónica Pérez-Poquet, MD, for her invaluable collaboration in the design of the figures of the manuscript. She was not compensated for her contribution.

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