In November 1997, rituximab was introduced to the United States (US) market, following approval by the US Food and Drug Administration (FDA) for the treatment of certain B-cell non-Hodgkin lymphomas (table I). This approval represented the FDA’s first licensure of a monoclonal antibody for the treatment of malignant disease, and a contemporary New York Times account touted the agency’s action as a “milestone” and a “turning point” in biotechnology [1,2]. The early post-market-regimen, and all ten patients achieved remission within 3 months.

Building on these encouraging experiences, the first open-label pilot trial of rituximab for AAV in the US was initiated at the Mayo Clinic in 2003 [15]. Ten patients with active GPA – had severe, refractory disease – were treated with rituximab accompanied by a protocolized oral glucocorticoid tapering regimen, and all ten patients achieved remission within 3 months.
Rituximab is introduced to the US market, the first prospective, open-label pilot study examining the use of rituximab for the treatment of relapsed or refractory, low-grade or follicular B-cell non-Hodgkin lymphoma. The first use of rituximab for the treatment of ANCA-associated vasculitis is reported [15]. The FDA approves rituximab for remission induction in severe GPA and MPA in April 2011. The results of the RAVE trial also established rituximab as the preferred agent for patients with GPA or MPA presenting with severe relapses.

While the RAVE trial firmly established a role for rituximab in the treatment of active, severe GPA and MPA, several questions regarding the use of rituximab in AAV have remained unanswered. For example, the trial did not address the potential use of rituximab as maintenance therapy. Two retrospective studies in the US have examined this issue [18,19]. The first of these studies was reported in 2010, with Rhee et al. describing the experience of their practice in Boston with the use of regularly-scheduled rituximab for maintenance therapy in AAV [18]. Thirty-nine consecutive patients with AAV in complete or partial remission were treated with rituximab every 4 months for at least one year, and disease control was maintained in all 39 patients. In the second retrospective study to address this issue, the Mayo Clinic experience was described in a report of 53 patients with refractory GPA treated with rituximab for long-term remission maintenance [19]. Among this cohort, the repeated depletion of B-lymphocytes with rituximab appeared safe, and all relapses occurred after reconstitution of peripheral B-cells. Taken together, these reports are encouraging, and they suggest that rituximab may prove safe and effective in preventing disease relapse.

There are several additional unanswered questions regarding the use of rituximab in AAV. First, despite the encouraging initial experiences with rituximab for maintenance therapy, the optimal timing and dosing for this use remain undetermined. Second, it remains unclear what maintenance therapy, if any, should be administered to patients with newly-diagnosed AAV who achieve remission induction with rituximab. Third, it is not known whether rituximab will prove effective in ANCA-negative patients or those with limited disease.

A final unanswered question regarding the use of rituximab in AAV relates to its role in the treatment of EGPA. Patients with EGPA were not included in the RAVE trial, and the experience with rituximab in EGPA remains limited. Several case reports from Europe have described the successful treatment of refractory EGPA with rituximab [20–24]. In 2011, a small, prospective, open-label pilot study in the US examined the safety and efficacy of rituximab in three patients with EGPA who achieved remission induction with rituximab. Among these patients, rituximab was well tolerated, and all three achieved control of their renal disease activity. These results are favorable, but further study is required to assess the safety and efficacy of rituximab in EGPA.

### Timeline of key events in the US experience with rituximab for ANCA-associated vasculitis

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>Rituximab is introduced to the US market, having achieved FDA approval for the treatment of relapsed or refractory, low-grade or follicular B-cell non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>2001</td>
<td>The first use of rituximab for the treatment of AAV is reported [5]</td>
</tr>
<tr>
<td>2006</td>
<td>The first prospective, open-label pilot study of rituximab for AAV is reported [15]</td>
</tr>
<tr>
<td>2010</td>
<td>The RAVE trial is reported, establishing rituximab as a safe and effective alternative to cyclophosphamide for remission induction in severe GPA and MPA [16]</td>
</tr>
<tr>
<td>2010</td>
<td>The first retrospective study examining the use of rituximab for disease maintenance in AAV is reported [18]</td>
</tr>
<tr>
<td>2011</td>
<td>The FDA approves rituximab for remission induction in severe GPA and MPA</td>
</tr>
<tr>
<td>2011</td>
<td>The first prospective, open-label pilot study of rituximab for EGPA is reported [25]</td>
</tr>
</tbody>
</table>

*FDA: Food and Drug Administration; AAV: ANCA-associated vasculitis; RAVE: rituximab versus cyclophosphamide for ANCA-associated vasculitis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis.*
Despite the unanswered questions, in the fifteen years since rituximab was first introduced to the US market, it has become a well-established treatment option for AAV in the US. The FDA has recognized rituximab as a safe and effective alternative to cyclophosphamide for remission induction in severe GPA and MPA, and rituximab has become the preferred agent for the treatment of severe relapses in these syndromes. In addition, the early experience of US investigators with rituximab for remission maintenance in GPA and MPA, and for remission induction in EGPA, has been encouraging. While there remain areas of uncertainty that require further study, the US experience with rituximab for the treatment of AAV has been overwhelmingly positive, and it has established rituximab as a key agent in the armamentarium of AAV therapies.

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### References


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S2. Rituximab for ANCA-associated vasculitis: The UK experience

**Introduction**

In 2000, key areas of unmet need in the treatment of ANCA-associated vasculitis (AAV) were relapsing or refractory granulomatosis with polyangiitis (GPA) and the toxicity of standard