Rituximab for ANCA-associated vasculitis: The experience in the United States

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 1). 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-
The next major advance in the US experience with rituximab in AAV came with the conduct of the ‘Rituximab versus Cyclophosphamide for ANCA-associated Vasculitis’ (RAVE) trial, which was published in 2010 [16]. This multicenter, randomized, double-blind, double placebo-controlled trial compared the efficacy and safety of rituximab to cyclophosphamide for remission induction in severe GPA and MPA. The study cohort consisted of ANCA-positive patients with either GPA or MPA. A total of 197 patients were randomized to receive rituximab or cyclophosphamide, and all patients also received glucocortic treatment via a protocolized tapering regimen. Following induction of remission, patients in the cyclophosphamide group were given azathioprine for maintenance therapy, while those in the rituximab group received placebo. The study’s primary endpoint was disease remission without glucocorticoid therapy at six months. This endpoint was achieved by 64% of patients in the rituximab group versus 54% of those in the cyclophosphamide group, and rituximab therefore met criteria for non-inferiority. Rates of adverse events were similar in the two treatment arms, and among the subgroup of patients who had enrolled with severe relapses, rituximab was more efficacious than cyclophosphamide. On extended follow-up, the rates of sustained remission, as well as the frequency and severity of disease flares, remained similar between the two groups at 18 months [17]. Based on the data from the RAVE trial, the FDA-approved rituximab in combination with glucocorticosteroids 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 with active renal disease [25]. 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.

### Table I

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<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>
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<td>2001</td>
<td>The first use of rituximab for the treatment of AAV is reported [5]</td>
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<tr>
<td>2006</td>
<td>The first prospective, open-label pilot study of rituximab for AAV is reported [15]</td>
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<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>
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<tr>
<td>2010</td>
<td>The first retrospective study examining the use of rituximab for disease maintenance in AAV is reported [18]</td>
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<tr>
<td>2011</td>
<td>The FDA approves rituximab for remission induction in severe GPA and MPA</td>
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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.

Disclosure of interest: the authors have not supplied their declaration of conflict of interest.

References


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