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Case report

Rituximab as induction therapy in relapsing eosinophilic granulomatosis with polyangiitis: A report of 6 cases

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ABSTRACT

Objective: Recently few reports have suggested a potential benefit of rituximab in patients with eosinophilic granulomatosis with polyangiitis (EGPA). However, the current evidence is limited. We describe the efficacy and safety of rituximab in six patients with relapsing EGPA.
Methods: Candidates for rituximab therapy were selected from a cohort of 118 patients with EGPA. The main indication for B-cells depletion was moderately severe or severe relapsing disease that was refractory to conventional immunosuppression. A primary end-point was a complete or partial remission within 3 to 6 months after rituximab administration.
Results: All six patients (four ANCA-positive and two ANCA-negative) had active EGPA manifesting by severe lung disease and/or deteriorating peripheral neuropathy. The median duration of follow-up after the first rituximab dose administration was 10 months. All patients rapidly responded to rituximab treatment, e.g. disappearance of lung infiltrates, improvement of asthmatic symptoms, at least partial recovery of motor and sensory function. Within 3 to 6 months, complete (4/6) or partial (2/6) remission was achieved in all patients. After switching to rituximab all patients except one discontinued cyclophosphamide or other immunomodulators. Four patients continued maintenance treatment with rituximab. One patient developed severe bronchospasm during infusion and two patients presented with moderately severe purulent bronchitis that was successfully treated with intravenous antibiotics.
Conclusion: Our retrospective case series suggest that rituximab may be effective for induction of remission in selected EGPA patients. These data warrant further studies to evaluate safety and efficacy of rituximab in EGPA.

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis formerly known as Churg-Strauss syndrome [1]. Medium to high dose steroids are the current mainstay of treatment for EGPA. Cyclophosphamide is usually reserved for patients with organ- or life-threatening manifestations. Notably, up to two thirds of EGPA patients do not adequately respond to monotherapy with steroids and require addition of immunomodulators [2]. Rituximab may be an alternative to cyclophosphamide in patients with ANCA-associated vasculitides, e.g. granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). Its efficacy and safety in EGPA was shown in few case reports or relatively small case series [3–10] but the current evidence is still limited. We report 6 patients with EGPA who have been treated with rituximab.

1. Methods

We included in our retrospective series patients with a diagnosis of EGPA that was established according to the criteria of the American College of Rheumatology [11], and the Revised Chapel Hill Consensus conference nomenclature of vasculitides [12]. All patients were followed for at least 3 months after rituximab infusion. We defined complete remission of EGPA as a Birmingham vasculitis activity score (BVAS) of 0 for at least 3 months and a prednisolone dose of $\leq$ 7.5 mg daily. Criteria for partial remission included BVAS of 0 for at least 3 months and a prednisolone dose higher than 7.5 mg daily.

The off-label administration of rituximab was approved by the local Physicians' Committee. All six patients gave an informed written consent for treatment. Infusion of rituximab was started after

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standard premedication with intravenous prednisolone 180 mg, intramuscular clemastine 2 mg and paracetamol 500 mg orally.

We did not perform any statistical tests due to the low number of patients. If not otherwise indicated, median and range are reported.

2. Results

2.1. Characteristics of patients

In our clinic we followed 118 patients with EGPA. Six of them (5%) were treated with rituximab (Table 1). There were two males and four females (median age of 49 years, range of 26 to 67 years). Median duration of disease was 41 months (9 to 79 months). All patients presented with a history of bronchial asthma, peripheral blood eosinophilia and peripheral neuropathy. A history of lung infiltrates was present in four patients, alveolar hemorrhage in one, sinusitis in five, pericarditis in one. ANCA to myeloperoxidase (MPO) or proteinase-3 (PR3) were found in three and one patients, respectively. In one patient diagnosis was confirmed histologically by extravascular eosinophil infiltration of the lung tissue. A patient with PR3-ANCA had five of six ACR criteria for EGPA, including asthma, eosinophilia of 35% in peripheral blood, sinusitis, pulmonary infiltrates and polyneuropathy, while typical manifestations of granulomatosis with polyangiits, such as crusting, cavitation or orbital lesions, were absent.

2.2. Previous treatment

All patients had a history of glucocorticoid and cyclophosphamide (oral or intravenous) treatment. Median cumulative cyclophosphamide dose was 25.5 g (0.6 to 152). Immediately prior to rituximab administration patients were treated with glucocorticoids at a median daily dose of 35 mg of prednisolone (5 to 50 mg) along with cyclophosphamide ($n = 4$), azathioprine ($n = 1$) or mycophenolate mofetil ($n = 1$).

2.3. Rituximab therapy

The indications for rituximab administration included frequent relapses due to vasculitis and/or lung disease exacerbation: bilateral lung infiltrates and bronchial obstruction in five patients, recurrent hemorrhagic alveolities in one patient, and deteriorating peripheral neuropathy in three patients. In one case rituximab was used for induction of remission (after one cyclophosphamide infusion). Five patients presented with multiple complications of previous immunosuppressive treatment. Rituximab induction regimens consisted of four weekly infusions of 0.5 g in three patients, two infusion of 1 g given two weeks apart in one patient and two infusions of 0.5 g given two weeks apart in two patients. Four patients continued maintenance treatment with rituximab. Three of them received one infusion of 0.5 g after six months and one received ten infusions (0.5 g every six months). After switching to rituximab all patients except one discontinued cyclophosphamide or other immunomodulators (one patient continued azathioprine).

2.4. Response to rituximab

The median duration of follow-up after the first rituximab dose was 10 months (3 to 42 months). All patients rapidly responded to rituximab treatment, e.g. disappearance of lung infiltrates, improvement of asthmatic symptoms, at least partial recovery of motor and sensory function. At 3 months complete and partial remission was achieved in three and three patients, respectively, and at 6 months in three and two patients (in one patient the duration of follow-up was less than 6 months).

One patient discontinued steroids while 3 patients were able to reduce the dose of prednisolone below 7.5 mg. At 3 months a median dose of prednisolone was reduced from 40.0 to 8.75 mg daily. In two patients the attempts to reduce the dose or to discontinue corticosteroids were unsuccessful and were associated with minor relapses of EGPA (worsening of peripheral neuropathy in one patient and exacerbation of asthma and rhinitis and increase in eosinophil counts in the other). Both patients improved after increase in corticosteroid dose or addition of mycophenolate mofetil.

Immediately prior to rituximab administration MPO-ANCA levels were high in two patients. In both of them ANCA titers have normalized within 3 months. Other laboratory parameters were unremarkable as all patients received continuous treatment with medium to high dose steroids.

2.5. Safety of treatment

In three patients rituximab was well-tolerated. One patient developed severe bronchospasm during two infusions that necessitated high dose intravenous glucocorticoid administration. The following infusions of rituximab after intensified premedication with intravenous prednisolone 500 to 1000 mg in this patient were not associated with side effects. Two patients presented with moderately severe purulent bronchitis that was treated with intravenous antibiotics in the hospital. In one patient prolonged maintenance treatment with rituximab was not associated with adverse events.

3. Discussion

Rituximab is currently approved for remission induction in GPA and MPA as in RITUXVAS and RAVE trials it was at least as effective as cyclophosphamide [13,14]. The efficacy of rituximab for maintenance of remission in GPA and MPA was recently confirmed in the prospective, randomized, active-controlled MAINRITSAN trial [15]. The evidence for efficacy and safety of rituximab in EGPA is limited and may be subject to selection and publication biases. GPA and MPA share many histopathologic and clinical features and were frequently studied together in clinical trials while EGPA differs from other ANCA-associated vasculutides in many respects.

We report six cases of successful rituximab administration in a cohort of 118 patients with EGPA. The indication for rituximab administration were the relapses of EGPA manifesting by severe lung disease and/or deteriorating peripheral neuropathy. All patients rapidly responded to treatment and achieved complete or incomplete remission within 3 to 6 months following rituximab infusion. The favourable effect of rituximab should not be overestimated as in two patients the attempts to reduce the dose or to discontinue corticosteroids leaded to minor relapse that required intensification of treatment (increase in corticosteroid dose or addition of mycophenolate mofetil). In a similar cohort ($n = 9$) Thiel et al. also showed high efficacy of rituximab in the treatment of refractory or relapsing EGPA [9]. Recently, Mohammad et al. reported 41 patients with EGPA treated with rituximab in 4 centers [10]. By 6 and 12 months, remission or partial response were achieved in 83% and 87% of patients respectively.

In one patient (No. 2) we used rituximab as a primary agent for induction of remission. This 43-year-old woman with MPO-ANCA-positive EGPA presented with lung disease, peripheral neuropathy and pericarditis. She responded well to rituximab 2 g after one cyclophosphamide infusion and achieved complete remission of EGPA at six months. In fact, initially we offered this patient to continue standard treatment but she declined and insisted on rituximab that was recommended by her private physician. She was