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Q1 Biological drugs in ANCA-associated vasculitis

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ABSTRACT

The anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitides granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA) and microscopic polyangiitis (MPA) constitute a wide spectrum of clinical manifestations of systemic vasculitis which may range from limited disease to organ or life-threatening disease. The introduction of biologics for the management of severe ANCA-associated vasculitis and severe, relapsing disease refractory to conventional immunosuppressants, has significantly improved the clinical prognosis of these autoimmune disorders. Rituximab, an anti-CD20 monoclonal antibody is licenced for remission induction in severe GPA and MPA and the management of severe relapsing, refractory GPA and MPA. Belimumab, an anti-B lymphocyte stimulatory monoclonal antibody is in clinical trials for the management of the ANCA-associated vasculitis GPA. Mepolizumab and Omalizumab are biologics which have been reported to be efficacious in refractory asthma associated with EGPA. The role of anti-TNF therapy and T cell targeting drugs in ANCA-associated vasculitis is less clear due to limited study data. This review will summarise the clinical trials and clinical practice use of biologic treatment strategies for the management of ANCA-associated vasculitis.

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1. Introduction

Granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA) and microscopic polyangiitis (MPA) are small vessel vasculitides associated with the presence of anti-neutrophil cytoplasmic antibodies to proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA) [1]. The clinical manifestations of granulomatosis with polyangiitis range from limited upper respiratory tract necrotising granulomatous inflammatory disease to severe lower respiratory tract, renal and nervous system vasculitis [2]. Microscopic polyangiitis involves necrotising systemic vasculitis of the respiratory tract, kidneys and nervous system without the development of granulomatous lesions [2]. Eosinophilic granulomatosis with polyangiitis clinical manifestations include asthma, nasal polyps, peripheral blood eosinophilia and systemic vasculitis of the respiratory tract, skin and nervous system [2]. The management of ANCA-associated vasculitis (AAV) is in accordance with the disease severity and is based on extensive clinical trial and clinical practice data. The categories of AAV severity defined by the European Vasculitis Study Group (EUVAS) are as follows: localised upper and/or lower respiratory tract disease without any other systemic involvement or constitutional symptoms; early systemic vasculitis without organ-threatening or life-threatening disease; generalised systemic vasculitis with renal involvement serum creatinine $<500 \mu\text{mol/l}$ (5.6 mg/dl) or other organ threatening disease; severe systemic vasculitis with renal involvement serum creatinine $>500 \mu\text{mol/l}$

(5.6 mg/dl) or other vital organ failure and refractory progressive disease unresponsive to glucocorticosteroids and cyclophosphamide. Biologic drugs have a role in the induction of clinical remission in severe organ-threatening or life-threatening ANCA-associated vasculitis and also for the management of severe relapsing, refractory disease. This review will summarise the clinical trials and clinical practice use of biologic treatment strategies for the management of ANCA-associated vasculitis.

2. Methodology

A review of the medical literature on the use of biologics for the management of ANCA-associated vasculitis was performed by a MEDLINE search for publications up to November 2014 containing a combination of the following keywords: 'ANCA associated vasculitis', 'abatacept', 'adalimumab', 'alemtuzumab', 'belimumab', 'biologics', 'biological drugs', 'Churg–Strass syndrome', 'etanercept', 'eosinophilic granulomatosis with polyangiitis', 'granulomatosis with polyangiitis', 'infliximab', 'mepolizumab', 'microscopic polyangiitis', 'monoclonal antibodies', 'omalizumab', 'rituximab', 'Wegener's Granulomatosis' with further selection of papers from the bibliographies of relevant publications.

3. Rituximab for the management of AAV

Rituximab is an anti-CD20 IgG1 chimeric, murine/human monoclonal antibody which was approved by the United States Food and Drug Administration (FDA) in 2011 for the management of the ANCA-associated vasculitides GPA and MPA. Prior to this approval, rituximab had been prescribed off-licence for over a decade for the management

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of severe AAV with numerous case reports, case series, retrospective and prospective clinical trials reporting significant remission rates in patients with severe, refractory relapsing disease [3–9]. The RAVE randomised controlled clinical trial of rituximab dosed at 375 mg/m² of body surface area weekly infusions for 4 weeks plus daily placebo cyclophosphamide compared with oral cyclophosphamide plus placebo rituximab infusions followed by azathioprine for induction of clinical remission in newly diagnosed AAV (GPA and MPA) or relapsing AAV (GPA and MPA) reported the clinical efficacy of rituximab as a remission induction agent in patients with severe AAV [10]. The RAVE trial data indicated that rituximab was not inferior to oral cyclophosphamide for clinical remission induction and was equally efficacious in severe renal disease and alveolar haemorrhage. However rituximab was reported to be more effective than oral cyclophosphamide in remission induction in patients with severe refractory relapsing disease. In addition there were no significant differences in adverse event rates between the rituximab and oral cyclophosphamide regimens [10]. The RITUXVAS trial data indicated that rituximab dosed at weekly infusions 375 mg/m² of body surface area for 4 weeks plus intravenous pulsed cyclophosphamide and glucocorticosteroids was as effective as intravenous pulsed cyclophosphamide and glucocorticosteroids for 3–6 months followed by azathioprine maintenance therapy in newly diagnosed AAV (GPA and MPA) patients with severe renal disease. Both therapeutic strategies resulted in similar rates of maintenance of clinical remission at 12 months post-induction therapy without any significant differences in adverse events [11]. Patients in the RAVE clinical trial were observed over 24 months after induction therapy and the long-term follow-up data showed that rituximab was equally as effective at induction and maintenance of clinical remission in AAV as standard immunosuppressant drug regimens [12].

The licenced dosing schedule for induction of disease remission and management of severe, relapsing AAV GPA/MPA is Rituximab IV 375 mg/m² body surface area weekly for 4 weeks, however an alternative schedule of Rituximab IV 1 g on day 1 and Rituximab IV 1 g on day 15 has been utilised in clinical practice and has been found to be clinically effective [6]. Since the FDA and European Medicines Evaluation Agency (EMA) approved rituximab, several guidelines and recommendations have been published.

Rituximab as first-line induction therapy for newly diagnosed severe GPA or MPA is recommended by the American College of Rheumatology (ACR), British Society of Rheumatology (BSR), The French Vasculitis Study Group (FVSG) in cases in which cyclophosphamide would be indicated but may be preferable in young women where cyclophosphamide may increase the risk of ovarian failure or in patients at increased risk of infection. In addition, rituximab is recommended for the management of severe relapsing GPA or MPA refractory to conventional immunosuppressant drugs including a complete course of pulsed intravenous cyclophosphamide [13,14]. Rituximab is also indicated as a therapeutic option in severe AAV patients with incomplete or no clinical response to intravenous cyclophosphamide or in whom cyclophosphamide is contraindicated [14].

Maintenance of clinical remission after rituximab induction therapy has been studied in retrospective and prospective studies and the conclusion drawn is that rituximab is efficacious as a maintenance therapy in patients with relapsing, refractory GPA [15–17]. A fixed-interval rituximab protocol in which a single 1 g infusion of rituximab is administered every 6 months for 2 years has been shown to reduce the rate of clinical relapse compared to rituximab re-treatment at the time of relapse in patients with severe relapsing, refractory AAV [16]. Rituximab has been reported to be a superior maintenance therapy to conventional immunosuppressant drugs in severe relapsing, refractory AAV in a retrospective study of 80 patients [17]. Furthermore, a randomised controlled prospective clinical trial that compared rituximab to azathioprine for maintenance of clinical remission (MAINRITSAN) reported the superiority of rituximab in reducing the frequency of major AAV relapses compared to azathioprine without significant differences in

severe adverse events in both treatment arms of the study [18]. In this study of 115 AAV patients, 3 in the rituximab maintenance therapy group (5%) had a clinical relapse whereas 17 patients in the azathioprine maintenance group (29%) had a clinical relapse at month 28 (hazard ratio for relapse 6.61; 95% confidence interval 1.56 to 27.96; $p = 0.002$) [18].

At present, rituximab is not recommended in eosinophilic granulomatosis with polyangiitis (EGPA) as a result of the paucity of robust clinical trial data to support its use as induction or maintenance therapy in EGPA. The off-licence use of rituximab in EGPA has been reported in a number of case reports and retrospective case series which have highlighted positive responses to rituximab in severe, refractory cases of EGPA which are MPO-ANCA positive with systemic vasculitis as the predominant clinical manifestation of active disease [14,16,19–26].

Biologic drugs are associated with infusion-related adverse events such as rash, pruritis, rhinitis, fever, chills, hypotension, headache, myalgia and arthralgia which may be minimised by the administration of antihistamine, paracetamol and corticosteroid pre-medication [10,11,15]. Severe immunosuppression post-B cell depletion therapy; a reduction in serum immunoglobulin levels; an increase in the incidence of opportunistic infections or reactivation of viruses; progressive multi-focal leuco-encephalopathy associated with reactivation of JC virus; allergic or anaphylactic reactions, are important adverse events which have been reported in the medical literature to be associated with the use of rituximab [10,11,16,17,27].

4. Belimumab for the management of GPA

Belimumab, a human monoclonal IgG1 antibody against B lymphocyte stimulator (B-Lys), is under investigation as a potential therapeutic option for the management of AAV. B lymphocyte stimulator is a cytokine which promotes the survival, maturation and differentiation of B cells and has been found to be elevated in the serum of AAV patients, in particular patients with GPA [28–30]. The BREVAS clinical trial is a phase III multi-centre, multinational, randomised, double-blind study to evaluate the efficacy and safety of belimumab in combination with azathioprine for the maintenance of remission in GPA and MPA [www.clinicaltrials.gov NCT01663623].

5. Mepolizumab for the management of EGPA

Mepolizumab (MPZ) is a humanised anti-interleukin 5 monoclonal antibody which was first reported to show clinical benefit in the management of eosinophilic granulomatosis with polyangiitis in a case report of refractory disease [31]. The majority of EGPA patients treated with infusions of Mepolizumab IV 750 mg every 4 weeks in 2 open-label clinical trials, achieved clinical remission and there was a significant corticosteroid-sparing effect of this biologic drug, however discontinuation of mepolizumab resulted in clinical relapse [32–34].

6. Omalizumab for the management of EGPA

Omalizumab is a humanised anti-IgE monoclonal antibody which has been reported to be effective in the management of severe refractory EGPA-related asthma in a case report of a patient who was treated with omalizumab subcutaneous (subcut) 300 mg every 2 weeks for 3 months [35]. Omalizumab subcut 300 mg every 2 weeks has been prescribed in a paediatric case of severe refractory EGPA with subsequent improvement in respiratory symptoms in a 9 month follow-up period [36]. Clinical improvement and reduction in the peripheral eosinophil count have been reported in 2 patients with refractory EGPA treated with omalizumab subcut 150 mg every 4 weeks for 18 months [37].

7. Anti-TNF therapy for the management of AAV

7.1. Etanercept

Etanercept (ETN), a p75 Fc fusion protein against tumour necrosis factor alpha (TNF- α), is a biologic drug which has been studied in AAV. A randomised controlled trial (WGET) compared etanercept subcut 25 mg twice weekly plus standard therapy to placebo plus standard therapy for maintenance of clinical remission in GPA patients [38]. There were no statistically significant differences in remission maintenance rate, low disease activity maintenance rate or the relative risk of disease relapse between the 2 treatment arms of the WGET. Of note is the higher incidence of solid malignancies reported in the etanercept group compared to the placebo group [39,40].

7.2. Infliximab

Infliximab (IFX) is a chimeric murine/human monoclonal antibody against TNF- α which has been used in the management of AAV (GPA and MPA). Case series of AAV patients treated with infliximab have reported clinical remission in the majority of patients treated with infliximab and a low relapse rate [41–45]. However an open-label cohort study of infliximab plus standard therapy in AAV did not report clinical benefit of infliximab over standard therapy [46]. A prospective randomised controlled study of patients with severe refractory GPA compared infliximab and rituximab for remission induction found IFX and RTX to be effective in remission induction however the general data trended towards favouring rituximab over infliximab and all infliximab non-responders were switched to rituximab [47]. This data taken together with the WGET study results has largely resulted in the abandonment of etanercept and infliximab in ANCA vasculitis.

7.3. Adalimumab

Adalimumab (ADA) is a humanised anti-TNF- α monoclonal antibody which has been studied in AAV with renal involvement in a phase II open-label prospective study. Adalimumab subcut 40 mg every 2 weeks plus pulsed intravenous cyclophosphamide compared to pulsed intravenous cyclophosphamide found similar efficacy in remission induction and similar adverse events however the adalimumab group achieved a greater reduction in glucocorticosteroid doses [48].

8. Anti-T cell therapy for the management of AAV

8.1. Alemtuzumab

Alemtuzumab is a humanised anti-CD52 monoclonal antibody (CAMPATH-1H) capable of selectively depleting the peripheral circulation of T lymphocytes, monocytes and macrophages. Alemtuzumab has been studied in a small uncontrolled trial of AAV patients in whom all immunosuppressant drugs had been discontinued except prednisolone <10 mg/day. Alemtuzumab was administered on consecutive days at doses of 4 mg, 10 mg, 40 mg and 40 mg and patients were followed up for an average of 5 years. The majority of patients (85%) achieved clinical remission however a significant proportion of these patients relapsed (72%) at a median time interval of 9 months after completion of therapy. Adverse events such as severe infections, malignancy and Grave's disease were reported in the alemtuzumab treated patients [49].

8.2. Abatacept

Abatacept is a fusion protein composed of the Fc region of IgG1 fused to the extracellular domain of CTLA-4 which inhibits T cell costimulation. An open-label study of AAV patients with mild relapsing

GPA reported remission induction in the majority of patients (80%) and overall good tolerance [50].

9. Conclusion

Biologic drugs have an important role to play in clinical remission induction and maintenance of remission in severe ANCA-associated vasculitis. Rituximab is indicated for the induction of disease remission and management of severe, relapsing GPA/MPA with data suggesting a role of pre-emptive fixed-interval rituximab maintenance of remission therapy. Belimumab is undergoing clinical trials for efficacy and safety in AAV. Mepolizumab and Omalizumab have shown potential as future therapeutic options in the management of severe refractory EGPA-associated asthma. Anti-TNF- α biologic agents are at present not recommended for remission induction therapy in AAV however case reports and non-randomised open-label studies have provided data which could justify the use of these biologics in certain relapsing refractory cases. The limited data on alemtuzumab and abatacept suggest possible benefits however further studies are required to determine the safety and efficacy of these biologics.

In conclusion the potential benefits, adverse effects and risks of biologic drugs in the management of ANCA-associated vasculitis should be considered prior to the administration of these drugs for the induction and maintenance of disease remission.

Disclosures

PMKL has no disclosures. DDC has participated in clinical trials sponsored by Human Genome Sciences and GlaxoSmithKline and has consulted for Roche pharmaceuticals.

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