Full Review

B-cell therapy in antineutrophil cytoplasmic antibody-associated vasculitis

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ABSTRACT

Until recently, standard of care for patients with generalized or severe antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) has consisted of an induction regimen with cyclophosphamide (CYC) and corticosteroids followed by maintenance treatment with azathioprine. This regimen is associated with significant toxicity resulting in considerable morbidity and mortality whereas relapses are still not infrequent. In two controlled trials, the Rituximab in ANCA-associated Vasculitis study (RAVE) and the RITUXVAS trial of the European Vasculitis Study Group (EUVAS), rituximab (RTX) proved non-inferior to CYC for induction of remission. In addition, outcome at 18 months for the RAVE trial and 12 months for the RITUXVAS trial showed that RTX without maintenance treatment was as efficacious as CYC followed by azathioprine maintenance. To prevent relapses, which occur particularly in patients positive for PR3-ANCA, 500 mg RTX given every 6 months was shown to be superior to azathioprine in a French study. Thus, RTX is a new and promising therapeutic armamentarium for AAV although long-term safety has still to be established.

Keywords: ANCA-associated vasculitis, azathioprine, cyclophosphamide, maintenance treatment, rituximab

INTRODUCTION

The first report on autoantibodies reacting with cytoplasmic constituents of neutrophils as a diagnostic tool in patients with granulomatosis with polyangiitis (GPA, formerly Wegener’s granulomatosis) already indicated that B lymphocytes could play a role in the pathogenesis of this disease [1]. The autoantibodies were not only sensitive and specific for GPA, but their levels were higher during active disease. The target antigens of these now called antineutrophil cytoplasmic antibodies (ANCA) have been further characterized as proteinase-3 (PR3), primarily associated with GPA, and myeloperoxidase (MPO), more associated with microscopic polyangiitis (MPA) (reviewed in [2]). The high specificity of PR3-ANCA and MPO-ANCA for the associated diseases, in combination with a high degree of sensitivity, has led to the collective designation of these diseases as ANCA-associated vasculitides (AAV) in the recently revised Chapel Hill Consensus Conference classification of vasculitides [3]. The AAV include, besides GPA and MPA, renal limited pauci-immune crescentic glomerulonephritis and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss Syndrome) [3]. In the latter condition only ~40% of patients are ANCA-positive but this subcategory is primarily characterized by vasculitic lesions whereas the ANCA-negative EGPA-patients are more characterized by lesions dominated by tissue infiltration with eosinophils [4]. Genome-wide association studies (GWAS) showed that PR3-ANCA and MPO-ANCA, even more than their associated diseases, have different genetic backgrounds suggesting not only that PR3-ANCA vasculitis and MPO-ANCA vasculitis are different diseases but also that the autoantibodies are involved in the pathogenesis of these diseases [5]. Indeed, data from in vitro and in vivo experimental studies have provided evidence for the pathogenicity of ANCA (reviewed in [6]). This is particularly true for MPO-ANCA as based on experimental models in rats and mice [7] and the observation of vasculitis in a neonate via transplacental transfer of maternal MPO-ANCA [8]. For PR3-ANCA, evidence for its pathogenicity is less convincing regarding the granulomatous inflammation characteristic for GPA/PR3-ANCA-associated vasculitis. Here, T-cell-mediated pathogenetic pathways appear
B-CELL DEPLETION IN REFRACTORY AAV—OPEN SERIES

B-cell depletion using the chimeric anti-CD20 monoclonal antibody rituximab (RTX) was first performed in patients with refractory GPA. A total of 29 patients, both with systemic and localized granulomatous disease, all responded to RTX in combination with corticosteroids [15–17]. These data from the Mayo Clinics, USA, were confirmed by a report from the UK describing a series of 65 patients with refractory AAV treated with RTX of whom 49 (75%) reached complete remission and 15 partial remission [18]. A later report from the Mayo Clinics on 53 patients with refractory GPA treated with RTX also showed the efficacy of RTX in inducing remission [19]. Data from Bad Bramstedt, Germany, on 59 patients with refractory GPA treated with RTX reported complete remission in only 6 patients and partial response in 30 patients [20]. Patients with predominantly granulomatous manifestations responded less favourably than patients with primarily vasculitic presentations. In all series, relapses were common, occurring in up to 50% of patients. Relapses were associated with B-cell recovery and rise in ANCA-levels in the series from the Mayo Clinics, but less clearly in the series from the UK [18, 19].

B-CELL DEPLETION IN GENERALIZED AAV—CONTROLLED STUDIES

The favourable results of RTX in patients with refractory AAV led to the design of two randomized controlled studies with RTX in patients with generalized AAV. The RTX in the ANCA-associated vasculitis (RAVE) study tested the hypothesis that RTX, in combination with corticosteroids, is as effective as (oral) CYC, in combination with corticosteroids, for induction of remission in patients with ANCA-positive severe AAV, either GPA or MPA, with a Birmingham Vasculitis Activity Score (BVAS) of at least 3 [21]. Patients were randomized for one of the two arms and stratified for PR3-ANCA and MPO-ANCA. Primary end point was remission of disease without the use of prednisone at 6 months. Sixty-three out of 99 patients in the RTX arm reached the primary end point (64%) versus 52 out of 98 patients in the CYC-arm (53%), indicating that RTX is not inferior to CYC for inducing remission (P < 0.001). Interestingly, RTX was more effective than CYC in the patients included with relapsing disease (34 out of 51 patients versus 21 out of 50 patients reached the primary end point, P = 0.01). Patients in the RTX arm did not receive any maintenance treatment whereas patients in the CYC arm received azathioprine for maintenance of remission. At 18 months after enrolment, no differences in relapse rate were seen between both arms (39% of patients in the RTX arm versus 33% in the CYC–azathioprine arm were still in complete remission) [22]. Relapses occurred more frequently in PR3-ANCA patients as compared with MPO-ANCA patients. There were no differences between both arms in adverse events.

The RITUXVAS trial, initiated by EUVAS, included patients with newly diagnosed AAV and (severe) renal involvement. Forty-four patients were randomized, in a 3:1 ratio, to either RTX, with two intravenous pulses of CYC, or to intravenous CYC for 3–6 months followed by azathioprine, with prednisone tapering to 5 mg daily in both arms [23]. Primary end point was sustained remission at 12 months. Furthermore, 76% of patients in the RTX-group versus 82% in the control group were still in remission, in this study defined as absence of disease activity but being off prednisone was not required, P = 0.77. No differences in adverse events including mortality were seen between both arms.

The results of both studies demonstrate that RTX is not inferior to CYC for induction of remission, even in patients with severe renal involvement. RTX may be more efficacious than CYC in patients with relapsing disease. Data from the RAVE study suggest that the effect of RTX is long lasting as the percentage of patients in complete remission at 18 months did not differ between the group of patients treated with RTX only without maintenance treatment versus the group that received CYC for induction of remission followed by maintenance treatment with azathioprine. However, in both groups relapses were frequent. This might, at least in part, be related to the definition of complete remission that required the absence of use of steroids. The Assessment ofPrednisone in Remission Trial (TAPIR, NCT01940094) is currently testing whether tapering prednisone down to 5 mg/day results in a more durable remission than tapering prednisone to 0 mg/day. Second, the high relapse rate as observed in the RAVE study asks for maintenance treatment. It would be desirable to have biomarkers that predict relapsing disease. The RAVE study demonstrates that PR3-ANCA patients relapse more frequently than MPO-ANCA patients irrespective of the treatment arm. In addition, relapses were rare in the absence of both B cells and ANCA but new development or rising titres of ANCA did not reliably predict relapses [22].
**MAINTENANCE TREATMENT FOLLOWING INDUCTION OF REMISSION WITH RTX**

As mentioned, the 18 months outcome data of the RAVE study showed that the rate of persistent remission did not differ between the RTX arm without maintenance treatment and the CYC arm with azathioprine maintenance [22]. However, a single-centre retrospective study indicated that, after induction of remission with RTX, relapse-free survival was significantly higher in patients who received a conventional maintenance agent as compared with no additional immunosuppressive agent [24]. What about the use of RTX for maintaining remission? A retrospective analysis of recurrent RTX administration after induction of remission, that is 1 g of RTX every 4 months, suggests that remission can be maintained using such a regimen [25]. The French Vasculitis Study Group recently presented data of the MAINRITSAN study [26]. In this study on 115 patients, remission was induced with a CYC–glucocorticoid regimen followed by maintenance treatment with daily azathioprine for 22 months in 58 patients and with RTX, 500 mg at days 0 and 14 and at months 6, 12 and 18, in 57 patients. Three patients relapsed in the RTX arm (5%) and 17 in the azathioprine-arm (29%) without any difference in adverse events. EUVAS, together with the Vasculitis Clinical Research Consortium (VCRC), has started the RITAZREM study on 160 patients that compares RTX (1000 mg every 4 months) with azathioprine (or methotrexate in case of intolerance to azathioprine) for maintenance of remission. The question is still open what the interval of RTX administration for maintenance treatment should be and whether this should be based on biomarkers. For this reason, the French Group has started a second study with RTX for maintenance treatment in which in one arm treatment will be based on ANCA and number of B cells whereas in the other arm a fixed regimen of RTX administration will be applied (MAINRITSAN II, NCT 01731561).

**INTERVENTION IN B-CELL ACTIVATION**

As mentioned before, B-cells appear to be directly involved in the pathogenesis of AAV. B-cell activation resulting in the production of pathogenic IgG-class autoantibodies is a complex process. Besides cognate interaction between B- and T-cells, soluble factors play a role in this process. So, targeting T-cells could be an approach to prevent B-cell activation. This approach was first used to treat a patient with intractable systemic vasculitis who received the combination of a humanized anti-CD52 antibody (CAMPATH-1H) and a rat anti-human CD4 antibody resulting in complete remission with long-lasting suppression of B-cell responsiveness [27]. The humanized monoclonal antibody directed against CD52 (alemtuzumab, CAMPATH-1H) depletes circulating lymphocytes and macrophages. Walsh et al. [28] reported the long-term follow-up of 71 patients with relapsing or refractory AAV treated with CAMPATH-1H. Sixty out of these 71 patients came into remission but 43 patients relapsed and 31 patients died with a median survival time of 106 months. Adverse effects were frequently seen: infection in 28 patients, malignancy in 3 patients and 8 developed thyroid disease. So, these retrospective data indicate the potential of alemtuzumab to induce remission but the high relapse rate and the severe adverse effects do not support its current use for standard induction of remission in AAV.

Another approach is blocking the interaction between B- and T-cells required for B-cell activation. Abatacept consists of the ligand-binding domain of CTLA4 coupled to the modified Fc domain of IgG1 and inhibits T-cell activation by blocking the interaction between CD28 on the T-cell and B7 on the antigen-presenting cell/B cell. Abatacept has been used in an open label trial in 20 patients with non-severe relapsing GPA [29]. Eighteen patients showed improvement, 16 reached remission and 14 reached common closing with a remission duration of a median of 14.4 months. Abatacept was well tolerated and the majority of patients were able to reduce corticosteroids. A phase III trial (ABROGATE) with abatacept for induction of remission is underway.

As discussed before, B-cell depletion using RTX is useful not only for induction of remission but also, in all likelihood, for maintaining remission. However, long-term RTX treatment is associated with potential side effects. Several studies have shown that B-cell depletion is associated with an increase in levels of B-cell-activating factor (BAFF), a cytokine that is crucial for B-cell survival [30–33]. Intervention in BAFF and its receptors could be an alternative for RTX in maintaining remission in AAV.

**IMMUNODEFICIENCY INDUCED BY B-CELL DEPLETION**

B-lymphocyte depletion by RTX appears not to be associated with an increase of serious adverse events compared with standard treatment with CYC and azathioprine in AAV [22, 23]. The number of serious infections was comparable in both randomized trials [22, 23], however, in the RAVE trial fewer episodes of pneumonia were observed following B-lymphocyte depletion as compared with standard treatment. Leukopenia was less frequent after RTX, but was not associated with pneumonias or other infectious episodes. Following RTX, nearly all patients reconstitute their peripheral-blood B-lymphocyte numbers by 18 months. In the RAVE trial, serum levels of IgG, IgA and IgM, as well as the number of patients with low levels of immunoglobulin, did not differ significantly between the two groups and low IgG levels were not associated with severe infections [22]. This confirms the long-term experience with RTX in other autoimmune diseases such as rheumatoid arthritis [34]. In vivo antibody responses have not yet been studied following B-cell depletion in AAV. Small studies in other autoimmune diseases showed a profound effect on in vivo primary and secondary antibody responses as long as B-lymphocyte depletion persists. A weak primary IgM response was elicited to a neoantigen following RTX suggesting that some marginal zone B-lymphocytes resist RTX despite their expression of CD20 [35]. However, the absence of class-switching to IgG pointed to the sensitivity of
germal centre B lymphocytes to RTX. A memory B-lymphocyte response could not be generated in the presence of RTX [36]. The ability to mount specific antibody responses remained impaired for at least 6 months following RTX. Even T-lymphocyte responses may be reduced in parallel possibly due to the depletion of antigen-presenting B lymphocytes [35, 36]. Hence, RTX induces a moderate and transient immunodeficiency followed by recovery upon B-lymphocyte reconstitution. The effect of recurrent long-term administration of RTX on the immune system has to be awaited.

CONFLICTS OF INTEREST STATEMENT

None declared.

REFERENCES


Received for publication: 26.11.2014; Accepted in revised form: 10.2.2015