autoantibody specificity for myeloperoxidase or proteinase 3 in disease recognition and prognosis. Arthritis Rheum 2012; 64: 3452–3462

doi: 10.1093/ndt/gfv217

Opponent’s comments

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We agree with Dr Specks that rituximab increases our therapeutic armamentarium in the treatment of patients with ANCA-associated vasculitis, especially those with a relapsing and refractory disease course. In contrast, we believe that a general recommendation to initiate rituximab as ‘first-line treatment’ is not supported by the randomized controlled trials leading to approval.

Follow-up data of the Rituximab in ANCA-associated Vasculitis (RAVE) study did not show superiority of rituximab compared with the control group. Of importance, the authors of the RAVE trial did not provide concise data on patients with newly diagnosed ANCA-associated vasculitis after 18 months of follow-up. Overall, the primary end point was met by 39% in the rituximab and 33% in the control group. Patients included with a relapsing disease course achieved the primary end point in 37 and 20%, respectively. This may indicate that newly diagnosed patients in fact had a numerically better outcome after 18 months in the control group compared with the rituximab treated patients. This would be in line with the observation after 6 months when 63% in the control group achieved the primary end point compared with 61% in the rituximab group [1, 2].

Our aim in the ‘con’ debate was to focus on ‘primary treatment’ of rituximab and most post hoc analyses of the RAVE trial included both newly diagnosed and relapsing patients. Since a majority of patients with a relapsing disease course in the RAVE trial received cyclophosphamide prior to relapse (82% in the rituximab and 74% in the control group) which indicate a failure of this agent to achieve long-term remission, validity of these reports is questionable. A recent post hoc analysis revealed superiority of rituximab in PR3-positive patients to achieve complete remission after 6 months, but this effect ceased after 18 months (P = 0.39). No information about disease course prior to enrollment is provided and we believe recommendation of rituximab as ‘first-line treatment’ in this indication needs more evidence.

Notably, patients receiving rituximab in the Rituximab Versus Cyclophosphamide in ANCA-Associated Vasculitis (RITUXVAS) trial had two concomitant cyclophosphamide pulses and plasma exchange was allowed [3]. Since patients with respiratory failure were excluded from both trials and concomitant immunosuppression may have influenced results in the RITUXVAS trial, rituximab’s efficacy in treatment-naive patients with severe disease forms has to be assessed. In conclusion, several more investigations have to be conducted to recommend rituximab as the preferable choice in the ‘first-line treatment’ of ANCA-associated vasculitis.

We remain concerned about the relatively low rates of remission and high glucocorticoid exposures with either RTX or CYC induction and feel that neither provides optimal therapy. There is also a paucity of information on RTX induction in patients with low glomerular filtration rate. Observational studies have indicated acquired immunodeficiency is an important late adverse effect of RTX with 4.2% requiring immunoglobulin replacement [4]. Uncertainty over the long-term outcomes of these patients and cost of replacement need to be considered when balancing the attractiveness of RTX as compared with CYC.

REFERENCES

Experience with rituximab in patients with new ANCA-associated vasculitis (AAV) is still very limited, especially in patients with severe (organ- or life-threatening) AAV. Rituximab may be more effective in anti-PR3 AAV, but potentially less effective in some granulomatous manifestations of AAV. We do not know what the response is to rituximab on the tissue level. Rituximab induction needs to be followed by maintenance treatment, and potentially very long rituximab maintenance may result in higher risk of rituximab-related complications (e.g. decrease in IgG levels). Long-term experience with rituximab in AAV is insufficient. Treatment with rituximab is more expensive than the standard treatment with cyclophosphamide and corticosteroids and seems to be cost-effective only in patients primarily treated with cyclophosphamide. Rituximab can be used in some newly diagnosed patients with AAV (e.g. women with child-bearing potential, or patients with active vasculitis and severe infection), but with the available information, it may be too early to use it as a first-line treatment in all new AAV patients.

Until the end of the last century all patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) were treated with conventional standard immunosuppression (cyclophosphamide with gradually tapered corticosteroids as an induction and azathioprine with low-dose corticosteroids as a maintenance treatment) with remission rates frequently exceeding 90% [1], but still with high relapse rate (50% within 5 years), relatively high long-term mortality (5-year mortality of 22% in patients recruited to European randomized controlled trials [2]) and high short-term mortality especially in patients with severe renal (1-year mortality 25% [3]) and lung involvement, at least partly related to the toxicity of the treatment.

Major attention was thus paid to minimizing or completely avoiding the exposure to cyclophosphamide and corticosteroids and at the same time keeping the high efficacy of this treatment. Unfortunately, lower cumulative dose of cyclophosphamide and corticosteroids during the first 6 months of treatment seemed to be always associated with higher risk of relapses during the long-term follow-up, especially in patients with anti-PR3 antibodies [1, 4], some of these relapses being organ- or even life-threatening, or at least further increasing the accumulated organ damage. On one hand, the long-term outcome of the patients with AAV has definitely improved [5–7], but, on the other hand, the risk of increasing lifelong exposure to both corticosteroids and cytotoxic drugs due to still high relapse rate despite maintenance treatment, especially in anti-PR3-positive patients, has remained a difficult therapeutic challenge.

The only way to completely escape from this vicious cycle of early (putative) undertreatment resulting in (repeated) relapses with finally similarly high cumulative doses of both cyclophosphamide and corticosteroids was to find some new potentially more specific and less toxic mode of treatment. Very positive experience with rituximab in a small series of patients with mostly refractory or relapsing ANCA-associated vasculitis [8].