of five patients with Behçet’s syndrome had clinical improvement after rituximab with a full remission in one. Two have remained controlled on repeat rituximab but two have required other therapies. Experience in large vessel vasculitis, cryoglobulinaemia, polyarteritis nodosa, Henoch-Schönlein purpura and urticarial vasculitis has been too limited to draw meaningful conclusions.

Conclusions

The addition of rituximab to the management of AAV has been of major benefit to our patients permitting improved disease control and reduced immunosuppressive and glucocorticoid exposure. The published experience has been sufficient to enable treatment recommendations that emphasise the place of rituximab for relapsing or refractory disease and those in whom cyclophosphamide is contra-indicated [11]. Although we have found associations between B cell return and ANCA rises with relapse, there is considerable variability and some relapses are seen without changes in these indices. Falling immunoglobulin levels are a concern as patient exposure to rituximab increases, that will limit further use of this agent in such patients.

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References


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S3. Rituximab for ANCA-associated vasculitides: The French experience

Introduction

Rituximab is a chimeric murine–human monoclonal IgG1 antibody directed against CD20 expressed on lymphocytes. It was used to treat antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) for the first time in 2001 [1]. In France, rituximab treatment of refractory AAV started in 2002. Rituximab has been given to increasing numbers of patients, especially after the publication of the two randomized–controlled trials showing that it was as effective as cyclophosphamide (CYC) at inducing AAV remission [2,3]. We describe the French experience with rituximab in two situations: first, in prospective trials organized by the French Vasculitis Study Group (FVSG), and, second, in routine hospital practice, reported as retrospective studies.

Prospective studies organized by the French Vasculitis Study Group (FVSG)

The first randomized–controlled trial included 17 patients and was conducted between 2004 and 2007 [4]. It compared rituximab to infliximab for remission induction of refractory granulomatosis with polyangiitis (Wegener’s) (GPA). The rituximab protocol was one infusion (375 mg/m²) every week for 4 weeks, followed, when clinical improvement was observed at month 2, by an infusion of 375 mg/m² at months 4, 8 and 12. The infliximab protocol was 3 mg/kg on days 1 and 14. If complete remission was achieved, patients received 3 mg/kg every month, but if the remission was only partial, patients were given 5 mg/kg every month. At month 12, among the eight patients
receiving rituximab, four were in complete remission, one in partial remission, one had died and two were therapeutic failures. Among the nine patients on infliximab, two were in complete remission, one in partial remission, one had died and five were non-responders. That was the first trial to investigate rituximab and its results indicated the potential contribution of this biologic in the treatment for refractory AAV.

The FSVG’s main research axis is using rituximab as AAV maintenance therapy. The MAINRITSAN study (NCT00748644) was completed in October 2012. That open-label randomized–controlled trial, conducted on 117 AAV [GPA or microscopic polyangiitis (MPA)] patients, compared azathioprine (2 mg/kg/day) to rituximab (500 mg on days 1 and 15) and then every 6 months (five infusions). At 28 months, 5% of the rituximab-treated patients had suffered a major relapse versus 25% of those taking azathioprine. No major safety issue was raised. For that trial, a rituximab dose of 500 mg was chosen for several reasons: fewer side effects were expected by lowering the dose, use of less rituximab obviously lowered the cost of treatment and because usual doses (e.g. 1 g or 375 mg/m²) had been determined empirically.

An ongoing randomized trial (MAINRITSAN 2: NCT01731561) is comparing two rituximab-administration strategies for maintenance therapy. In one arm, patients receive the same rituximab regimen as in the original MAINRITSAN study, while in the second arm, after a first 500-mg infusion, rituximab is given again only if a patient’s CD19 count is > 0/mm³ or the ANCA titer becomes positive or rises.

The French experience reported in retrospective studies

As for other investigators, first reports on small numbers of patients focused on rituximab efficacy at inducing remission of relapsing or refractory AAV. In a study on eight patients followed for 6 months [5], three achieved complete remission, three relapsing or refractory AAV. In a study on eight patients followed patients focused on rituximab efficacy at inducing remission of AAV, the infectious complications of RTX are frequent, ranging from 7 to 28.9% (2,10). In our 80-patient study, 12 (15%) severe infectious complications were reported and led to four (5%) deaths. Other complications have been reported, e.g. macular edema [12].

Another study evaluated rituximab as maintenance therapy [13]. Among the 28 patients who received a median of 4 rituximab infusions, only two have relapsed, with a median follow-up of 38 months since diagnosis. Rituximab efficacy against GPA and MPA has been demonstrated but not for eosinophilic granulomatosis with polyangiitis (Churg–Strauss) (EGPA). Some patients, particularly those with renal involvement, might respond better than others with granulomatous disease (personal data), but no study has examined this possibility. However, two severe allergic manifestations (asthma) after rituximab infusions have been described [14].

Conclusion

Rituximab efficacy for induction remission and as maintenance therapy of GPA and MPA has been demonstrated. The addition of this biotherapy to AAV management is a major benefit to patients, particularly those with refractory or relapsing disease and already exposed to high cumulative cyclophosphamide doses, or for women < 40 years old to avoid cyclophosphamide-related ovarian failure. Nevertheless, rituximab was not superior at inducing AAV remission [2], was not compared to cyclophosphamide in patients with acute renal failure or severe granulomatous disease, and had no impact on the frequency of infectious complications. Under the auspices of FVSG, we are devising recommendations determining rituximab indications and the modalities of its use, particularly for infectious complications: systematic vaccinations, immunoglobulin dosages and co-trimoxazole prophylaxis.

Because of infectious concerns and rituximab efficacy even at a low dose (500 mg), we think that its future use means lower doses to a large AAV population.

Disclosure of interest

Loic Guillemin is member of the Scientific Council of the registry on Autoimmune Diseases in France. Roche pharmaceuticals provided in part rituximab for prospective trials in systemic vasculitis.

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References

L13. Apoptosis, Apoptotic cell clearance and resolution of inflammation

The resolution of inflammation is increasingly being recognised as an active and manipulatable phenomenon that could lead to the identification of novel therapeutic targets for the treatment of both acute and chronic inflammatory diseases [1–5]. Inflammatory leukocytes, especially granulocytes and macrophages, have evolved to be efficient cells for host defence in the fight against continuous invasion by organisms such as bacteria, parasites, fungi and viruses. However, excessive leukocyte accumulation, dysregulated leukocyte activation and/or failed clearance of effete cells will result in cellular and tissue damage occurring in tissues affected by chronic inflammatory diseases (e.g. vasculitis, rheumatoid arthritis, bronchitis, inflammatory bowel disease, cardiovascular disease, etc.) [6–10]. The recent focus, by my group and others, on the processes and mechanisms governing the resolution of inflammation has identified new potential pharmacological intervention strategies.

The process of catabasis, defined as a return to normal cellular and tissue homeostasis, during an episode of inflammation involves the active process of resolution. The cellular processes occurring during inflammation resolution include a form of programmed cell death commonly referred to as apoptosis and non-phlogistic phagocytosis of apoptotic cells by phagocytes (e.g. macrophages and dendritic cells) often called efferocytosis [1–5]. These processes, if executed in controlled fashion, result in attenuation of inflammation as a consequence of:

- the termination of inflammatory cell responsiveness occurring during apoptosis and;
- the phagocytosing cells changing from a pro-inflammatory to a more anti-inflammatory or pro-resolution phenotype.

Thus, pharmacological interventions which induce granulocyte (neutrophil or eosinophil) apoptosis resulting in non-inflammatory macrophage efferocytosis is an attractive therapeutic strategy [5,11]. An example of such an approach includes evidence derived from in vitro human cellular work and animal (mouse and zebrafish) in vivo experiments showing that cyclin-dependent kinase (CDK) inhibitor drugs promote resolution of inflammation. These drugs, which are under development and undergoing clinical trials for a variety of cancers, induce profound concentration- and time-dependent human neutrophil and eosinophil apoptosis [12–14]. Importantly however, when CDK inhibitor drugs are administered once inflammation has been established in a variety of mouse models, they drive caspase-dependent granulocyte apoptosis to promote inflammation resolution [12,14,15]. The specific molecular mechan-