Short Communication

Rituximab in the Management of Rheumatoid Arthritis: Current Practice and Future Developments

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Abstract

Rituximab is a chimeric human-mouse monoclonal antibody directed against the CD20 antigen on B-cells surfaces that leads to the elimination CD20-positive B-cells through several mechanisms of action. Rituximab arthritis (RA) is a chronic, autoimmune inflammatory disease characterised by a symmetrical inflammatory polyarthritis and has a number of extra-articular manifestations. B-cell depletion is a therapeutic strategy for the treatment of RA as B-cells are thought to have a role in its immunopathogenesis. Clinical trials have demonstrated that rituximab improves the clinical features of RA and also slows the rate of progression of radiological joint damage when given alongside methotrexate. Several evidence-based guidelines have been developed to regulate the use of rituximab with regards to its efficacy, safety, tolerability and cost-effectiveness. It remains a well-tolerated treatment but there is a need for further research to explore reduced dose regimens which would have several advantages both for the patient and the healthcare provider. As the patent expires for rituximab's originator medicine (MabThera®, Rituxan®), rituximab biosimilars have been developed, providing more treatment options for patients with RA and greater commercial competition for stakeholders. As we transition to biosimilar use in RA, it is important to involve patients in decision-making with regards to their treatment and exercise pharmacovigilance as new medicinal products join conventional treatments in the management of RA.

INTRODUCTION

Rituximab is a biological medication that is utilised in the therapy for diseases associated with B-cell disorders such as haematological malignancies, and autoimmune conditions like RA, connective tissue disease, and multiple sclerosis. RA is a chronic, autoimmune inflammatory disease characterised by a symmetrical inflammatory polyarthritis. RA also has the potential to cause a number of extra-articular manifestations. RA typically affects small joints although it may affect any synovial joint. It can lead to bone erosions, joint damage and destruction, and can affect a patient’s function and quality of life [1].

MECHANISM OF ACTION OF RITUXIMAB IN RA AND KEY CLINICAL TRIALS

Rituximab is a chimeric human-mouse monoclonal antibody directed against the extracellular domain of CD20 antigen on B-cells. It can cause B-cell elimination via a number of mechanisms including complement-mediated lysis, antibody-dependent cell-mediated cytotoxicity, or apoptosis [2]. Although the precise contribution of B-cells to the immunopathogenesis of RA is not yet fully understood, B-cells act as antigen-presenting cells, secrete pro-inflammatory cytokines such as Tumour necrosis Factor-α (TNF-α), produce rheumatoid factor and other autoantibodies such as anti-Cyclic Citrullinated Peptide (anti-CCP Ab) and activate T-cells. [3,4]. T-cell activation is thought to be involved in the pathogenesis of RA and eradication of B-cells may remove one source of antigen-presenting cells that maintains this activation. It therefore follows that B-cell depletion is a potential therapeutic strategy for the treatment of RA. [5-7] in 1999, Protheroe et al., published a case report of a patient with an inflammatory arthritis who developed a non-Hodgkin’s lymphoma. The inflammatory arthritis remitted after B-cell depletion therapy with rituximab for the patient’s lymphoma [8]. A number of small case series followed this case report and led to the development of clinical trials that established the therapeutic efficacy of rituximab in RA. In 2004, Edwards et al published an industry funded randomised, double-blind, placebo controlled, parallel group study designed to evaluate the efficacy and safety of rituximab alone or in combination with either cyclophosphamide or methotrexate (MTX) in patients with active RA [9]. The primary endpoint of the study was the proportion of patients with an ACR50 response at week 24. The American College of Rheumatology (ACR) response criteria take into account both physician and patient assessment of global disease activity, the level of an acute phase reactant (ie. CRP) and physical disability (as measured by a Health Assessment Questionnaire). The ACR response may be classified as ≥ 20%, ≥50% and ≥70%. In this trial, 43% of patients receiving rituximab and MTX met the primary endpoint compared to 13% of the control group (MTX alone) (p=0.005). In 2006, Emery et al published a phase IIb randomised, double blind, placebo-controlled, dose-ranging trial (DANCER) [10]. In this study, patients were randomised to receive one of two different rituximab regimens (1000mg x 2 or 500mg x 2) or placebo and all treatment arms received weekly MTX. The primary endpoint was the proportion of
patients achieving ACR20 response at week 24. Both rituximab regimens were found to be superior to placebo (p<0.0001), although the rituximab 1000mg x 2 regimen showed a trend towards improved secondary endpoints (ie. ACR70 response). The efficacy of rituximab was shown to be independent of the administration of oral steroids although premedication with IV methylprednisolone reduced the incidence and severity of infusion related reactions. In 2006, a phase III study by Cohen et al on the Randomised Evaluation of Long-term Efficacy of rituximab in RA (REFLEX) concluded that a single course of rituximab (1000 mg on days 1 and 15), in combination with MTX and glucocorticoids produced significant clinical and functional benefits at 24 weeks in patients with active RA who have had an inadequate response to one or more TNF-α inhibitors. 51% of patients in the rituximab group met the primary endpoint of achieving an ACR20 response at week 24 compared to 18% of the placebo group. (p< 0.0001) [11]. Follow-up data from the REFLEX study suggested that in patients with an inadequate response to TNF-α inhibition, treatment with rituximab in combination with MTX is associated with significant and sustained inhibition of radiographic joint damage. [11,12]. The SERENE study published in 2010 found that rituximab in combination with MTX was an effective first line biologic therapy in patients with an inadequate response to MTX [13].

CURRENT RECOMMENDATIONS FOR THE USE OF RITUXIMAB IN RA

Rituximab has been approved by the US Food and Drug Administration and by the European Medicines Agency for the treatment of patients with RA who has had an inadequate response to, or is intolerant of a TNF-α inhibitor. According to the license, rituximab should be administered intravenously as two 1000mg infusions, separated by 2 weeks, with concomitant methotrexate [14]. Patients with RA should receive treatment with 100 mg IV methylprednisolone 30 minutes prior to each infusion of rituximab in an attempt to reduce the rate and severity of acute infusion reactions [1]. The rituximab license and dose are based on the results of the REFLEX randomised controlled trial [11]. This regimen is also supported by a number of other phase III clinical trials conducted in patients with an inadequate response to MTX [10,13] and MTX-naïve patients [15]. These trials all demonstrated similar clinical and functional outcomes when the 500mg x 2 rituximab regimen was compared to the 1000mg x 2 rituximab regimen. However, the IMAGE study suggested that in MTX-naïve patients, the 1000mg x 2 regimen demonstrated improved radiographic outcomes when compared with the 500mg x 2 regimen for the first year of treatment (although both rituximab regimens significantly reduced joint damage progression between 6 months and 1 year) [15,16]. In the UK, the use of rituximab for the management of RA is regulated by the National Institute for Health and Care Excellence (NICE), an independent body that provides national evidence-based guidance and advice to improve health and social care. The current guidelines support the use of rituximab in combination with MTX as a treatment option in adults with severe active RA who have had inadequate response to, or are intolerant of, other disease-modifying anti-rheumatic drugs (DMARDs), including at least one TNF-α inhibitor and treatment with rituximab should be given no more frequently than once every 6 months [17]. Moreover, treatment should be continued only if there is an improvement in Disease Activity Score (DAS-28) of 1.2 points or more, showing a maintained and adequate response. Further recommendations were made by the British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHRP) in 2011 after reviewing up-to-date literature on the use of rituximab in rheumatoid arthritis [18]. The group produced a number of recommendations including:

- If MTX is contra-indicated, rituximab may be used either as Monotherapy or in combination with leflunomide.
- In patients in whom TNF-α inhibitor therapy is contraindicated, rituximab may be given before TNF-α inhibitor therapy.
- Patients who are rheumatoid factor or anti-CCP positive are more likely to respond to rituximab.
- Patients on rituximab should be assessed for response ideally at 24 weeks.
- Immunoglobulin levels should be checked before commencing rituximab as well as 4-6 months after infusions and prior to any re-treatment.
- The use of rituximab is contraindicated in patients who have active infection or who are severely immunocompromised.
- Screening for hepatitis B and C infection should be undertaken in all patients before going on to rituximab.
- Patients who have not already had Pneumococcus immunisation should ideally receive these 4-6 weeks before commencing the first course of rituximab.

DEVELOPING RITUXIMAB REGIMENS FOR RA

Currently the approved regimen for the treatment of RA with rituximab involves two 1000mg intravenous infusions administered two weeks apart (constituting one course of treatment). However, this recommendation is not without risks and drawbacks. Indeed, the prolonged depletion of B-cells and immunoglobulins raises concerns about the risk of infection, particularly with repeated courses of treatment. The risk of severe infection is crucial when assessing the risk: benefit ratio for biological drugs to treat RA. Clinical trials performed with rituximab in RA to date demonstrate a numerically higher rate of serious infections in patients receiving rituximab 1000 mg x2 compared with those receiving placebo [10, 11]. Moreover, it is known that rituximab retreatment may be associated with low IgG levels which, in turn are potentially associated with an increased risk of serious infections [19]. Such infections potentially include progressive multifocal leukoencephalopathy (PML) (although it is not known whether this is related to cumulative rituximab dosage or not). A total of 6 cases have been described in patients treated with rituximab for RA, and summarised in a systematic review of the FDA Adverse reporting System from 2012 [20]. These risks would justify further research into novel dosing regimens to minimise drug exposure. Mariette et al conducted an open-label, prospective, multicentre, non-inferiority study where 234 patients with RA received one course of rituximab (1000mg
x2 with MTX followed by randomisation at week 24 to either rituximab retreatment at 1000mg x1 or 1000mg x2. The study concluded that following a clinical response to a first course of rituximab in RA at the licensed dose of 1000mg x2, retreatment with rituximab at 1000mg x1 results in efficacy outcomes that are non-inferior to those achieved with retreatment at 1000mg x 2 [16]. Aside from potential patient safety benefits, there are also potential cost savings and health economic implications to a lower dose rituximab regimen. The cost of a single course of rituximab is £3492 (two 1000-mg intravenous infusions) although costs may vary in different settings due to negotiated procurement discounts and infusion costs [21]. A single-dose 1g rituximab regimen rather than a standard double-dose regimen may therefore reduce costs considerably. For example, a recent report by Roberts et al. conducted in Newcastle-Upon-Tyne, UK, calculated the mean number of treatments given to their cohort of patients with RA as 1.66 1g infusion courses per year. If this infusion number was halved to 1.66 1g infusions per year (rather than 1.66 infusion courses), the estimated annual saving to their department would be £435,000 [22].

BIOSIMILARS

Another emerging development is the approval of biosimilars as treatment options for patients with RA as the patent expires for individual bio-originator medicines. The European Commission and European Medicines Agency have recently approved Rixathon® (manufactured by Sandoz) and Truxima® (manufactured by Napp) as biosimilar medications of Roche’s rituximab (MabThera®/Rituxan®). These biosimilars are approved in Europe for use in all rituximab-approved indications, including non-Hodgkin’s lymphoma, chronic lymphocytic leukaemia and RA. A biosimilar medicine is a biological medicine that is developed to be highly similar and clinically equivalent to an existing biological medicine [23]. A biosimilar contains a version of an active substance of an already approved biological medicine, which is referred to as the ‘reference medicine’ or ‘originator medicine’. Similarity to the reference medicine in terms of quality, structural characteristics, biological activity, safety and efficacy must be established based on a comprehensive scientific comparability exercise such that they do not have any clinically meaningful differences from the reference medicine in terms of quality, safety and efficacy [24,25]. Biosimilar medicines are not the same as generic medicines which contain simpler chemical structures and are identical, in terms of molecular structure, to their reference drugs [23]. This is because biological medicines are derived from living cells and consist of large, highly complex molecular entities which may be difficult to characterise. Biosimilars have been approved for use in an effort to increase choice for patients and clinicians and enhance value propositions for individual medicines. This is particularly relevant in the context of Future Focused Finance in the UK which is looking at how the National Health Service (NHS) can be supported to take value-based decisions [26]. As biosimilars are more expensive to develop, they cannot offer the same percentage price reductions as traditional generic medicines. However, there are significant savings associated with increased competition between biological medicines, including biosimilars [27].

CONCLUSION

Rituximab is an effective treatment option in RA and its use is regulated by specific evidence-based guidelines. There is a large body of evidence with regards to its efficacy, safety and tolerability but more research is needed to explore reduced dose regimens to minimise drug exposure in patients, with the added benefit of reducing costs to healthcare providers. The development of Rituximab biosimilars such as Rixathon® and Truxima® now provides more treatment options to patients with RA and greater commercial competition leading to better cost efficiencies which in turn may support the treatment of an increasing number of patients. As biosimilars are new medicinal products, ongoing pharmacovigilance is required, as well as clear guidance on how to switch patients from bio-originator rituximab onto this new treatment, in consultation with the patient.

REFERENCES


