Anti-CD20 Monoclonal Antibody in Rheumatoid Arthritis and Systemic Lupus Erythematosus

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Abstract Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are both chronic autoimmune rheumatic diseases. In the last few years, evolution in the understanding of RA and SLE pathogenesis and underlying molecular mechanisms has resulted in development and availability of novel therapies. In particular, the recent acknowledgement of a more significant role for B cells in the pathogenesis of RA, in contrast to the view that it was predominantly a T cell disorder, provided rationale for trials of B cell depletion therapy with the chimeric anti-CD20 monoclonal antibody rituximab. The efficacy and favourable safety profile of rituximab have resulted in the recent approval by the European Medicines Agency for
its usage in patients with RA unresponsive to conventional therapies. The salient features from the pivotal open and randomised controlled trials are reviewed in this chapter. Given the recognition of B cell dysfunction as central to SLE pathogenesis, the use of anti-CD20 antibody therapy for this patient group has also been established. Results of the open trials have been encouraging, particularly in patients not responding to usual therapies, and a randomised controlled trial is underway.

1 Introduction

In recent years a number of exciting new therapies have been developed for rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), reflecting advances in the understanding of disease pathogenesis and molecular mechanisms. Various biological modifiers, including anti-tumour necrosis factor-α (TNF-α) agents and interleukin-1 receptor antagonists have been developed in recognition of the important role of these pro-inflammatory cytokines in RA. Based on an increased appreciation of the likely pathogenic role for B cells autoimmune diseases such as RA and SLE, targeted therapy against B cells has also been explored. Therapeutic B cell depletion with the anti-CD20 monoclonal antibody rituximab was initially licensed in 1997 for treatment of relapsed low grade B cell follicular NHL and over 700,000 patients have now been treated for this condition. Following this success, experimental use in autoimmune disorders was undertaken, with initial promise demonstrated in chronic idiopathic thrombocytopenic purpura (ITP) (Stasi et al. 2001). B cell depletion therapy for RA has now undergone open and randomised controlled trials and has been recently approved by the European Medicines Agency for usage in patients with RA unresponsive to conventional therapies (Leandro et al. 2002a; Edwards et al. 2004; Emery et al. 2006). Similarly, there have been a number of open studies of B cell depletion therapy for treatment of refractory SLE, and there are two ongoing phase II/III trials currently evaluating safety and efficacy in patients with severely active disease and nephritis. Importantly, however, there has not yet been a large double blind randomised control trial and it is imperative this be performed in the near future. This chapter summarises the role of B cells in pathogenesis of RA and SLE, the current knowledge of the mechanism of B cell depletion by rituximab and the main clinical trials of anti-CD20 monoclonal antibody treatment for RA and SLE. Salient features of new B cell targeted therapies, epratuzumab and anti-B Lymphocyte Stimulator (BLys) monoclonal antibody therapy will be briefly discussed.

Whilst other anti-human CD20 monoclonal antibodies exist, including a fully humanised antibody (Phase I/II controlled trial recently completed recruitment) and radioisotope conjugated antibody, rituximab is currently the most extensively studied and hence will form the basis of this chapter. Rituximab is a chimeric monoclonal antibody directed against human CD20, fusing variable regions of a murine anti-human CD20 B cell hybridoma with the constant region of human immunoglobulin IgG1κ. B cell ontogeny is characterised by a series of changing surface phenotypes and the CD20 surface marker (a 33–37 kDa membrane-associated phosphoprotein) expressed during intermediate stages of development is