Chapter 5

B-cell directed therapy

Introduction

Appreciation of the role of B-lymphocytes in the pathogenesis of rheumatoid arthritis (RA) has gone through various cycles. The discovery of rheumatoid factors as a specific marker for the disease pointed to a possible role for humoral (antibody-mediated) immunity and this was further strengthened by the discovery of anti-citrullinated peptide antibodies (ACPAs) many decades later [1,2]. However, animal model research in the 1970s and 1980s strongly supported the view that RA-like inflammation could be induced almost exclusively through T-cell-mediated immunity, and the first biologics to be tested in RA were directed against the T lymphocytes, albeit with mixed success. The subsequent successes with anti-tumor necrosis factor (TNF) approaches emphasized the importance of macrophage-like cells in RA inflammation, and a commonly held view was that B cells only played a very minor role in this disease. Despite all this, Professor Jonathan Edwards in London remained convinced that B cells were of greater importance in RA and published a hypothesis suggesting rheumatoid factor of the immunoglobulin G (IgG) isotype could form small immune complexes that would specifically trigger inflammation in the target tissues of RA (Figure 5.1) [3].

Based on this model he proposed that a strongly B-cell depleting therapy would break the vicious cycle of RA inflammation, and he initiated a small uncontrolled treatment trial where corticosteroids and cyclophosphamide were combined with the then relatively new lymphoma therapy rituximab. In the first case series several remarkable improvements were
noted and a more formal drug development program was initiated [5]. These and subsequent trials firmly established that B-cell depletion can be an effective therapeutic principle in RA.

**Overview of B-cell therapy for rheumatoid arthritis**

**Rituximab**

**Introduction**

Rituximab (Mabthera, Rituxan) is a chimeric monoclonal antibody directed against the CD20 molecule, which is present on all mature B cells. On binding to CD20, rituximab triggers cells death through antibody-mediated cellular cytotoxicity; following infusion of rituximab complete depletion of B cells from the peripheral blood can be documented within a matter of days. This monoclonal antibody was originally approved for the treatment of non-Hodgkin lymphoma and became one of the most widely used biologics in hematology. Since its original development in the field of hematology it has been used ‘off-label’ for the treatment of many autoimmune diseases and studied formally in some of these; it has been approved for the treatment of anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis [6,7] and there are many studies suggesting efficacy in at least some patients with systemic lupus erythematosus (SLE) [8] and multiple sclerosis [9].