Chapter 6

T-cell directed therapy

Overview of T-cell directed therapy for rheumatoid arthritis

The role of the T lymphocyte in the pathophysiology of rheumatoid arthritis (RA) remains somewhat unclear. On the one hand, T cells are abundantly present in the inflamed synovium, and in some animal models T cells can be identified as the main effector cells of the inflammatory response. Moreover, the demonstration that human leukocyte antigen (HLA)-DR genotypes are associated with the risk for RA points at the T cell, because the function of the class II major histocompatibility complex (MHC) molecule in the immune response is exerted through binding to the T-cell receptor. On the other hand, it was demonstrated that the human rheumatoid synovium does not present abundant evidence for T-cell activation, and cyclosporin-A, the one conventional antirheumatic agent that is believed to work almost exclusively through inhibition of T cells, has only limited efficacy in RA. Nonetheless, the first biologics to be tested for RA were directed at T lymphocytes. Approaches using anti-CD4 (targeting T-helper [Th] cells) were ineffective [1] and although alemtuzumab (Campath-1H), an anti-CD52 monoclonal that targets all T cells, did demonstrate efficacy in RA [2], it is thought to be too toxic for general use in this condition. Currently, the only successful approach directed at T lymphocytes is through targeting co-stimulation.
Abatacept

The T-cell directed biologic abatacept (Orencia) has demonstrated efficacy in RA and is an approved treatment in this setting. Abatacept is a construct of the naturally occurring cytotoxic T lymphocyte-associated molecule 4 (CTLA-4) coupled to an immunoglobulin G (IgG) framework. CTLA-4 is produced by T cells around 48 hours after activation and it interferes with the binding of the CD28 molecule on the T-cell surface and the CD80/86 (B7) molecule, which is present on antigen-presenting cells. The latter interaction is a ‘second signal’ that enhances the T-cell response, and therefore blocking it serves to downregulate T cells. The physiologic role of CTLA-4 is believed to be the termination of T-cell activation and the prevention of excessive inflammation. The development of this molecule as a therapeutic agent was therefore a logical step, and indeed, several trials confirmed that abatacept has good clinical efficacy in the treatment of RA in different stages of the disease [3]. Efficacy that was comparable to anti-tumor necrosis factor (TNF) was demonstrated in patients who had an incomplete response to methotrexate (MTX) [3], and good clinical efficacy was also demonstrated in patients who had previously failed anti-TNF [4] (Figure 6.1).

Abatacept was also shown to inhibit radiologic progression [6,7] and to be effective in patients with early RA [8], even in those with early undifferentiated arthritis [9]. Perhaps most impressively, a head-to-head comparison with adalimumab, when both were given in combination with MTX, showed almost identical efficacy for the two agents [10]: the percentages of responders according to the American College of Rheumatology (ACR) criteria were virtually identical at all time points and the time to response for the two drugs was also almost identical. The recent Avert trial in early RA confirmed that abatacept plus MTX was more effective in early RA than either drug alone [11].

The safety profile of abatacept in clinical trials was favorable. Small increases of infections and other minor adverse events were observed, as was the case with all immunomodulatory agents, but this treatment does not seem to be associated with major risks. Screening for tuberculosis is recommended but an increased risk for reactivation of latent tuberculosis has not been demonstrated.