Overview of biologic therapies

Brief historical review of the emergence of biologics for rheumatoid arthritis

The discovery of the technology for producing monoclonal antibodies by Kohler and Milstein in 1975 [1] heralded a new era in therapeutics: it became possible to design a molecule with a very specific predetermined biological effect for use in a relevant disease. Applications of the technology rapidly entered the medical fields of oncology and transplantation medicine. In rheumatoid arthritis (RA) treatment, the first attempts at biological therapy focused on T lymphocytes, with great initial excitement but subsequent disappointment as the treatments were found to be either ineffective (anti-CD4) [2,3] or too toxic for general use (anti-CD52) [4]. Meanwhile, in a parallel development in critical care medicine the use of biologic antagonists of tumor necrosis factor (TNF) were pioneered for use in septic shock. These developments also resulted in disappointment [5–8]. However, in a remarkable twist, researchers at the Kennedy Institute in London concluded that in vitro data from their studies suggested that TNF antagonism would benefit patients with RA, and they were able to convince the company that had produced one of the anti-TNF monoclonal antibodies to let them do trials with it [9]. The results exceeded all expectations and a new era in RA therapeutics was born.
Overview of currently available biologic therapies

At present, nine different biologic agents are approved for the treatment of RA in the US and in Europe: five TNF-antagonists and four biologics with a different mechanism of action (Figure 3.1).

In addition, a small-molecular agent with biologic-like effects has been approved in the US (and many other countries around the world), an anti-TNF biosimilar has been approved in Europe, and additional biologics are in late-stage development for RA.

The five approved TNF antagonists are summarized in Table 3.1. They differ in structure, half-life, route of administration (intravenous or subcutaneous), dose, frequency, and in some practical aspects, but they are remarkably similar in both efficacy and safety. National and international recommendations and guidance documents generally treat these medications as a single group.

The other four approved biologics are blockers of interleukin (IL)-1, IL-6, a T-cell costimulation antagonist, and a B-cell depleting agent, and these are summarized in Table 3.2. All these medications will be discussed in more detail in subsequent chapters.

Biologic versus synthetic disease modifying antirheumatic drugs: similarities and differences

The introduction of biologics into the rheumatologic armamentarium marked a dramatic shift in this therapeutic area (Box 3.1).

The approval and subsequent adoption into practice of the first two anti-TNF agents, etanercept and infliximab, was associated with enormous enthusiasm within the profession but also – as is fair to point out – marketing efforts unprecedented in the world of inflammatory diseases. On one level, the biologic medications that are used for RA can be regarded simply as disease modifying anti-rheumatic drugs (DMARDs); and indeed the designations cDMARDs and bDMARDs for conventional and biologic DMARDs, respectively, have been gaining ground. From a regulatory point of view the approval of a biologic in the treatment of RA is based on the same requirements as for conventional pharmaceuticals: clinical efficacy has to be proven in at least two randomized trials of sufficient size, and radiological efficacy in terms of