DEVELOPMENT OF ANTICYTOKINE AGENTS FOR RHEUMATOID ARTHRITIS

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1 INTRODUCTION

Rheumatoid arthritis (RA) is a common systemic inflammatory disease [1] characterized by joint destruction and extra-articular inflammation, resulting in severe morbidity and increased cardiovascular mortality [2]. The past decades have witnessed the gradual development of orally administered immunomodulatory treatments with methotrexate and sulfasalazine being the most frequently used nonbiological agents in the United Kingdom. Experience with these drugs has resulted in the concept of "disease-modifying" anti-rheumatic drugs (DMARDs), which can be introduced early after a diagnosis of RA has been made to reduce the rate of progression of joint damage.

Despite the success of methotrexate and other disease-modifying agents, many patients with RA fail to respond adequately to these drugs. This might be because these drugs have been used too late, at the wrong dose, or more likely because they do not adequately target the right disease processes. Recent years have witnessed the exciting development of biological therapeutics that use antibody or protein technology to target, with high specificity, particular molecules involved in the inflammatory pathway, thus disrupting the cellular communication necessary for the orchestration of inflammation. Their use in combination with traditional DMARDs has led to highly effective gold standard treatments in which clinical remission has at long last become possible [3–5].

2 CASE STUDY: ANTI-TNF AGENTS

Neutralization of tumor necrosis factor (TNF) was the first example of specific targeting of a cytokine in RA [6], and its enormous success has meant it is now available as part of routine clinical practice. The identification of TNF as a clinically relevant target highlights several concepts central to any discussion of the development of anticytokine agents. Though the subject of several reviews by Feldmann and Maini who pioneered this field [6, 7], the key points are summarized below.

While work by Feldmann's group demonstrated that multiple cytokines were present in the rheumatoid synovium, it was initially suspected that their number was so great and function so redundant that the neutralization of only one cytokine would have a minimal effect on inflammation [6, 7]. Interleukin-1 (IL-1) was viewed as a key molecule of interest, since it exhibited prolonged expression in cultures of rheumatoid synovial cells, in contrast to its transient expression in models of infection where the inflammation resolved [6]. The concept thus emerged that the dysregulated, chronic production of cytokines was responsible for the persistent inflammation seen in RA [6, 8]. The key observation came when an anti-TNF antibody was added to rheumatoid synovial cell cultures resulting in cessation of IL-1 production [6, 9]. When it was later demonstrated that the neutralization of TNF also led to reductions in other inflammatory molecules such as IL-6 and IL-8, the concept emerged that TNF was a master

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