We have witnessed unprecedented advances in the past quarter of the century in our understanding of the pathophysiology of RA. Fortunately, for the majority of people presenting with this condition today, the outlook is much better than it would have been for those a generation ago. Many contemporary trainees in rheumatology might listen with incredulity when their senior colleagues describe the nature of outpatient clinics, inpatient work and pharmacotherapeutic approaches that were employed in the management of RA in previous decades. RA still poses a formidable burden on the lives of many people. Moreover, the impact of this condition on the health-care economy is an enormous challenge, compounded by the costliness of protein-based therapies that specifically target molecules relevant to the pathobiology of RA.

Evaluating the economic impact of biologic therapies has not been without controversy. There are difficulties in accurately ascertaining the true cost-effectiveness over the course of a condition that persists over a lifetime from presentation. Yet, it is apparent to rheumatologists familiar with biologic approaches in the clinical management of RA that the gains in quality of life, preservation of functional and employment status, clearly evident in many patients, justifies the use of such costly therapies [1]. Although few people would disagree that we in the UK must be wise custodians of a limited health-care budget, the conclusions extrapolated from the everyday experience of rheumatologists are in contrast with the findings of health economic analysis adopted by National Institute for Health and Clinical Excellence (NICE) that, while rigorous, declines to take into account the broader societal implications of biologic use [2].

The biologic era came about as a consequence of two concurrent advances. First, in the 1980s, as appropriate tools and methodologies became available to catalogue cytokines in tissues derived from the rheumatoid joint, a range of known cytokines could be detected; many with pro-inflammatory activity as might be predicted and more surprisingly, some with anti-inflammatory activity. Secondly, rapid advances in protein engineering allowed production of clinical grade antibodies or engineered derivatives specifically targeting molecules relevant to the pathology of RA.

The first cytokine to be identified as a potential therapeutic target in RA was TNF in work undertaken at the Kennedy Institute of Rheumatology in the UK. This development was achieved through a series of preclinical studies of the immunobiology of synovial tissue harvested from patients with active disease and preclinical animal model studies [3]. Full validation of TNF as a target came about in the form of clinical trials on human beings, which unequivocally showed significant benefit in most patients treated [4]. Biologic inhibition of TNF, in combination with concomitant MTX, not only improved symptoms and signs of RA in many patients, but perhaps also most dramatically halted the structural damage previously thought to be an inexorably progressive feature of RA [5]. Preservation of functional capability is a consequence of both reduction in disease activity and prevention of joint damage and as such, not surprisingly, the most impressive benefit of biologic TNF inhibitors has been demonstrated when therapy is initiated in the early stages of RA [6–8]. Biologic anti-TNF therapies have set the height of the bar to which all biologics directed at alternative molecular targets have had to aspire to achieve the magnitude of improvement in symptoms and signs, prevention of joint destruction and preservation or improvement in function.

TNF is a pleiotropic cytokine with both pro-inflammatory and immune regulatory functions. The diverse activities are mediated via ligand interaction with two different receptors, TNFR1 and TNFRII, which activate separate transduction pathways resulting in distinct biological effects. In RA, the amplified and dysregulated production of this cytokine mediates enhanced synovial proliferation, and enhances angiogenesis, production of prostaglandins and metalloproteinases. In this way, TNF plays a major role in tissue destruction in involved joints and may contribute to peri-articular osteoporosis observed early in the course of RA. TNF also regulates other pro-inflammatory cytokines [9].

Despite these efficacy gains in many, but not all, patients, an ever-present concern from the earliest days of biologic anti-TNF therapies was that of target-related toxicity. Certain adverse events were predictable given the knowledge of TNF biology and the highly specific inhibition of the target associated with biologic intervention. These included the risk of infectious complications, particularly concerning intracellular pathogens. Cases of tuberculosis were reported in approximately 1 in 1000 patients treated in the early days of the anti-TNF era, but this rate has significantly reduced by routinely screening patients for a history or evidence of latent TB before initiation of biologic [10]. But there were also other theoretical concerns around tumour surveillance and possible rare complications where the relative risk might be enhanced despite a very small absolute risk, raising the possibility that detectable signals might not be generated.
in clinical trials. An example of this might be lymphoma risk.

The British Society for Rheumatology (BSR) biologics registry was set up to investigate and gather data from a cohort of size powered to detect a 2-fold increase in lymphoma risk in comparison with a DMARD-treated cohort. However, after more than a decade of clinical experience with anti-TNF biologics, there is no evidence that the risk of lymphoma increases with this class of biologics compared with RA controls treated with classical DMARD [11, 12]. Currently, it is the total inflammatory burden over time that predisposes to increased risk of lymphoma in RA and that is why there is an increase in lymphoma risk in anti-TNF-treated RA cohorts as compared with healthy controls [13]. And much of the data from various registries largely comprise RA patients who had persistently elevated disease activity for some time before being exposed to an anti-TNF biologic.

We have over a decade of clinical use of biologic anti-TNFs in the management of RA and have learnt that this particular magic bullet, while not without associated adverse effects, has a remarkable overall safety record [14] when compared with other widely used classes of drugs such as non-steroidal anti-inflammatories. As a result of the overall safety record and impressive efficacy in some recipients, the development of biologics targeting TNF for the treatment of RA paved the way for a broader evolution of biologics in the management of a range of chronic inflammatory disorders.

Despite all the success of biologic therapies in RA and the anti-TNF class in particular, considerable unmet needs remain in addition to adverse events related to TNF inhibition. These include primary non-response in ~25% of patients and loss of response over time in others, incomplete pain relief despite improvement in other generic features of inflammation and incomplete clinical responses in the majority of patients treated. Incomplete clinical response poses a challenge for the treat-to-target recommendations when the desirable goals of remission or low disease activity remain aspirational for many patients. Also, of course, the unacceptably high drug costs have a very negative impact on any health-care economy. In some, such as the UK, rationing denies treatment to many individuals who would have otherwise received the drugs if they lived in Sweden, The Netherlands or North America. Thus, further advances in protein engineering that might lead to significant reductions in production costs are welcome. However, the possible emergence of biosimilars and bioexacts in the near future, as well as all the competitive pressures of market forces, might drive prices downwards in the coming years.

Other challenges for the future will be how to improve the magnitude of efficacy currently achievable and also how to increase the proportion of patients with the highest levels of response. Excluding IL-1RA (which is rarely used in RA management), of the currently available biologic drugs for RA encompassing four different classes of action (five biologics targeting TNF, one targeting IL-6R, one co-stimulation blocker and one B-cell depleting agent) have all shown a broadly comparable proportion of patients achieving the ACR 20, 50 and 70% categorical responses at 6 months. Other biologic approaches are in trials but none has shown evidence of exceeding these proportions to date [15]. This observation suggests that finding a way to inhibit multiple targets might be necessary to improve efficacy, but at the same time avoiding an unacceptably level of toxicity by incapacitating the ability to mount physiologically appropriate immune responses, for example to infectious agents. Thus, to normalize an immune disequilibrium and restore physiological responses, rather than to abrogate capability for immune responses in an attempt to down-regulate pathological inflammation, is a desirable goal. Whether this is achievable remains to be seen; in addition, attempts to date to combine biologic therapy to two targets have demonstrated no efficacy benefit rather a significant increase in infectious complications. However, biologics are likely to play a role in investigating these issues further through their use as tools for molecular dissection of the relevant pathogenic pathways driving a common phenotypic expression through a diversity of immunological aberrations that may occur in RA.

In summary, the identification and validation of TNF as a key therapeutic target, and subsequent introduction of biologic anti-TNF therapies, especially when used in combination with concomitant MTX, has changed the treatment paradigm for RA and greatly improved the outlook for those individuals diagnosed with RA.

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