Editorial

Biologic agents in rheumatology: Act II

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The majority of rheumatologists actively engaged in the clinical practice of rheumatology in 2010 readily recall the times before the introduction of biologic agents. With regard to the therapeutic choices available, few have any nostalgia for those days. It is hardly hyperbole to state that the development of novel immunomodulatory therapies and their introduction into the clinic has revolutionised the care of patients with a number of serious autoimmune conditions, most notably rheumatoid arthritis (RA). The basis for this is the growing recognition that biologic therapies, in particular tumour necrosis factor (TNF) inhibitors, have proven effective not only in markedly improving the signs and symptoms of disease for many patients, but also in improving functional status and impeding or preventing the progression of joint damage as assessed radiographically (1). The success achieved by these agents has resulted in several important developments. Thus, the bar has been raised with regard to the goals of treatment for patients with RA and other conditions, including psoriatic arthritis and ankylosing spondylitis. As opposed to the pre-biologic era, where "doing better" may have been considered a success, rheumatologists currently desire the greatest improvement possible for patients suffering from these pernicious diseases. Indeed, the results achieved with TNF inhibitors have also effected an alteration in the utilisation of traditional drugs, such as methotrexate, with treatment paradigms that would have been considered overly aggressive in years past. The improvement in outcomes for patients with RA that has been observed in recent years no doubt relates in large part to these developments (2). In addition, such success has provided the impetus for further research in rheumatology, both in the development of new therapies as well as in the testing of new treatment strategies. Rheumatologists themselves have also been transformed, from being largely observers of the natural course, trying to "first, do no harm" to what may be called 'therapeutic immunologists'.

Interestingly, rheumatologists still tend to refer to TNF inhibitors as "new" therapies. However, this description becomes increasingly inaccurate, as these agents have been available in the clinic for more than a decade! This has important implications for clinical practice, particularly regarding safety, where the breadth and length of exposure in diverse populations provide critical information. With a wealth of relevant clinical experience, the key question at present is not whether TNF inhibitors should be used, but rather how to use them optimally in order to achieve the best possible outcomes for our patients. This becomes all the more germane as new biologic agents, including additional TNF inhibitors, as well as biologic agents with other mechanisms of action, have been brought to the clinic. In this journal, experts from around the world address several important aspects of the treatment of RA relevant to the optimal use of TNF inhibitors.

Any consideration of future therapeutic direction begins most appropriately with an assessment of the past and present. In the first article, Dr. Daniel Furst provides a succinct yet comprehensive review of the development of TNF inhibitors (3). Initially, these drugs were tested in clinical trials and also utilised in the clinic predominantly for RA patients with severe long-standing disease that remained active despite available therapies. With growing experience, building on the success in refractory patients, therapy has evolved and expanded, and patients with earlier RA have been treated. A number of studies have explored novel treatment

paradigms, increasingly in patients with early RA in an attempt to obviate irreversible damage. With the introduction of new TNF inhibitors, further testing and refinement of treatment strategies can be expected. This will no doubt have direct relevance to the practising clinician.

Most rheumatologists are inveterate tinkerers. Perhaps this derives in part from our tradition of using corticosteroids, in which adjustment of dosing is inherent to their best possible use. This proclivity for dose adjustment was further entrenched in rheumatology by the expanding use of methotrexate – the cornerstone drug for the management of RA – for which changing the dosage for individual patients is generally considered key to achieving better clinical benefit while minimising toxicity. So it should be no surprise perhaps that rheumatologists have also made attempts at varying the dosing regimens of TNF inhibitors. In this journal, Dr Bernard Combe reviews the data surrounding dosage adjustments with the various TNF inhibitors in a way that can provide important guidance to the practitioner (4).

As noted above, the success achieved with TNF inhibitors has elevated the goals of therapy for RA. Indeed, perhaps the greatest testimony to the progress that has been made in treating RA is that remission, a concept once as unachievable as it is sublime, is now considered attainable. Indeed, with many rheumatologists stating unequivocally that it should be the goal for all patients, how best to define remission has become the subject of intense discussion. Although some definitions of remission in RA were suggested many years ago, they received scant attention at the time due in some part to the lack of highly effective therapies. Now, with the availability of newer agents, the use of more aggressive treatment paradigms, and also with the introduction of sensitive imaging modalities, accurate definitions are much more relevant. Dr. Josef Smolen and Dr. Daniel Aletaha rigorously review the composite measures used to assess disease activity in RA, and explore their utility as well as their potential limitations (5). As we rapidly enter an era where treatment guidelines are utilised to standardise medical practice, consensus among expert rheumatologists on the most appropriate definitions of outcomes, including remission, is absolutely critical (6).

Another key to the successful treatment innovations that have occurred in RA is the significant advancement in outcome measures over the past quarter century. Single measures, such as tender joint counts, served as the primary outcome for some older studies. However, composite indices such as the ACR70 and DAS28 have now become standard due to their superior performance in assessing response to treatment in RA. While the utility of these measures in assessing the efficacy of RA treatments is undeniable, the clinical success achieved with TNF inhibitors has raised the question of whether all of the relevant aspects of improvement are captured with the outcome measures commonly collected. Most clinical rheumatologists can clearly recall patients who relay dramatic positive experiences with treatment that do not seem entirely explained by the typical measures used in clinical trials and, increasingly, in the clinic. In a paper that addresses other potential outcomes, Dr Peter Taylor focuses on the patient experience as it relates to anti-rheumatic therapy (7). This paper systematically reinforces what should be obvious to all compassionate clinicians – we should indeed be listening to our patients! In this paper, Dr Taylor lays the groundwork for doing so in a systematic manner. This issue is of consequence not only to clinicians but also for future clinical trial design.

When speaking of biologic agents, rheumatologists prefer to focus on things such as their efficacy and immunomodulatory mechanisms of action. However, the '800 pound gorilla' in the clinic that people tend to ignore is cost (8). Despite their notable clinical benefits and good tolerability profile, it is clear that the expense of newer therapies definitely affects their utilisation. This is true worldwide; whether the patients are in a system where the government provides all health care or where they pay out of their own pockets. Although the acquisition costs of newer therapies exceed those of older treatments, to the extent that they achieve better results, they may have an incremental cost-effectiveness. To capture this, a complete view of all the aspects of RA is required. In their review Dr Vibeke Strand and Dr Dinesh Khanna comprehensively address this topic, looking particularly at the effect of effective treatments on the ability of RA patients to maintain employment and to perform home activities that dramatically affect quality of life (9). Given the limits to health care funding worldwide, such discussions are crucial. Although some may feel such political aspects of healthcare distasteful, rheumatologists need to be strong advocates for their patients, so as to assure them access to highly effective therapies.

As we enter 'Act II' with biologic agents in rheumatology, the topics reviewed in this journal add important information that will facilitate the optimal care of our patients. Some questions still remain. Safety is an ever-present concern, and additional data from clinicians will help determine the best manner to use novel therapies in diverse patients. Despite notable successes, there are areas for improvement in our use of biologics. For example, we are presently unable to predict which patients will go into remission with a given agent, or alternatively those who will not respond at all, or who might experience toxicity related to therapy. Given the tremendous progress in understanding the immunopathogenesis of disease and the mechanisms of action of the therapies we use, this is vexing. Nevertheless, there is hope that biomarkers may help us further optimise therapy (10). Finally, the lessons learned in RA are likely to translate into similar benefits for patients with other autoimmune conditions. Future developments are eagerly awaited!

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