Promoting science over serendipity in prescribing anti-TNF therapy

In the past, rheumatologists may have been perceived by some specialist colleagues as purveyors of toxic drugs for only modest benefits. Some physicians may have had the opinion that we treated complex conditions which were poorly understood with potent drugs whose mechanism of action was largely unknown. The withdrawal of several anti-rheumatic drugs over the years and the ensuing publicity may have perpetuated this idea; for example, benoxaprofen was withdrawn in 1982 due to hepatotoxicity and more recently some COX-2-specific inhibitors were also withdrawn due to an increased risk of ischaemic events. As rheumatologists now adopt management strategies to prevent disability rather than just managing it, perceptions of the risk–benefit relationship of DMARDs too may be changing. Many of the original DMARDs arose out of serendipity rather than science; as a direct result of an improved understanding of the pathophysiology of rheumatic conditions we now have targeted biological therapies, the first of which was anti-TNF-α therapy.

Anti-TNF-α drugs were developed to target a specific inflammatory cytokine known to be vital in inflammation. This novel treatment has revolutionized the management of RA and is increasingly being used in the treatment of other autoimmune rheumatic diseases. While it was initially used with caution a decade ago, it is now widely used in clinical practice and has transformed the lives of many RA patients, dispelling visions of chronic disability and giving hope of an improved quality of life to many. Double-blind randomized controlled trials—the primary instruments for measuring treatment effects and defining common adverse events in a select group of patients—not only proved the significant benefit of anti-TNF-α therapy but also highlighted the risks of infection and tumours [1]. Patients in routine clinical practice, however, often have comorbidities and will be on co-existing therapies, which not only influence efficacy but may reveal new side-effects. As patients will also invariably be on the drugs indefinitely, the potential long-term effects continue to give cause for concern. A decade on, less common but equally important adverse events associated with anti-TNF-α treatment are becoming apparent; for example, anti-TNF-α treatment in some may not only induce autoantibodies but in a minority may also lead to clinical expression of autoimmune diseases [2]. Some of these adverse events may also provide insights into the pathogenesis of other poorly understood disorders.

There has been some evidence suggesting that TNF-α plays an important role in the pathophysiology of sarcoidosis and there have been over 30 case reports of patients with sarcoidosis being successfully treated with anti-TNF-α drugs and one positive double-blind randomized controlled trial [3]. It is therefore paradoxical that in this issue, Immediato Daien et al. [4] should report the occurrence of sarcoid-like granulomatosis in patients treated with anti-TNF-α drugs in France. In the absence of a formal French Biologics Register, they contacted members of the French ‘Club Rhumatismes et Inflammation’, which consists of rheumatologists and internal medicine physicians throughout France, asking for reports of sarcoidosis during anti-TNF-α therapy. Only cases confirmed histologically were included; 10 were identified out of 28 000 French patients treated with anti-TNF in 2008. It is conceivable that this association may simply be a manifestation of reporting bias and requires to be confirmed by interrogating established treatment registries. The mean time between the onset of anti-TNF-α drug use to diagnosis of sarcoidosis in this series was 18 months and there was little correlation with duration of anti-TNF-α treatment, ranging from 1 to 51 months. Five patients were treated with etanercept and five with monoclonal antibodies. Four patients were treated for RA and six had a spondyloarthropathy. Switching to a monoclonal anti-TNF-α drug improved symptoms of sarcoid in one patient with RA while causing relapse in another with AS. They also searched the published literature for other reports of sarcoidosis occurring in the context of anti-TNF-α therapy and found 16 other cases—nine in RA patients, three in patients with AS, two had PsA and two in patients with JCA. Twelve of these 16 cases were treated with etanercept.

Based on these data, the occurrence of sarcoid appears to be independent of the underlying indication of treatment but may be influenced by the modality used to inhibit anti-TNF-α as out of the 26 published cases, 17 patients were on etanercept. It is also interesting that etanercept has not shown the extent of benefit seen with monoclonal antibodies against TNF-α in Crohn’s disease, a disorder characterized by granuloma formation [5]. Thus, this observation, if confirmed, may further delineate differences between anti-TNF-α agents. Indeed, etanercept in a double-blind study did not benefit patients with ocular sarcoid [6], whereas infliximab in a double-blind placebo-controlled study showed some benefit in chronic pulmonary sarcoid [3].

Immediato Daien et al. [4], published in this issue, also offer a plausible explanation for the occurrence of sarcoid-like granulomatosis in their patients. They suggest that anti-TNF-α drugs modulate the cytokinic and cellular environment, possibly facilitated by the increased susceptibility to infection during anti-TNF-α therapy, leading to increased production of IFN-γ. IFN-γ is a key player in granuloma formation, thus the increased production induced by anti-TNF-α therapy drives the process leading to sarcoid-like granulomatosis. As TNF-γ is fundamental in granuloma formation, Schweiz and Baughman [7] have extended a previous observation [8] that etanercept can lead to rebound higher levels of TNF as a potential explanation for the more frequent occurrence of sarcoid with its use.

This case series highlights the importance of pharmacovigilance, defined by the World Health Organization as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem [9]. Pharmacovigilance and post-marketing surveillance play an integral part in the detection of rare or unexpected adverse events [10]. Having learnt from previous experiences with adverse events leading to withdrawal of drugs used by many rheumatology patients, biologics registries were established by several independent rheumatology societies. The British Society of Rheumatology Biologics Register (BSRBR) was established in 2002, the goal being to register and follow up individuals on each anti-TNF-α therapy to establish any short- or long-term hazards. It also aimed to establish data on a comparator cohort on conventional DMARD therapies. Since its inception, the BSRBR has published widely on infection, malignancy, pregnancy outcomes and morbidity in patients on anti-TNF-α therapy [11–14]. Rheumatologists in Spain, Germany and Sweden have constructed their own registries [15]. These have started to yield useful data, as highlighted by the recent report of herpes zoster from the German database. Interestingly, unlike the association with sarcoid, the risk of herpes zoster was more frequent in those treated with monoclonal antibodies compared with those on etanercept [16].
These databases thus represent an unprecedented resource for continued drug surveillance and are at the forefront of pharmacovigilance methodologies providing information that are otherwise not available from double-blind controlled studies. Of equivalent importance is the use of systematic reviews, the Cochrane database and meta-analysis in formulating the use of anti-rheumatic therapies. This, in conjunction with the use of guidelines, can help further refine prescribing as an empirical, structured decision-making process rather than one based on observation or anecdote.

Rare or unexpected adverse events such as those highlighted in the report by Immediato Daien et al. [4], if confirmed, may lead to a better understanding of disease processes opening even more avenues for drug discovery. It is important to remember that ineffective assessment of the available evidence can lead to poorer patient outcome, not just from adverse events but also through lack of knowledge of the potential benefits [17]. The biologies registries form a very useful resource for further research into biologic therapies not only to highlight potential problems, but also to validate the benefits and define more fully the risk–benefit equation of these newer medications. Evidence-based information about the long-term effects of biologic therapy is essential, not only for patients and clinicians, but also for regulatory and approval bodies and for future drug development, to provide optimal care to patients while upholding the adage ‘primum non nocere’.

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