REVIEW 2

ANTI-TNF AGENTS AS THERAPEUTIC CHOICE IN IMMUNE-MEDIATED INFLAMMATORY DISEASES: FOCUS ON ADALIMUMAB

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The complex pathogenesis of immune-mediated inflammatory diseases (IMIDs) has been extensively investigated and dysregulation of cytokines, such as tumour necrosis factor (TNF), has been shown to play a dominant role in the pathogenesis of various IMIDs, such as rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriasis and psoriatic arthritis. The subsequent development of biological agents capable of blocking TNF has led to important advances in the pharmacotherapy of such diseases and confirmed the concept of a common pathophysiology among IMIDs with TNF having a predominant role. Five TNF inhibitors have currently been approved for treatment of one or more IMIDs; these include infliximab, etanercept, adalimumab, golimumab and certolizumab pegol. Given the similarities in the pathogenic background of IMIDs, one could expect that anti-TNF agents be similarly effective and with comparable tolerability profiles; however, this may not be the case. Structural and pharmacological differences among the anti-TNF drugs are likely to result in differences in efficacy and tolerability among the agents in the different IMIDs, together with differences in potency, therapeutic dose ranges, dosing regimens, administration routes, and propensity for immunogenicity. Among the five TNF inhibitors approved for treatment of IMIDs, adalimumab has

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the widest range of indications. Data from controlled clinical trials of adalimumab, showing its excellent efficacy and tolerability in a wide range of indications, are supported by real-world long-term data from observational studies, which confirm the value of adalimumab as a suitable choice in the management of IMIDs.

In recent years, the complex pathogenesis of immune-mediated inflammatory diseases (IMIDs) have been elucidated and dysregulation of cytokines has been shown to play a major role. Consequently, treatments for IMIDs have moved away from an approach mainly based on symptom relief (i.e. analgesics, steroids, and non-steroidal anti-inflammatory drugs [NSAIDs] such as cyclooxygenase-2 inhibitors) to a mechanism-based strategy, in which biological therapies target specific dysregulated proteins or cell receptors that have been shown to play a key role in the altered immune response underlying these disorders (1). As a result, the traditional symptom-based approach meant that individual chronic inflammatory diseases were treated by the specialist for that particular organ, whereas a mechanism-based strategy demands a more holistic multi-disciplinary approach.

Over expression of tumour necrosis factor (TNF) has been shown to play a dominant role in the pathogenesis of various IMIDs, such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), Crohn's disease, ulcerative colitis (UC), psoriasis and psoriatic arthritis (PsA). In addition to evidence from mechanistic studies, pointing out the common pathogenesis and role of TNF among IMIDs, findings from epidemiological and genetic studies support the theory that IMIDs are related disorders, with a common genetic susceptibility, thus explaining the co-occurrence or 'genetic overlap' and familial patterns of these diseases (2-6).

The subsequent development of biological agents able to block TNF has led to important advances in the pharmacotherapy of such diseases (7). The effectiveness of targeted anti-TNF therapy in many different IMIDs has confirmed, indeed, the concept of a common pathogenesis, with TNFα having a central role (7). TNF inhibitors have been shown to promote dramatic clinical remission and improved quality of life (QoL) even in patients with inadequate response to conventional pharmacotherapy. They are also well tolerated, can prevent disease progression, and in many cases they have been shown to reverse the target organ damage in different disorders (7-13).

Five TNF inhibitors have currently been approved for the treatment of one or more IMIDs; these include infliximab, etanercept, adalimumab, golimumab and certolizumab pegol. Each agent has been approved for specific therapeutic indications, some of which coincide. Among the available anti-TNF agents, adalimumab has received regulatory approval in nine IMID indications to date. As such, it has the widest approved use of all biological agents and could, therefore, be best suited for treatment of these combined and co-occurring disorders.

Objective and methodology

The aim of this narrative review is to review pharmacological and clinical data on the differences among the available anti-TNF agents, as well as to review clinical trials and real-world data on the use of adalimumab in the treatment of IMIDs. Combined automated and manual literature searches were performed on PubMed using the search terms 'anti-TNF'/'anti-TNF-alpha [α]'/'TNF inhibitor'/'TNF-alpha [α] inhibitor' AND ('rheumatoid arthritis' OR psoriatic arthritis' OR 'psoriasis' OR 'axial spondyloarthropathy' OR 'ankylosing spondylitis' OR 'Crohn's disease' OR 'ulcerative colitis' OR 'juvenile idiopathic arthritis'). Appropriate papers for this review were manually selected from the search results and the bibliographies of previous review articles.

Differences among anti-TNF agents

Structural differences

Anti-TNF drugs are either whole antibodies (infliximab, adalimumab and golimumab) or contain fragments of antibody in their structure (etanercept and certolizumab). Antibody structure (an Fc domain connected to two antigen binding Fab' domains) means that it can bind two molecules of the same antigen simultaneously. The Fc domain interacts with specific receptors, designated as Fc-Rn and Fcγ-R (14). Fc-Rn is expressed mainly on endothelial cells of blood vessels, enabling antibodies to adhere

to the inner surface of vessels and then return to the circulation in an active form. In this way, vascular endothelium acts as a depot to prolong the half-life of circulating antibodies. Fcγ-R receptor is expressed on various cell populations and mediates phagocytosis, production of cytokines or antibodies, complement-dependent cytotoxicity (CDC), antibody-dependent cell cytotoxicity (ADCC) and degranulation of mast cells or granulocytes (15, 16).

Being whole IgG_1 monoclonal antibodies, infliximab, adalimumab and golimumab, bivalently bind TNF, to form multimeric 'antigen-antibody' complexes. Adalimumab and golimumab are fully human monoclonal antibodies (17, 18), whereas infliximab is a mouse-human chimeric monoclonal antibody (19). Etanercept is the only soluble TNF inhibitor consisting of a constant Fc fragment of human IgG_1 connected via a hinge region to two extracellular human TNF receptor (TNFR) domains (20). Unlike infliximab, adalimumab and golimumab, etanercept forms a monovalent bond with TNF, likely because of a lack of flexibility of the hinge region. Certolizumab pegol consists of single IgG_1 Fab' fragment of a humanized monoclonal antibody bound to two 20-kD polyethylene glycol chains; the resulting expanded molecular mass increases the plasma half-life of the drug (21). Since it is not equipped with an Fc region, certolizumab interacts with TNF in a monovalent fashion (15, 22).

TNF exists either as a soluble TNF (sTNF) or a transmembrane TNF (tmTNF) exposed on the surface of TNF-expressing cells. All anti-TNF agents bind to and neutralize sTNF and exert different effects on tmTNF-expressing cells, but differences in affinity and avidity for sTNF and tmTNF have been observed (23). Differences in the molecular structures of anti-TNF drugs result in differences in pharmacokinetic and pharmacodynamic profiles, as described below, and give rise to variations in the anti-TNF effect on cell apoptosis, CDC and ADCC (23).

Pharmacodynamic differences

The most significant pharmacodynamic differences among anti-TNF drugs may be grouped into two main categories: 1) the ability to form complexes and 2) the presence or absence of an Fc region.

Ability to form complexes

A differential ability to establish links with the divalent or monovalently bound TNF determines whether large or small drug-TNF complexes are formed and influences their ability to activate reverse signalling processes (23). Large molecular complexes, generated by binding of TNF with infliximab, adalimumab or golimumab, allow: a) high stability of the drug-sTNF complex; b) faster clearance of these complexes from the bloodstream; c) slower dissociation of sTNF from the drug (this property translates into a reduced ability of sTNF to be released from the antibody binding, to return free in the bloodstream and to regain its pro-inflammatory activity); d) a greater ability to activate processes of reverse signalling by tmTNF, resulting in an enhancement of the anti-inflammatory activity. By contrast, small complexes, formed when sTNF binds with etanercept or certolizumab, are characterized by: a) reduced stability; b) slow rate of removal from the bloodstream; c) high speed of dissociation of sTNF from the drug with reacquisition of pro-inflammatory activity; d) complexes of tmTNF with etanercept or certolizumab show less or no ability to evoke anti-inflammatory processes through reverse signalling (22, 24).

Presence or absence of Fc region

The presence or absence of the antibody Fc region in the drug molecule determines whether the drug can activate Fc-dependent effects, including CDC and ADCC (22, 24).

Different propensities to activate CDC and ADCC may explain the differences in clinical effects observed with different anti-TNF agents, with those also having CDC and ADCC activity being more effective clinically than those that only neutralise TNF.

Since infliximab, adalimumab and golimumab are equipped with a complete Fc region, they can interact with Fcγ-R and activate Fc-dependent effects, including CDC and ADCC. These drugs also interact with Fc-Rn, allowing them to remain in circulation, or extend their plasma half-life. Etanercept, despite being equipped with an Fc region, does not have the CH1 domain, and this feature seems to explain its low propensity to induce CDC. Moreover, the Fc region of etanercept shows a low affinity for Fc-Rn,

and this could explain its shorter plasma half-life. Certolizumab is devoid of an Fc region and therefore cannot induce CDC or ADCC (25, 26).

Pharmacokinetic differences

The pharmacokinetic profiles of anti-TNF in humans are difficult to compare due mainly to the lack of direct comparative studies and also because of the different dosages, routes and frequencies of administration. Nevertheless, some authors have used algorithms to extrapolate the pharmacokinetic profiles of these drugs at the steady state in order to allow comparisons among them. Infliximab, being administered intravenously, reaches high peak plasma concentrations (C_{max}; 118–192 mg/L) in approximately 7 days (T_{max}), followed by marked reductions in circulating levels to <1 mg/L just prior to administration of the next dose (trough serum concentration). By contrast, adalimumab, golimumab, etanercept and certolizumab, being administered by subcutaneous injection, reach lower C_{max} (4.7–7.7, 5–6, 1.1–2.4, and 43–49 mg/L, respectively) in shorter T_{max} (approximately 5.5, 2–6, 2.1–3 and 2.2–7.1 days, respectively). Although C_{max} are lower than those achievable with infliximab, they are subject to less fluctuation between one administration and the next. Another important parameter, which affects the duration of the anti-TNF effect, is the long plasma half-life ($t_{1/2}$), which is an index of the propensity of a drug to remain in the bloodstream. Although published data are heterogeneous (infliximab, 7.7–12 days; adalimumab, 10–20 days; golimumab, 7-20 days; etanercept, 3-4 days; and certolizumab, 14 days), etanercept's shorter half-life than the other anti-TNF agents may be due to its low binding affinity for vascular endothelial Fc-Rn receptors (24, 26). The lack of a Fc region prevents certolizumab from interacting with the vascular endothelial Fc-Rn receptors (15). This should favour blood clearance of certolizumab with a faster subsequent reduction of its plasma half-life. However, this problem has been solved via the addition of two PEG chains, which allow the compound to remain in the blood circulation with a plasma half-life comparable to that of infliximab, adalimumab and golimumab.

Differences in efficacy

Since TNF has a central role in the pathogenesis and pathophysiology of IMIDs, one would expect that all five anti-TNF agents – adalimumab, etanercept, infliximab, certolizumab pegol and golimumab – would be similarly effective in the treatment of patients with any IMID; however, this does not appear be the case. Among the five agents, although infliximab and etanercept were introduced first, adalimumab has been shown to be effective for the widest range of indications. Within specific indications, direct head-to-head comparisons of efficacy are lacking (27) and data on the differences in clinical efficacy among the anti-TNF drugs by indirect comparisons are not reliable.

Not surprisingly, most data have been published for RA. A large Bayesian meta-analysis of studies of biological agents in RA (28) showed differences in efficacy of anti-TNF drugs used in combination with the disease-modifying anti-rheumatic drug (DMARD) methotrexate (MTX). In this analysis, etanercept was significantly more effective in improving American College of Rheumatology (ACR) 20/50/70 outcomes as compared with adalimumab and infliximab, without significant differences between etanercept and certolizumab pegol (28). However, an indirect comparison of the efficacy of eight biologics (including certolizumab pegol, infliximab, etanercept, adalimumab and golimumab) in RA, based on ACR50 outcome, showed that the efficacy among the agents was not significantly different, although all were significantly more effective than MTX and placebo (29). Another systematic review showed that the efficacy of all five anti-TNF agents was significantly higher than placebo but similar to MTX, and that the anti-TNF/MTX combination was superior to either MTX or TNF-blocker alone, without differences among the anti-TNF agents (30). No difference in efficacy was also shown in another systematic indirect comparison (31).

The mechanism for increased efficacy of anti-TNF agents with MTX versus anti-TNF alone is not clear, but greater longer-term effectiveness with the combination may be due to a reduced likelihood of anti-drug antibody (ADA) formation with adjunctive MTX; this is certainly observed with infliximab therapy. This issue is discussed in more detail in the section entitled 'Advantages of combination therapy with MTX' below.

A dose-response meta-analysis, performed for quantifying the relative efficacy of biologics in RA, showed that, although all anti-TNF displayed a similar dose-response relationship, significant differences in efficacy among the anti-TNF were observed due to differences in the clinical dose ranges available: at the suggested starting dose, golimumab was the least efficacious, followed by infliximab, adalimumab, etanercept, and certolizumab (32).

Some data suggest that the TNF inhibitory effect varies among the agents, translating into different consequences for the highly complex pathogenic mechanisms involved in the various forms of IMID. Differences in the efficacy and tolerability among the anti-TNF agents in different IMIDs are likely to depend on structural and pharmacological differences among the agents.

Administration and regimen differences

Anti-TNF agents are given either as subcutaneous injection (etanercept, adalimumab, certolizumab and golimumab) or intravenously (infliximab). Although the intravenous infusion of infliximab has to be performed at the clinical or infusion centre, it only has to be administered once every 4–8 weeks. Etanercept, adalimumab, certolizumab and golimumab can be self-administered, but they are given more frequently (once or twice a week for etanercept, every 2 weeks for adalimumab and certolizumab, and every 4 weeks for golimumab).

Patients with AS were shown to appreciate having a choice in their anti-TNF therapy and cited different reasons for choosing intravenous or subcutaneous therapies (33). For infliximab, patients reported a reduced frequency of injections, administration by a trained professional and use of infusion time for leisure activities as the reasons for their preference, whereas for subcutaneous anti-TNF drugs, patients cited flexibility with timing of treatment, shortened administration time and convenience as the main reasons for their choice (33). In RA patients, results from the RIVIERA survey – a questionnaire-based study investigating patient preferences of anti-TNF therapies in RA – showed that the treatment choice was important to patients and approximately half preferred intravenous and half subcutaneous administration (34). Reasons for choosing intravenous therapy were safety and reassuring physician presence, whereas reasons for choosing subcutaneous therapy were convenience and home treatment (34). Generally younger patients prefer self-administration and older patients prefer to visit a clinic (35). In patients with inflammatory bowel disease (IBD), two-thirds indicated a preference for intravenous or subcutaneous anti-TNF, whereas one-third of patients did not indicate a preference for either, and a trend towards a preference for infliximab versus adalimumab was reported; most of the patients who preferred infliximab did not like the idea of self-injecting, and most patients who preferred adalimumab appreciated the convenience of injecting at home; other reasons cited for the choice were the frequency of administration, mode of administration, or differing 'times in the market-place'; infliximab has been on the market for a longer period of time in Crohn's disease than adalimumab (36).

Differences in immunogenicity

Although current evidence for differences in efficacy among anti-TNF agents is inconsistent, such differences tend to emerge when the therapeutic response to one anti-TNF agent is lost over time, but patients retain the ability to respond to other drugs of the same class (15, 26). A systematic review of 28 studies showed an improvement in effectiveness with a second anti-TNF agent (adalimumab, etanercept or infliximab) as compared with the therapeutic response achieved before switching, in patients who had discontinued a previous TNF inhibitor (27). The increasing lack of therapeutic response over time is thought to depend mainly on the formation of ADAs – a process that has been reported with many biological drugs and has been associated with all five anti-TNF agents, although with varying degrees of incidence, depending on the molecule and disease being considered (37). The immunogenicity displayed by adalimumab and infliximab appears to be linked to subtherapeutic serum drug levels and a loss of clinical response, while for etanercept, golimumab and certolizumab, data on immunogenicity are quite limited (38). However, based on current evidence, immune cross-reactivity among anti-TNF drugs does not appear to occur. Additional research, aimed at assessing the immunogenicity of anti-TNF drugs (39), determining

optimal treatment regimens and the concomitant use of DMARDs e.g. MTX and immunosuppressants, to minimize ADA formation or investigating the use of neutralizing immunotherapy to reduce the likelihood of ADA formation, is presently ongoing (37).

Differences in safety profile

Among the five TNF inhibitors approved for treatment of one or more IMIDs – infliximab, etanercept, adalimumab, golimumab and certolizumab pegol – most tolerability issues appear to be class effects (e.g. increased risk of some malignancies, serious infections and tuberculosis reactivation (40)), and there are very few clinically relevant differences among these agents apart from those related to the administration (e.g. infusion reaction with infliximab); however, data on certolizumab pegol and golimumab are limited (41). Findings from a recent meta-analysis suggest that etanercept may have the best tolerability profile in RA (30); tuberculosis and other granulomatous infections may occur more frequently with monoclonal anti-TNF antibodies, such as infliximab and adalimumab, than with soluble TNF receptors such as etanercept (42). Demyelination has been reported with etanercept, infliximab and adalimumab and is likely to occur also with the newer agents. Therefore, anti-TNF agents are contraindicated in patients with multiple sclerosis (41). Screening is advised to identify patients with multiple sclerosis, other demyelinating diseases, latent tuberculosis, HIV and hepatitis infection, to allow a risk/benefit analysis to be performed in the individual patient (41). Long-term safety data are limited even for etanercept, infliximab and adalimumab in RA (43) and interpreting long-term safety data is complicated by the fact that the same adverse events (AEs) are noted to be elevated in patients with autoimmune disease even in those not receiving biological therapy (44). All agents appear to have a propensity to trigger the development of anti-nuclear antibodies (ANAs) and double-stranded DNA antibodies (dsDNA-Abs) as well as to cause auto-immune diseases such as lupus-like disease or vasculitis, but the risk may be higher with infliximab (41).

All the anti-TNF agents are thought to be safe, at least for short-term therapy, in early stage pregnancy (45); however, they cross the placenta from the end of the second trimester, and, due to some reports of increased infection rates in children exposed in utero and concerns about the impact on the developing immune system, experts have suggested that anti-TNF drug therapy should be stopped during the second trimester (45).

Advantages of combination therapy with MTX

All anti-TNF agents can be given as monotherapy in patients unresponsive to or unable to tolerate MTX (apart from infliximab and golimumab in RA which must be given with MTX). In RA, biological therapy plus MTX has been shown to be more effective than MTX alone, even in patients with an inadequate response to MTX prior to initiation of the biological therapy (46, 47). The advantages of combination therapy with MTX have also been observed in patients with early RA with minimal or no previous MTX treatment (48).

Although the mechanism is not known, concomitant use of MTX appears to reduce the immunogenicity of the anti-TNF agent and thus the risk of ADA formation (49, 50). Due to the particularly high risk of immunogenicity reported with infliximab in RA, concomitant use of MTX is required, and this combination appears to reduce the need for dose escalation over time (51).

Evidence comparing efficacy among the anti-TNF drugs with MTX is limited, but a Bayesian mixed-treatment comparison of the efficacy of anti-TNF agents in RA patients, who did not previously respond to MTX alone, highlighted some differences. In particular, using ACR 20/50 and Health Assessment Questionnaire [HAQ] scores, etanercept was more effective than infliximab and golimumab, and certolizumab was more effective than infliximab and adalimumab (52). Analysis of ACR outcomes showed an improved efficacy of certolizumab versus golimumab, and HAQ analysis showed that adalimumab, certolizumab, etanercept and golimumab were superior to infliximab, and etanercept displayed higher efficacy as compared with adalimumab (52).

Evidence for efficacy of adalimumab in IMIDs

The pivotal randomized controlled trials (RCTs) of adalimumab in all approved indications are summarised in Table 1.

Controlled clinical trials

Rheumatoid arthritis

In a 1-year multicentre study, adalimumab plus MTX was more effective than MTX alone at inhibiting the progression of structural joint damage, reducing the signs and symptoms, and improving physical function in 619 patients with active RA who had an inadequate response to MTX (53). Similarly, in the 1-year PREMIER study the combination therapy with adalimumab plus MTX was more effective in all outcomes measured than MTX alone or adalimumab alone in patients with early, aggressive RA who had not previously received MTX treatment (54).

Juvenile idiopathic arthritis (juvenile rheumatoid arthritis)

In the 48-week DE038 study adalimumab plus MTX was more effective than MTX or adalimumab alone or placebo, and this combination was well tolerated in children aged 4 to 17 years with active juvenile RA who had previously received treatment with NSAIDs (55).

Ankylosing spondylitis

The Adalimumab Trial Evaluating Long-Term Efficacy and Safety in AS (ATLAS) study was a randomised, double-blind, placebo controlled, 24-week trial in which adalimumab was shown to have significantly greater efficacy over 24 weeks versus placebo (56). Although the rates of AEs was higher with adalimumab as compared with placebo, the rates of infections was similar and most AEs were mild-to-moderate(56). The subsequent 2-year open-label extension study showed that the efficacy was improved or maintained up to 2 years and that the long-term adalimumab treatment was well tolerated, without cases of tuberculosis, congestive heart failure, lupus-like symptoms, or demyelinating disease (57).

Psoriatic arthritis

In the ADEPT randomized, double blind, placebo-controlled study in 313 patients with active PsA, adalimumab significantly improved all efficacy variables including joint and skin symptoms, and disability; it counteracted also the structural changes as compared with placebo, and was well tolerated. In the long-term open-label extension of ADEPT, the clinical and radiographic efficacy of adalimumab was sustained and the risk-benefit profile in patients with PsA was favourable over the 2 years of treatment (58, 59).

Psoriasis

In the REVEAL study – a 52-week, multicentre trial – 1212 patients with chronic plaque psoriasis were randomized to receive adalimumab (40 mg) or placebo every other week (eow) for the first 15 weeks, and then, depending on ≥75% improvement in PASI score, subjects were re-randomised to adalimumab or placebo (60, 61). A ≥75% improvement in PASI score was achieved in 71% of patients receiving adalimumab and only 7% in placebo recipients. A loss of response was then observed in 28% of the patients re-randomised to placebo and only 5% treated with adalimumab (60).

In the 16-week CHAMPION study, 271 patients with moderate-to-severe chronic plaque psoriasis were treated with adalimumab, MTX or placebo; adalimumab was shown to provide superior efficacy and more rapid improvements as compared with either MTX or placebo, with similar patterns of tolerability (62).

Crohn's disease

In the CHARM study, conducted on 854 patients with moderate-to-severe Crohn's disease, the enrolled subjects received open-label adalimumab for 4 weeks and were then stratified by response, defined as a decrease in Crohn's Disease Activity Index (CDAI) of ≥70 points from baseline, and randomized to adalimumab 40 mg eow or weekly or placebo for additional 52 weeks. Rates of clinical remission (CDAI <150) were significantly higher with adalimumab versus placebo at 26 and 56 weeks of treatment, but no differences between the eow and weekly dose regimens were recorded (63). In a subgroup analysis of the CHARM trial, stratification by disease duration showed that adalimumab treatment resulted in greater remission rates than placebo over 1 year regardless of duration; in Crohn's disease patients treated for 3 years, the remission rates with adalimumab were the highest in patients with the shortest disease duration, and the incidence of serious AEs was also lower in this group (64).

In the CLASSIC II trial, the efficacy of open-label adalimumab for maintaining remission in Crohn's disease was evaluated in 55 patients who achieved remission with adalimumab in CLASSIC I (n=299) (65). In these patients, the remission at week 56 was achieved by 79% with eow treatment, 83% with weekly adalimumab and 44% with placebo. In addition, 204 patients, who did not achieve remission, received open-label adalimumab 40 mg eow and 46% achieved remission at week 56 (65).

In the EXTEND trial, of 135 patients with moderate to severe ileocolonic Crohn's disease, those receiving adalimumab were significantly more likely to achieve and maintain muscosal healing and achieve clinical remission than those receiving placebo (66).

Ulcerative colitis

In the 1-year randomized, double-blind, placebo-controlled ULTRA 2 study, adalimumab was more effective than placebo in achieving and maintaining clinical remission. It was also well tolerated in patients with moderate-to-severe UC with an inadequate response to conventional steroid or immunosuppressant therapy (67). In a subgroup analysis of 248 patients treated with adalimumab, 123 (49.6%) achieved a response at week 8, and of these 30.9%, achieved clinical remission at week 52; early response was a significant predictor of a positive outcome at 1 year (68).

Observational clinical practice studies

Findings from post-registration observational studies have substantially confirmed that the outcomes recorded in RCTs can legitimately be extrapolated to the patients managed in the clinical practice.

Inflammatory bowel diseases

An observational study in UC showed that adalimumab is effective in these patients (69). The Productivity Safety and Efficacy: Long-Term Results in AdaliMumab-Treated Patients With Crohn's Disease (PYRAMID study) – the largest and longest study of adalimumab in the management of moderate to severe Crohn's disease patients – is an ongoing observational 6-year safety study, started in September 2007 in 24 countries to investigate adalimumab safety in the long-term treatment of Crohn's disease (70). The 3-year data in 5080 patients (9249 cumulative patient-years exposure; median duration of exposure 1.66 years) have shown that adalimumab is well tolerated with low, stable AE rates between years 2 and 3, without observation of new clinical concerns or safety signals. Indeed, the rates of serious infections were lower in patients receiving adalimumab monotherapy as compared with those receiving concomitant immunosuppressants or concomitant corticosteroids and immunosuppressants (70).

Real-life data for effectiveness of adalimumab in UC have been obtained in a retrospective observational Italian study in 88 patients (71). Adalimumab was effective despite patients had highly active UC at the start of treatment and despite most of the patients had been previously treated with infliximab (71). These data support those obtained in an uncontrolled prospective study in which 20 patients with active UC, who had lost their therapeutic response or developed intolerance to infliximab, responded well to adalimumab (72).

A retrospective observational study assessed the need for adalimumab dose escalation and de-escalation in a large cohort of 720 patients with active Crohn's disease. The results showed that dose escalation was required in 34% of patients and that it was successful in 67%; subsequent de-escalation following the induction of therapeutic response was attempted in 54%, and it was successful in 63%; by this strategy, 71% of patients maintained a long-term response on adalimumab (73).

Rheumatoid arthritis

A German observational study, investigating the outcomes of adalimumab treatment for RA, showed that adalimumab had a significant impact on therapeutic success during routine clinical practice (74). Factors predictive of positive outcome included high baseline DAS28 and male gender, whereas a high baseline functional capacity was associated with reduced gains in functional capacity and older age; in addition multiple previous biologics were associated with a reduced likelihood of therapeutic response (74).

In the Research in Active Rheumatoid Arthritis (ReAct) study, adalimumab was shown to be effective

in RA patients previously treated with etanercept or infliximab in clinical practice. The risk of serious infections was similar regardless of whether patients had received anti-TNF therapy or not (75). The study showed also that adalimumab was effective and well tolerated either alone or in combination with traditional DMARDs (76).

Psoriasis

In the long-term open-label extension of the PRIDE study on efficacy and safety of adalimumab for moderate to severe chronic plaque psoriasis, the rate of disease recurrence following adalimumab discontinuation and subsequent retreatment was investigated (77). Of 525 patients withdrawn from adalimumab therapy, 285 had stable psoriasis control. Of these, 178 (62%) relapsed before the planned treatment reinitiation at 40 weeks off-therapy. However, over two-thirds of these patients regained clinical efficacy following treatment reinitiation (77).

A small observational, prospective study, comparing monthly versus bi-weekly adalimumab therapy in 17 patients with moderate-to-severe chronic plaque psoriasis who responded well to an initial 24-week course of standard adalimumab therapy, showed that both regimens achieved control (defined as PASI75) in most patients by week 24 and this effect was maintained up to week 60 (78).

Registries

Several national registries provide clinical data from the real-world setting. The main aim of rheumatology drug registers is drug safety; however, they also highlight other important issues that otherwise would be missed in RCTs, such as drug usage, real-life long-term effectiveness, the impact on QoL, the safety of adalimumab treatment in the clinical setting and related economic issues (79, 80).

A number of registries have examined the safety of anti-TNF agents. For example, the Research Axed on Tolerance of Biotherapies (RATIO) registry, which investigated the incidence of lymphoma and opportunistic infections in all indications, showed an increased risk of *Legionella pneumophila* infection, a higher risk of tuberculosis with infliximab and adalimumab, and higher rates of opportunistic infections and lymphoma with anti-TNF monoclonal antibodies versus etanercept (81).

In RA, the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry compared the remission criteria used in clinical trials and showed that DAS28 <2.6 and minimal disease activity criteria were achievable in clinical practice after 6 months of anti-TNF therapy, although a residual disease activity was likely to remain. ACR/EULAR remission criteria were less likely to leave residual disease activity, but they were less achievable in clinical practice (82). The analysis of DREAM data showed also that the risk of serious infections in patients with RA treated with adalimumab or infliximab was similar, while being higher than with etanercept (83). Significant predictors for developing a serious infection during anti-TNF therapy in RA patients were age, corticosteroid use, VAS pain, HAQ, TJC28 and the presence of comorbidities at baseline (84).

DANBIO is a Danish registry of biological treatments of RA in clinical practice. DANBIO data from 8 years of treatment were used for a direct comparison of treatment responses, remission rates, and drug adherence in patients with RA treated with adalimumab, etanercept, or infliximab (85). The analysis of data showed that infliximab had the lowest rates of treatment response, disease remission, and drug adherence, while adalimumab had the highest rates of treatment response and disease remission, and etanercept had the longest drug survival rates. The following factors were identified as negative predictors of a clinical response and remission: older age, low functional status, and concomitant prednisolone (85). Additional data from DANBIO showed significantly reduced radiographic progression with anti-TNF treatment as compared with previous DMARD treatment in 517 patients with RA (86).

Data from the GISEA registry were used to analyse the risk of serious infections with long-term anti-TNF therapy – adalimumab, etanercept and infliximab – in RA. Findings showed that anti-TNF therapy is associated with a small, but significant, risk of serious infections; predictors of risk were concomitant use of steroids, advanced age, and the anti-TNF agent – highest for infliximab (65.1/1000 patient-years), followed by adalimumab (23.7/1000 patient-years), and then etanercept (12.8/1000 patient-years) (87). GISEA data showed also that the 4-year global drug survival with adalimumab,

Table 1. *Pivotal clinical studies of adalimumab in immune-mediated disease*

Reference (study acronym)	Patients (N)	Design	Treatment	Endpoints	Efficacy outcomes	Safety outcomes
Keystone et al. (53)	Active RA on MTX (619)	R, DB, PC, 1 year	Adalimumab 40 mg eow Adalimumab 20 mg qw PBO	Week 52 mTSS Week 24 and 52 ≥20% improvement in ACR20 Week 52 HAQ-disability index	Change in mTSS greater with Adalimumab vs PBO; week24 ACR20 63% and 61% for Adalimumab 40 and 20 vs 30% with PBO; week 52 ACR20 59% and 55% for Adalimumab 40 and 20 vs 24% with PBO; HAQ mean change -0.59 and -0.61, vs -0.25 All p≤0.001	AEs similar in adalimumab and PBO; serious infections higher with Adalimumab (3.8%) vs PBO (0.5%); p≤0.02
Breedveld et al. (54) (PREMIER)	Early aggressive RA, MTX naïve (799)	R, DB, 2 year	Adalimumab 40 mg eow + MTX MTX alone Adalimumab 40 mg eow alone	1- and 2-year ACR50; mean change in mTSS	Combination therapy superior to mono in all efficacy outcomes measured: ACR50 62%, vs 46% with MTX and 41% with Adalimumab alone (p<0.001 for both); less radiographic progression at 1 and 2 yrs (p≤0.002)	AE profiles were similar in all 3 study groups
Lovell et al. (55) (DE038)	Juvenile rheumatoid arthritis (poly-articular) (171)	R, PC, 2 years DB weeks 16-32 based on week 16 response	Adalimumab 24 mg/m^2 BSA (max 40 mg) eow ± MTX PBO ± MTX	Disease flares Week 16 and 32 ACRpedi30	Week-16 ACRpedi30 74% in Adalimumab alone and 94% in Adalimumab +MTX Disease flares: No MTX: 43% with Adalimumab and 71% PBO (p=0.03). With MTX: 37% Adalimumab and 65% PBO (p=0.02). Week-48 ACRpedi30: With MTX – significantly greater for ADA vs PBO No MTX – No significant differences between Adalimumab and PBO	Safety profiles similar among groups
Van der Heijde et al. (56) (ATLAS)	Ankylosing spondylitis (315)	R, DB, PC for 24 weeks	Adalimumab 40 mg eow PBO	% of pts with ASAS20 at week 12 ASAS20 and week 24, ASAS40, ASAS partial remission, individual ASAS response components; BASFI, BASDAI	Week 12, ASAS20: 58.2% Adalimumab and 20.6% PBO (p<0.001). Week 12 ≥50% improvement in BASDAI 45.2% with ADA and 15.9% with PBO (p<0.001). ASAS40 and ASAS5/6 response significantly greater with Adalimumab vs PBO at weeks 12 and 24 (p<0.001).	AE rate with Adalimumab 75.0% vs 59.8% with PBO; p<0.05). Most AEs were mild or moderate in severity.

					Partial remission greater with Adalimumab vs PBO (22.1% versus 5.6%; p<0.001).	
van der Heijde et al. (57) (ATLAS OL extension)	Ankylosing spondylitis (311)	OL for 2 years	Adalimumab 40 mg eow PBO	≥20% improvement in ASAS20 ASAS40, ASAS partial remission, individual ASAS response components; BASFI, BASDAI	ASAS responses sustained during long-term treatment; ASAS20 64.5%, ASAS40 50.6% and ASAS partial remission 33.5%; Changes in ASAS response components sustained or improved; BASDAI and BASFI improved over 2 years.	Long-term safety similar to short-term profile - Adalimumab well tolerated. No cases of TB, CHF, lupus-like symptoms, or demyelinating disease reported.
Mease et al. 2005 (58) (ADEPT)	Psoriatic arthritis (313)	R, DB, PC 24 weeks	Adalimumab 40 mg eow PBO	≥20% improvement in ASAS20 Change in mTSS; measures of joint and skin disease, disability and QoL	Week 12: ACR20 58% with Adalimumab and 14% with PBO (p<0.001). Week 24: ACR20 response rates similar to wk 12 and change in the mTSS -0.2 with Adalimumab and 1.0 with PBO (p<0.001). Week-24 PASI75 in 59% ADA and 1% with PBO (p<0.001). Disability and QoL measures significantly improved with Adalimumab vs PBO.	Adalimumab was generally safe and well-tolerated
Mease et al. 2009 (59) (ADEPT OL extension)	Psoriatic arthritis (245)	OL 2 years	Adalimumab 40 mg eow PBO	ACR20/50/70; measures of joint disease and skin disease, disability and QoL, mTSS	Compared with 24-week responses, inhibition of radiographic progression and improvements in joint disease were maintained during long-term, open-label Adalimumab. Improvements in skin disease were maintained, with >20% of pts achieving PASI100.	The nature and frequency of AEs during long-term Adalimumab were consistent with short-term treatment.
Menter et al. (60) (REVEAL)	Psoriasis (1212)	R, PC, DB for 15 weeks then re-randomised at week 16 based on PASI75 response, treated for 1 year	Adalimumab 40 mg eow PBO	PASI75 at week 16 Week 33-52 proportion of pts with lost response (<50% improvement in PASI response and ≥6-point increase in PASI score from week 33)	Week 16, PASI75 71% with Adalimumab and 7% with PBO. Weeks 33 to 52, lost response rate 28% with pts re-randomised to PBO vs 5% with continued Adalimumab.	-
Saurat et al. (62) (CHAMPION)	Psoriasis (271)	R, DB, PC 16 weeks	Adalimumab 80 mg then 40 mg eow MTX PBO	Week 16, proportion of pts achieving ≥75% improvement in PASI75.	16 weeks PASI75 with Adalimumab 79.6% and MTX 35.5% (p<0.001 vs. Adalimumab) and PBO 18.9% (p<0.001 vs. Adalimumab). Complete clearance of disease rate 16.7% with Adalimumab,	AEs similar across treatment groups.

					7.3% with MTX and 1.9% with PBO Adalimumab 57% improvement in mean PASI observed at week 4.	
Gordon et al. (61) (REVEAL OL extension)	Psoriasis	OL extension of pts receiving Adalimumab in the DB phase, groups by response, 3 year	Adalimumab from baseline to 3 yrs Adalimumab from week 16 to 3 years	In pts on continuous Adalimumab: Efficacy according to DB response: 1) ≥75% improvement in PASI75 at weeks 16 and 33; (2) <PASI 75 at week 16; (3) ≥PASI 75 at week 16 with 50–<75% improvement in PASI score at week 33. 4) Pts who began adalimumab after 16 weeks PBO	1)& 3) Efficacy was well maintained over 3 years. 2)Some pts achieved long-term PASI 75 responses. 4)Efficacy consistent with other 3 groups.	AE rates were consistent with those during REVEAL.
Colombel et al.(63) (CHARM)	Crohn's disease (777)	OL induction 0–4 weeks then DB, R to week 56	Adalimumab 40 mg eow Adalimumab 40 mg qw PBO	Stratification by week 4 response: decrease in CDAI of ≥70 points % of week-4 responders with CDAI <150 (clinical remission) at week 26 and 56.	% of responders in remission significantly greater with Adalimumab 40-mg eow and 40-mg weekly groups versus PBO at week 26 (40%, 47%, and 17%, respectively; p<0.001) and week 56 (36%, 41%, and 12%, respectively; p<0.001). No significant differences in efficacy between adalimumab eow and weekly dose regimens.	Adalimumab was well-tolerated
Schreiber et al. (64) (CHARM subgroups enrolled into ADHERE follow-on trial)	Crohn's disease (777)	Subgroup analysis by disease duration: 3 categories: <2 (n=93), 2–<5 (n=148), and ≥5 years (n=536)	Adalimumab PBO	Clinical remission and response rates at weeks 26 and 56	Week 56 clinical remission rates significantly greater for Adalimumab vs PBO in all 3 duration subgroups (19% versus 43% for <2 years; p=0.024; 13% versus 30% for 2 to <5 years; p=0.028; 8% versus 28% for ≥5 years, p<0.001). Shorter duration significant predictor for higher remission rate in Adalimumab -treated pts.	SAEs with Adalimumab lowest with disease duration <2 years.
Sandborn et al. (65) (CLASSIC II)	Crohn's disease (276)	OL for 2 weeks then pts achieving remission entered R phase and	Adalimumab 40 mg wk 1 and 2; pts in remission at weeks 0 and 4 re-randomised to Adalimumab 40	Week 56 maintenance of remission (CDAI <150)	Remission rates at week 56: Randomised: 79% with Adalimumab 40 mg eow and 83% 40 mg weekly and 44%	Adalimumab generally well-tolerated in all pts.

		those not achieving remission continued on OL ADA for 56 weeks	mg eow, 40 mg weekly, or PBO Pts not in remission: Adalimumab 40 mg eow; dose increased to 40 mg weekly on non-response or flare		PBO ($p<0.05$). OL ADA: 46%	
Rutgeerts et al. (66) (EXTEND)	Moderate to severe ileocolonic Crohn's disease (135)	R, DB, PC 52 weeks	Induction Adalimumab 160 mg at week 0 and 80 mg at week 2 then randomised to: Adalimumab 40 mg eow PBO	Mucosal healing at week 12	Mucosal healing: Week 12: 27% Adalimumab vs 13% PBO ($p=0.056$). Week 52: 24% and 0, respectively ($p<0.001$). Week-12 remission rates (CDEI): 52% for Adalimumab and 28% for PBO ($p=0.006$). Week 52: 28% and 3% ($p<0.001$). Remission (CDAI) greater among pts given continuous Adalimumab vs PBO at weeks 12 (47% vs 28%; $p=0.021$) and 52 (33% vs 9%; $p=0.001$).	5 serious and 3 opportunistic infections
Sandborn et al (67) (ULTRA 2)	Ulcerative colitis (494)	R, DB, PC 52 weeks	Adalimumab 160 mg week 0, 80 mg at week 2, then 40 mg eow PBO	Remission at weeks 8 and 52	Overall remission rates: Week 8: 16.5% Adalimumab and 9.3% PBO ($p=0.019$) Week 52: 17.3% and 8.5% ($p=0.004$). Anti-TNF naive pts remission rates: Week-8: 21.3% Adalimumab and 11% PBO ($p=0.017$) Week 52: 22% and 12.4% ($p=0.029$). Previously received anti-TNFs remission rates: Week 8: 9.2% Adalimumab and 6.9% on PBO ($p=0.559$) Week 52: 10.2% and 3% ($p=0.039$).	SAE rate 12% in both groups Serious infections in 1.6% Adalimumab and 1.9% PBO.
Sandborn et al (68) (ULTRA 2 subgroup analysis)	Ulcerative colitis; pts receiving Adalimumab achieving clinical response at week 8 in ULTRA 2 (123)	R, DB, PC 52 weeks	Adalimumab 160 mg week 0, 80 mg at week 2, then 40 mg eow PBO	Pts assessed for week 52 clinical remission, clinical response, mucosal healing, steroid-free remission and steroid discontinuation rates, overall and by prior anti-TNF use.	Clinical remission rate 30.9% Clinical response rate49.6% Mucosal healing rate 43.1% Responders using corticosteroids (N = 90), 21.1% achieved steroid-free remission and 37.8% were steroid-free at week 52. Adalimumab had positive benefit/risk balance for week 8 and 52 response or remission without serious AEs or serious infections.	No safety concerns were identified.

ACR, American College of Rheumatology; ACRPedi30, American College of Rheumatology Pediatric 30 response; AE, adverse event; ASAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BSA, body surface area; CDAI, Crohn's Disease Activity Index; DB, double-blind; eow, every other week; HAQ, Health Assessment Questionnaire; mTSS, modified total Sharp score; MTX, methotrexate; PC, placebo-controlled; Pts, patients; qw, every week; R, randomised; RA, rheumatoid arthritis; SAE, serious adverse event. PBO, Placebo; OL, open-label; TB, tuberculosis; CHF, congestive heart failure; CDEI, Crohn's Disease Endoscopic Index of Severity

etanercept and infliximab was <50%, with etanercept having the best retention rate. Concomitant use of MTX was a strong predictor of adherence to anti-TNF therapy (88).

Results from the US Consortium of Rheumatology Researchers of North America (CORRONA) registry have supported an early use of anti-TNF therapy, with disease duration being an independent predictor of remission in RA patients initiating therapy (89). A comparison of the effectiveness of adalimumab, etanercept and infliximab in biologically naive and switched RA patients showed no differences in the response or remission rates among the anti-TNF drugs, although infliximab was associated with greater persistence in naive patients. In those who were switched to an anti-TNF, the response, remission and persistence were lower as compared with naive patients (90). In an analysis of data from the RADIUS registry, persistence with etanercept, infliximab and adalimumab were all similar with approximate rates of 50% for the first and second-line use (91).

The British Society for Rheumatology Biologics (BSRB) Register – launched in 2001 to monitor the real-world effectiveness and safety of anti-TNF agents and other biologics in RA, and then expanded to other indications – has produced a wide range of data on anti-TNF treatment (in comparison with a non-biologic DMARD control arm) in a range of indications including RA (92, 93), PsA (94), AS (95) and juvenile idiopathic arthritis (JIA) (96). In addition to providing long-term real-world effectiveness and safety data, the BSRB registry has also enabled the evaluation of anti-TNF switching patterns (92).

The TREAT registry was initiated to collect long-term safety data for infliximab and other therapies used in Crohn's disease. Data from more than 5 years' follow-up show an increased risk of serious infections in patients with moderate-severe disease, or treated with either steroids or infliximab or opioid analgesic. As far as risk of mortality is concerned, the higher and significant risk was associated either to age or steroids use or opioid analgesic use (97).

PSOCARE is an Italian registry programme – initiated by AIFA (the Italian Medicines Agency) in 2004 and conducted in collaboration with both scientific dermatological societies (SIDeMaST and ADOI) and ADIPSO (an association of patients affected by psoriasis) – designed to evaluate the real-world long-term outcomes of systemic treatment of psoriasis, including QoL, predictors of clinical response and other factors influencing treatment and outcomes (98-102). Published PSOCARE data suggest that biologic agents are becoming the treatment of choice due to their long-term efficacy and benign tolerability (100). Another PSOCARE data analysis has shown that higher body mass index of patients is associated with a reduction in early clinical response to systemic treatment (102) and, recently, Gisondi et al. reported that many systemic treatments used for long-term management of psoriasis affect a range of metabolic parameters, such as lipid and glucose levels, liver enzymes and renal markers; this has been noted particularly with the retinoid acitretin and cyclosporine, but also with methotrexate and biological agents (98).

Registries can also be used for comparison purposes. For example, a control cohort of RA patients receiving DMARD treatment from a Norwegian registry was compared with data on adalimumab therapy from the DE033 open-label extension study, and it was observed that patients with RA who received adalimumab experienced considerably longer periods of work and continuous employment than patients receiving DMARDs in the setting of clinical practice (103).

Another registry in patients with JIA – the Juvenile Idiopathic Arthritis Registry (STRIVE) is currently ongoing (http://clinicaltrials.gov/ct2/show/NCT00783510).

Future anti-TNF treatment strategies

Anti-TNF agents have been used predominantly as second-line therapy in patients failing multiple DMARD therapy, but clinical data indicate greater clinical benefits when biologics are used earlier in the disease course as first-line therapy – resulting in a prevention of irreversible target organ damage in some patients, for example, in RA (54, 104) and IBD (8).

The OPTIMA study, conducted in 1032 patients with active early RA, demonstrated a clear benefit of initiating anti-TNF therapy early; the combination of adalimumab with MTX allowed to achieve higher ACR20/50/70 responses, more clinical remissions, greater mean reductions in disease activity, no radiographic progression, and normal functional

status at 6 months as compared with MTX alone ($p<0.001$ for all) (104). The PREMIER study was a 2-year, randomized, double-blind clinical trial of combination therapy with adalimumab plus MTX versus MTX or adalimumab alone in 799 patients with early, aggressive RA (54). The results showed that, in patients who had not been previously treated with MTX, the initiation with a combination of adalimumab plus MTX was significantly superior to either MTX alone or adalimumab alone in improving signs and symptoms of disease, inhibiting radiographic progression, and promoting clinical remission; in addition, tolerability was similar in all treatment groups (54).

Recommendations for early treatment of RA from the EULAR guidelines are conservative and advocate MTX as first-line therapy in patients at risk of persistent or erosive disease based on its efficacy, safety profile, and on its beneficial outcomes in treatment combinations (11, 105). According to EULAR guidelines, biological therapy should be considered when poor prognostic factors are present or in patients with insufficient response to MTX and/or other traditional DMARDs, and the standard practice would be to start a TNF inhibitor in combination with MTX (11). With regard for biological therapy, guidelines emphasize the importance of a regular monitoring of disease activity and AEs in guiding the decisions on treatment choice and changes, and recommend a careful evaluation of the individual benefit/risk ratio for each patient (105). Although RA treatment guidelines advocate a tighter control of disease activity to prevent progression, many clinicians would prefer to use anti-TNF agents earlier in the disease course than treatment guidelines currently recommend (106, 107).

Recommendations for the use of biologics in early Crohn's disease state that, while data suggest that biologic therapies may be more effective in some patients, current evidence does not support a widespread early use of biologics in all patients. Early use of biologics should be considered on an individual basis in patients with Crohn's disease with a predictable severe disease course, such as those with extensive disease, severe rectal disease, young age, severe perianal diseases at diagnosis and need for steroids at diagnosis (12, 108).

When considering dermatological indications, currently there are no data or recommendations supporting the use of anti-TNF therapy in the early disease.

Although there are observational data identifying patients who may be more responsive to anti-TNF therapies (95) or more likely to succumb to infections (84), further clinical studies are required to identify patients most likely to benefit from anti-TNF therapy early in their disease course. Pharmacogenetic studies might be able to aid in such identification (109, 110).

CONCLUSIONS

Targeting TNF by means of biologic anti-TNF agents is one of several possible ways to bring the dysregulated immune system under control. This strategy offers effective therapeutic options with good tolerability in patients with IMIDs. Since TNF plays a central role in the pathogenesis and pathophysiology of all IMIDs, it is not surprising that five anti-TNF agents – adalimumab, etanercept, infliximab, certolizumab pegol and golimumab – have been shown to be effective in one or more IMIDs. Given the similarity in IMID pathology, one could expect that the anti-TNF agents would display similar patterns of effectiveness and have comparable tolerability profiles. However, this may not be the case. Structural and pharmacological differences among the anti-TNF agents are likely to result in differences in their efficacy and tolerability in the different IMIDs. Although there is no definitive evidence supporting differences in the clinical efficacy of the various anti-TNF drugs, clear differences in potency, therapeutic dose ranges, dosing, administration regimens, and propensity for immunogenicity do exist.

Among the five TNF inhibitors approved for treatment of IMIDs, adalimumab has the widest range of indications and is, therefore, best placed for treatment of co-occurring inflammatory disorders. Data from controlled clinical trials, showing an excellent efficacy and tolerability of adalimumab in a wide range of indications, supported by real-world long-term findings from observational studies, confirm the value of adalimumab as a suited choice in the management of IMIDs. Further clinical studies are required to identify patients who may be more responsive to anti-TNF therapies and those who are

most likely to benefit from anti-TNF therapy early in the disease course, in order to ensure that treatment can be optimised and tailored to the individual patient.

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