International Journal of Immunopathology and Pharmacology
Volume 27, No.1(S), January – March 2014

CONTENTS

Immune-mediated inflammatory diseases and anti-TNF therapy: focus on adalimumab

C. Blandizzi, P. Gionchetti, A. Armuzzi, R. Caporali, S. Chimenti, R. Cimaz, L. Cimino, G. Lapadula, P. Lionetti, A. Marchesoni, A. Marcellusi, F.S. Mennini, C. Salvarani, G. Girolomoni. The role of tumour necrosis factor in the pathogenesis of immune-mediated diseases..... 1

A. Armuzzi, P. Lionetti, C. Blandizzi, R. Caporali, S. Chimenti, L. Cimino, P. Gionchetti, G. Girolomoni, G. Lapadula, A. Marchesoni, A. Marcellusi, F.S. Mennini, C. Salvarani, R. Cimaz. Anti-TNF agents as a therapeutic choice in immune-mediated inflammatory diseases: focus on adalimumab.... 11

G. Lapadula, A. Marchesoni, A. Armuzzi, C. Blandizzi, R. Caporali, S. Chimenti, R. Cimaz, L. Cimino, P. Gionchetti, G. Girolomoni, P. Lionetti, A. Marcellusi, F.S. Mennini, C. Salvarani. Adalimumab in the treatment of immune-mediated diseases..... 33

REVIEW

THE ROLE OF TUMOUR NECROSIS FACTOR IN THE PATHOGENESIS OF IMMUNE-MEDIATED DISEASES

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Immune-mediated inflammatory diseases (IMIDs), such as rheumatoid arthritis, psoriatic arthritis, psoriasis, axial spondyloarthropathies, Crohn's disease, ulcerative colitis and juvenile idiopathic arthritis, comprise a group of chronic disorders characterized by an immune-mediated pathogenesis. Although at clinical presentation these diseases appear unrelated, they have been recognized to share similar pathogenic mechanisms. Data from epidemiological and genetic studies further support the concept that IMIDs are interrelated, as they can co-occur in the same patient and share a similar genetic susceptibility. The specific aetiologies of IMIDs remain unknown, but all are known to involve dysregulation of the immune system, including an over-expression of the pro-inflammatory cytokine tumour necrosis factor (TNF). The pivotal role played by TNF in the pathogenesis and pathophysiology of IMIDs has been documented by extensive preclinical and clinical investigations, and confirmed by the efficacy of anti-TNF biotechnological drugs, such as etanercept, infliximab and adalimumab, in the therapeutic management of these disorders. In this narrative review, we discuss the available data on the TNF-dependent pathogenesis of IMIDs and associations among the different disorders. Although much remains to be discovered about the pathogenesis and aetiology of IMIDs, their common inflammatory

Key words: Tumour necrosis factor (TNF), immune-mediated inflammatory disease, pathogenesis

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0394-6320 (2014)

pathological features may explain why they can be successfully targeted by anti-TNF drugs. Among these, adalimumab, a fully human monoclonal antibody, has been approved for treatment of nine distinct IMID indications and it is likely to become a valuable therapeutic tool for this complex cluster of chronic inflammatory disorders.

Immune-mediated inflammatory disease (IMID) is a term used to describe a wide array of chronic disorders resulting from an immune-mediated inflammatory pathogenesis (1). Diseases such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), psoriasis, axial spondyloarthropathies (SpA), including pre-radiographic SpA and ankylosing spondylitis (AS), juvenile idiopathic arthritis (JIA), and inflammatory bowel diseases (IBDs), including Crohn's disease and ulcerative colitis (UC), appear, on clinical presentation, to be unrelated, as they display very different signs and symptoms. However, they have been recognized to share common pathogenic mechanisms. The specific aetiologies leading to the onset of each of these diseases remain unknown, and, therefore, it is not clear whether the causative factors are similar among the IMIDs. To date, risk factors for some inflammatory diseases – including genetic and environmental determinants – have been identified, but whether the relationship is causal or not remains to be established. For instance, environmental factors implicated in IBDs include cigarette smoking, appendectomy, urbanization, pollution, diet, antibiotic use, hygiene status, socioeconomic status and microbial exposure (2).

As IMIDs are all inflammatory conditions, it is not unexpected that they share some common pathological pathways, regardless of the specific clinical presentation and underlying risk factors. In particular, all involve dysregulation of the immune system due to an imbalance or inappropriate release of inflammatory cytokines such as interleukin (IL)-12, IL-6 and tumour necrosis factor (TNF) (1, 3, 4). The role of these cytokines has been recognized as being pivotal in the pathogenesis and pathophysiology of IMIDs, particularly TNF (5, 6). This concept has been substantiated by the efficacy of targeted biotechnological drugs – particularly TNF inhibitors, such as etanercept, infliximab and adalimumab, which have been shown to act as modifiers of disease activity in the management of a wide array of apparently clinically distinct inflammatory disorders (3).

Epidemiological studies have revealed that the overall prevalence of this cluster of inflammatory diseases is approximately 4% of the US population (approximately 12 million people) (7) and 5–7% of Western populations (8), with prevalence rates of individual diseases ranging from 0.04% to 8.5%, depending on geographical and ethnic factors (Table 1; Figure 1). Furthermore, the overall prevalence of IMIDs is expected to increase as the number of diseases classified as IMIDs grows (9). Epidemiological data further support the concept that IMIDs are interrelated and display disease co-occurrence and associations (7). Recently, in addition to the common pathological features, genome-wide association studies have identified genes conferring an increased risk of developing IMIDs, and have highlighted a common background of genetic susceptibility, which lends additional credibility to the reported epidemiological evidence of a co-occurrence ('genetic overlap') of IMIDs (10-13).

Given the prevalence and association of IMIDs, together with the substantial clinical morbidity, disability, reduced quality of life (QoL) and lost work productivity (14, 15), it is not surprising that the socio-economic burden of these disorders is substantial (4, 14-18).

Objective and methodology

The aim of this narrative review was to discuss current data on TNF-mediated pathogenesis of IMIDs and associations among the various disorders. Combined literature searches were performed on PubMed using search terms: 'immune-mediated inflammatory disease/disorder' AND 'tumour necrosis factor/TNF' 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 selected manually from the search results and from the bibliographies of previous review articles.

TNF as a key factor in the pathogenesis of immune-mediated diseases

TNF belongs to a large group of cytokines collectively designated as the 'TNF superfamily', which comprises cytokines that share molecular and functional similarities. Besides TNF, the TNF superfamily includes: lymphotoxins (comprising lymphotoxin-a3 – previously designated as TNF-b lymphotoxin-a1b2 and lymphotoxin-a2b1); Fas (a pro-apoptotic factor); CD40 (a factor regulating B lymphocytes); receptor activator of nuclear factor kappa-B. These cytokines are involved in the regulation of several steps of the biological processes related to inflammatory and immune responses, through the control of important cellular functions, such as proliferation, differentiation, programmed cell death (i.e. apoptosis) as well as the biosynthesis and release of a wide array of molecular factors and mediators (19, 20).

TNF is a pleiotropic cytokine deputed to regulate a number of inflammatory reactions and immune functions through the control of various cellular processes, such as proliferation, differentiation, apoptosis, and the release of several molecular factors (21). It is produced by a wide range of cell types, including macrophages, T lymphocytes, mast cells, granulocytes, NK (natural killer) cells, fibroblasts, neurons, keratinocytes and smooth muscle cells (19, 21). Biologically active TNF is a homotrimeric molecular complex consisting of three identical polypeptide subunits. Following biosynthesis, the individual monomers are exposed on the surface of

Table I. *Prevalence of immune-mediated inflammatory diseases*

Reference or source	Disorder	Country	Prevalence
Robinson et al. (7)	IMIDs	US	4%
El-Gabalawy et al. (8)	IMIDs	Western society	5–7%
Helmick et al. 2008 (59)	RA	US	1.3 million (0.4%)
Symmons et al. (60)	RA	UK	1.16% in women and 0.44% in men
Myasoedova et al. (61)	RA	US	0.72% in 2005, increased from 0.62% in 1995
Helmick et al. 2008 (59)	JIA	US	294,000 (0.1%)
Helmick et al. 2008 (59)	SpA	US	0.6–2.4 million adults (0.2–0.8%)
http://www.spondylitis.org/about/overview.aspx	Axial spondyloarthritis	US	2.7 million (0.9%)
http://www.patient.co.uk/doctor/ankylosing-spondylitis	AS	Worldwide	0.1–2% (higher in Northern European countries and lowest in people of Afro-Caribbean descent)
http://www.ccfa.org/what-are-crohns-and-colitis/what-is-crohns-disease/	IBD Crohn's disease UC	US	1.4 million (0.4%) 0.7 million (0.2%) 0.7 million (0.2%)
https://www.psoriasis.org/learn_statistics	Psoriasis	US	7.5 million (2.2%)
https://www.psoriasis.org/learn_statistics	Psoriasis	Worldwide	125 million (2–3%)
Parisi et al. (62)	Psoriasis	Worldwide	From 0.91% (US) to 8.5% (Norway)
Gladman et al. (63)	PsA	Worldwide	From 0.04% to 0.1%

AS, ankylosing spondylitis; IMID, immune-mediated inflammatory disease; JIA, juvenile idiopathic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthropathy; UC, ulcerative colitis.

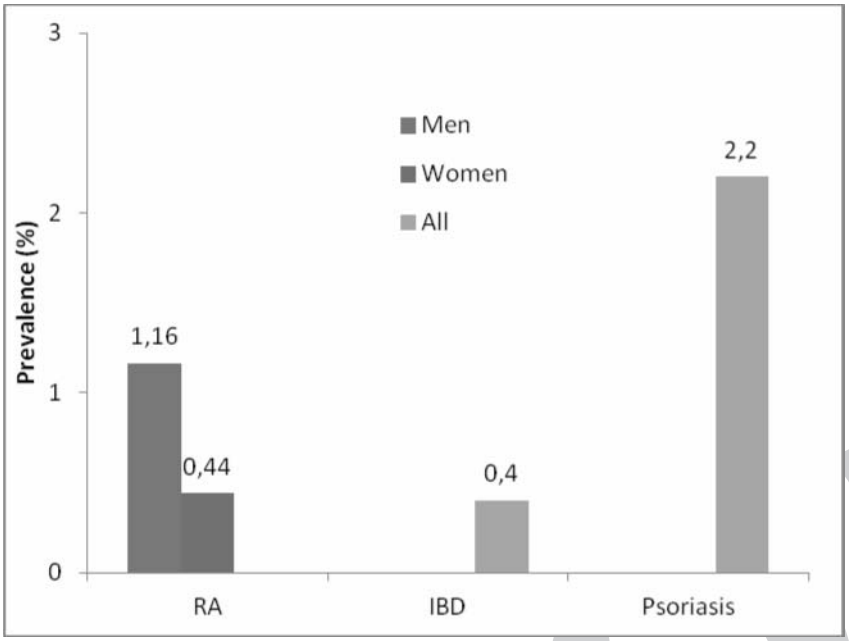

Fig. 1. *Prevalence of RA, IBD and psoriasis.*

cell membrane, where they are assembled to form the membrane-bound homotrimeric transmembrane TNF (tmTNF). tmTNF can then be cleaved by TNF-α converting enzyme (TACE) to generate the homotrimeric soluble form (sTNF), which is released into the extracellular fluids and thereby into the blood stream. TNF is biologically active in both its trimeric forms – i.e. the membrane bound tmTNF and the circulating sTNF. The monomeric form of sTNF circulates also in the blood and, while it does not appear to exert any biological activity as such, it can assemble with other monomers to generate biologically active trimeric sTNF complexes (21, 22).

TNF carries out its biological actions through interaction with two specific receptors, designated as TNF receptor 1 (TNFR1 [p55, CD120a]) and receptor 2 (TNFR2 [p75, CD120b]). Both receptors are trimeric glycoproteins localized on the cell membrane surface, but they differ in terms of cellular expression, affinity for the different molecular forms of TNF and transduction mechanisms. TNFR1 is constitutively expressed in the majority of cell types, and displays preferential affinity for tmTNF. TNFR2 expression is mainly inducible, particularly in hematopoietic and endothelial cells, and has a preferential affinity for sTNF (21, 23). tmTNF, owing to its cell membrane location, can interact with target cells equipped with TNF receptors and can exert a dual action: on one hand it can stimulate cell surface receptors on the target cell to elicit a biological response in the target cell through the activation of transduction pathways linked to the membrane receptor (signalling); on the other hand, tmTNF itself can be activated by its binding to the receptors on the target cell (reverse signalling), thus becoming able to mediate anti-inflammatory/immunomodulatory actions, such as inhibition of T cell proliferation, inhibition of pro-inflammatory cytokine release and apoptosis. Of note, the anti-inflammatory responses mediated by reverse signalling can be activated also by binding of tmTNF with the large molecular complex generated by the interaction of sTNF with anti-TNF drugs, such as infliximab and adalimumab (21, 24).

TNF plays a central role in the pathogenesis of most IMIDs (5). Over-expression of TNF has been shown indeed to promote pro-inflammatory conditions. In particular, along with the dysregulation of other cytokines and a variety of cell types, TNF is

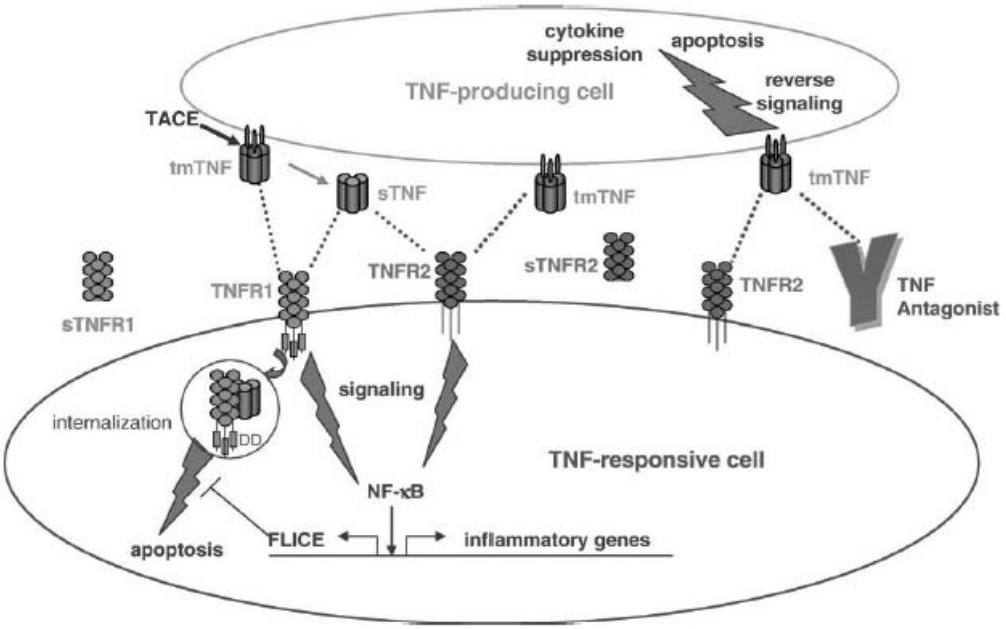

Fig. 2. *Schematic diagram showing the involvement of TNF in immune-mediated inflammatory disorders. Reproduced with permission from Tracey D, et al. Pharmacol Ther 2008;117:244-79 (21) <<Permission will be required from Tracey D, et al. Pharmacology & Therapeutics 2008;117, Fig. 1 page 249, to re-use this figure.>>*

implicated in the pathogenesis of RA, Crohn's disease, psoriasis, PsA, systemic lupus erythematosus, type 1 diabetes, multiple sclerosis, asthma, allergy and UC (3) (Figure 2).

Preclinical and clinical studies on RA have paved the way towards our understanding of the pivotal role played by TNF in the pathophysiology of IMIDs and the identification of this inflammatory cytokine as a relevant target for their therapeutic management (21). The main pathologic hallmark of RA is represented by chronic synovial inflammation leading to progressive joint cartilage and bone destruction. Studies aimed at identifying the molecular pathogenesis of these processes highlighted both TNF and IL-1 as key factors promoting inflammation and matrix disruption (25, 26). It was then established that abnormal elevations of TNF concentrations at the sites of inflammation were a primary factor accounting for the disease activity, and these observations generated the hypothesis the removal of TNF excess from inflamed joints would have conferred therapeutic benefits (27, 28). In support of these concepts, transgenic mice over-expressing TNF were found to spontaneously develop an arthritic pathology which displayed clinical and histological features similar to RA (29). Furthermore, in an experimental model of collagen-induced arthritis, the blockade of TNF was effective in reducing the disease activity (30, 31).

A number of experimental and clinical studies have provided compelling evidence to support a strong role of TNF in the pathogenesis of IBDs (32, 33). The major findings in this field can be concisely summarized as follows: 1) elevated levels of TNF, along with high concentrations of IL-1, transforming growth factor-α and interferon-γ, are present in the inflamed mucosa of patients with Crohn's disease (32); 2) there is an enhanced expression of TNF in patients with both Crohn's disease and UC (34, 35); 3) studies in animals with experimental bowel inflammation have shown that TNF functions as a driving factor of disease activity (36, 37), and that TNF inhibition or genetic suppression can prevent disease onset and/or reduce disease severity (38).

TNF is involved in a number of mechanisms underlying the pathogenesis of both psoriasis and PsA (39). In the setting of psoriasis, the main TNF-dependent mechanisms include: stimulation of the maturation of Langerhans cells and dendritic cells, with skewing of lymphocyte differentiation (40); promotion of dendritic cell migration from

the skin to lymph nodes (41, 42); accumulation of leukocytes in the inflamed skin through induction of adhesion molecules and chemokines on dermal microvascular endothelial cells, keratinocytes, and dermal fibroblasts (43, 44); induction of dermal vascular changes via production of vascular endothelial growth factor by keratinocytes and hyperproliferation of keratinocytes (45); induction of itching through the activation of TNF receptors on sensory nerve endings (39). With regard for PsA, TNF has been shown to play a primary role in the determinism of inflammation and joint-bone damage by virtue of the following mechanisms: production of lytic enzymes, such as matrix metalloproteases (46); contribution to synovial vascular proliferation by induction of angiogenic growth factors; stimulation of bone resorption, inhibition of bone formation, and inhibition of synthesis of proteoglycans, with subsequent occurrence of bone erosions up to osteolysis, new bone deposition, or both; in particular, based on evidence provided by preclinical investigations, it has been appreciated that TNF can promote osteoclastogenesis either directly, via actions on osteoclast precursors and osteoclasts, or indirectly, via induction of synovial inflammation and various osteoclastogenic factors (39, 47, 48).

Inflammatory and autoimmune pathology

It is worth noting that several IMIDs also harbour an autoimmune component. Indeed both autoimmune diseases and IMIDs arise when adaptive and innate immune system responses are impaired. An autoimmune disease occurs when the organism fails to recognize its own molecular components as self constituents, thereby leading to an adaptive immune response against its own cells and tissues. On the other hand, an IMID results from a dysregulation of the normal body's innate immune functions. An inability to regulate the magnitude and duration of the immune (or autoimmune) response leads to the onset of an inflammatory state or a condition of overreaction of the immune system. Subsequent downstream signalling by proinflammatory mediators, such as TNF, interleukins, interferons, etc., gives rise, eventually, to the occurrence of symptoms and end-organ damage. For instance, the complex pathogenesis of IBDs, although not yet completely elucidated, is known to involve both auto-immune and immune-mediated mechanisms, with a serious dysregulation of the innate immune system, due to infection or trauma, leading to a chronic inflammatory state and abnormalities of the acquired immune system, which result in an autoimmune response (49). In RA, besides the direct targeting of synovial tissues by autoantibodies, cytokines produced by synovial cells are thought to be involved in the pathogenesis of the disease in its early stage, and, in this context, TNF has been shown to play a major positive feedback role through the activation of cytokine and chemokine expression, in combination with a plethora of other actions, mediated by a variety of cell receptors and molecular factors, leading ultimately to RA clinical symptoms and joint damage (50). In diseases that appear to result from a combination of both autoimmune and inflammatory pathogenic mechanisms, it still remains unknown how the two components interact or whether one can trigger and maintain the other. Several autoimmune diseases do not appear to be preceded by inflammation, although some do, and many although not all autoimmune diseases cause inflammation. Even though the same mediators, including TNF, are often involved in the pathogenesis of inflammation and autoimmune responses, the relationship between these two processes is far from clear. Indeed, autoimmunity can, and often does occur in the absence of overt inflammation, and vice versa, chronic inflammation can exist in the absence of autoimmunity. The picture is further complicated by the involvement of other factors, such as environmental triggers, genetic predisposition and comorbidities.

Associations of immune-mediated inflammatory diseases

The contention of a common pathophysiology of IMIDs is corroborated by the clinical evidence that, often, two or more IMIDs co-exist in the same patient (7). Certain diseases are more likely than others to present in the same patient: these combinations are designated as 'disease associations' – also termed 'immune-mediated inflammatory syndromes' or 'clustering' (3, 51, 52).

A large US-based epidemiological study has lent support to the concept that IMIDs are interrelated and has shown that a common pathogenic

background translates into similar patterns of disease co-occurrence, with patients affected by at least one IMID having a higher risk of developing another IMID (7). In addition, genome-wide association studies have identified genes conferring an increased risk of developing an IMID and have revealed a common genetic susceptibility among IMIDs (10-13).

Among the currently available TNF antagonists – etanercept, infliximab, adalimumab, certolizumab pegol and golimumab – adalimumab has been approved for use in nine distinct IMID indications (namely RA, PsA, SpA/AS, Crohn's disease, paediatric Crohn's, UC, JIA, psoriasis and Behcet's disease). Within these indications, the IMIDs that have been found to occur in the same patient include: RA + UC (53, 54); AS + Crohn's disease or UC (55); PsA + psoriasis, Crohn's disease or UC (56); Crohn's disease + psoriasis (56, 57); UC + psoriasis (58). In these settings, the use of a multi-indication drug, such as adalimumab, to treat two or more indications in the same patient, decreases the drug burden, thus considerably making this TNF inhibitor a very useful tool for the treatment of co-occurring IMIDs.

At present, the reasons for the occurrence of some disease combinations and not others are not clear. In addition, due to the above-mentioned genetic susceptibility, IMIDs are also more likely to occur in relatives of patients affected by an IMID (3).

CONCLUSIONS

Although much remains still to be discovered about the pathogenesis and aetiology of IMIDs, there is presently clear evidence that these diseases share similar pathological inflammatory pathways, and that TNF represents one of the immune mediators known to play a key role in their pathophysiology. The common pathological background of IMIDs, supported by their association in the same patient, have been noted in clinical practice and confirmed by epidemiological studies. Along the same lines, genetic studies have also revealed common patterns of genetic susceptibility. TNF is involved in a wide array of biological activities including a number of stimulating and inhibitory actions on several cellular components within and outside the immune system, resulting from molecular signalling and reverse signalling mechanisms. The advances made in understanding the role of TNF in the pathophysiology of chronic inflammatory disorders have led to the development of biotechnological drugs acting as TNF inhibitors, most of which are currently employed for the therapeutic management of one or more IMIDs. Among these, adalimumab has been approved for the treatment of nine distinct IMID indications and it is therefore expected to become a valuable therapeutic tool across this complex cluster of inflammatory disorders.

ACKNOWLEDGEMENTS

Medical writing assistance was provided by Mary Hines on behalf of HPS, Health Publishing & Services Srl, Milan. The assistance was supported by funding from AbbVie Srl, Italy.

CB has been member of advisory boards for Abbvie.

RC has been member of advisory boards for Abbvie.

GG has received advisory/speaker honoraria and/or research funding from AbbVie, Almirall, Boehringer Ingelheim, Celgene, Dompè, Eli-Lilly, Galderma, GSK, Janssen, Leo Pharma, Otsuka, Merck-Serono, Maruho, MSD, Novartis and Pfizer.

AA has received Consulting fees from Abbvie, Hospira, Lilly, MSD and lecture fees from Abbvie, Chiesi, Ferring, MSD, Nycomed and Otsuka.

AM has received consulting fees and/or speaker fees from Abbvie, Pfizer, Merck, UCB.

The other authors have no conflicts of interest to declare.

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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

Keywords: Tumour necrosis factor (TNF), immune-mediated disorders, anti-TNF therapy

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0394-6320 (2014)

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 TNF–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 trial 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 effect seen with different anti-TNF agents, with those also having CDC and ADCC activity being more effective clinically than those that simply 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 subsequent reduction of its plasma half-life. However, this problem was 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 RA studies of biological agents in RA (28) showed differences in efficacy of anti-TNF 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 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 in 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 a 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 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 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 disease 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 adverse events (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). (67, 68). 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, etanercept and infliximab was <50%, with etanercept having the best retention rate. Concomitant use of MTX was a strong predictor of adherence to anti-

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	ADA 40 mg eow ADA 20 mg qw PBO	Week 52 mTSS Week 24 and 52 ≥20% improvement in ACR20 Week 52 HAQ-disability index	Change in TSS greater with ADA vs PBO; week24 ACR20 63% and 61% for ADA 40 and 20 vs 30% with PBO; week 52 ACR20 59% and 55% for ADA 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 ADA and PBO; serious infections higher with ADA (3.8%) vs PBO (0.5%); p≤0.02
Breedvald et al. (54) (PREMIER)	Early aggressive RA, MTX naïve (799)	R, DB, 2 year	ADA 40 mg eow + MTX MTX alone ADA 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 ADA alone (p<0.001 for both); less radiographic progression at 1 and 2 yrs	AE profiles were similar in all 3 study groups
					(p≤0.002)	
Lovell et al. (55) (DE038)	Juvenile rheumatoid arthritis (poly-articular) (171)	R, PC, 2 years DB weeks 16-32 based on week 16 response	ADA 24 mg/m^2 BSA (max 40 mg) eow ± MTX PBO ± MTX	Disease flares Week 16 and 32 ACRpedi30	Week-16 ACRpedi30 74% in ADA alone and 94% in ADA+MTX Disease flares: No MTX: 43% with ADA and 71% PBO (p=0.03). With MTX: 37% ADA and 65% PBO (p=0.02). Week-48 ACRpedi30: With MTX – significantly greater for ADA vs PBO No MTX – No significant differences between ADA and PBO	Safety profiles similar among groups
Van der Heijde et al. (56) (ATLAS)	Ankylosing spondylitis (315)	R, DB, PC for 24 weeks	ADA 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% ADA 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 ADA vs PBO at weeks 12 and 24 (p<0.001). Partial remission greater with	AE rate with ADA 75.0% vs 59.8% with PBO; p<0.05). Most AEs were mild or moderate in severity.

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 naïve 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

					ADA 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	ADA 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 - ADA 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	ADA 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 ADA and 14% with PBO (p<0.001). Week 24: ACR20 response rates similar to wk 12 and change in the mTSS -0.2 with ADA 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 ADA vs PBO.	ADA was generally safe and well-tolerated
Mease et al. 2009 (59) (ADEPT OL extension)	Psoriatic arthritis (245)	OL 2 years	ADA 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 ADA. Improvements in skin disease were maintained, with >20% of pts achieving PASI100.	The nature and frequency of AEs during long-term ADA 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	ADA 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 ADA and 7% with PBO. Weeks 33 to 52, lost response rate 28% with pts re-randomised to PBO vs 5% with continued ADA.	–
Saurat et al. (62) (CHAMPION)	Psoriasis (271)	R, DB, AC, PC 16 weeks	ADA 80 mg then 40 mg eow MTX PBO	Week 16, proportion of pts achieving ≥75% improvement in PASI75.	16 weeks PASI75 with ADA 79.6% and MTX 35.5% (p<0.001 vs. ADA) and PBO 18.9% (p<0.001 vs. ADA). Complete clearance of disease rate 16.7% with ADA, 7.3% with MTX and 1.9% with PBO ADA 57% improvement in	AEs similar across treatment groups.

(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

					mean PASI observed at week 4.	
Gordon et al. (61) (REVEAL OL extension)	Psoriasis	OL extension of pts receiving ADA in the DB phase, groups by response, 3 year	ADA from baseline to 3 yrs ADA from week 16 to 3 years	In pts on continuous ADA: 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	ADA 40 mg eow ADA 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	% of responders in remission significantly greater with ADA 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).	ADA was well-tolerated
				and 56.	No significant differences in efficacy between adalimumab eow and weekly dose regimens.	
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)	ADA PBO	Clinical remission and response rates at weeks 26 and 56	Week 56 clinical remission rates significantly greater for ADA 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 ADA-treated pts.	SAEs with ADA 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 those not achieving remission continued on OL ADA for 56 weeks	ADA 40 mg wk 1 and 2; pts in remission at weeks 0 and 4 re-randomised to ADA 40 mg eow, 40 mg weekly, or PBO Pts not in remission: ADA 40 mg eow; dose increased to 40	Week 56 maintenance of remission (CDAI <150)	Remission rates at week 56: Randomised: 79% with ADA 40 mg eow and 83% 40 mg weekly and 44% PBO (p<0.05). OL ADA: 46%	ADA generally well-tolerated in all pts.

years' follow-up show an increased risk of serious infections in patients with moderate-severe disease, or treated with either steroids or infliximab or narcotic analgesic. As far as risk of mortality is concerned, the higher and significant risk was associated either to age or steroids use or narcotic 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

			mg weekly on non-response or flare			
Rutgeerts et al. (66) (EXTEND)	Moderate to severe ileocolonic Crohn's disease (135)	R, DB, PC 52 weeks	Induction ADA 160 mg at week 0 and 80 mg at week 2 then randomised to: ADA 40 mg eow PBO	Mucosal healing at week 12	Mucosal healing: Week 12: 27% ADA vs 13% PBO (p=0.056). Week 52: 24% and 0, respectively (p<0.001). Week-12 remission rates (CDEI): 52% for ADA and 28% for PBO (p=0.006). Week 52: 28% and 3% (p<0.001). Remission (CDAI) greater among pts given continuous ADA 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	ADA 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% ADA and 9.3% PBO (p=0.019) Week 52: 17.3% and 8.5% (p=0.004). Anti-TNF naive pts remission rates:	SAE rate 12% in both groups Serious infections in 1.6% ADA and 1.9% PBO.
					Week-8: 21.3% ADA 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% ADA and 6.9% on PBO (p=0.559) Week 52: 10.2% and 3% (p=0.039).	
Sandborn et al (68) (ULTRA 2 subgroup analysis)	Ulcerative colitis; pts receiving ADA achieving clinical response at week 8 in ULTRA 2 (123)	R, DB, PC 52 weeks	ADA 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. ADA 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; ADA, adalimumab; AE, adverse events; 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 events.

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 (JIA) 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.

ACKNOWLEDGEMENTS

Medical writing assistance was provided by Mary Hines on behalf of HPS, Health Publishing & Services Srl, Milan. The assistance was supported by funding from AbbVie Srl, Italy.

CB has been member of advisory boards for Abbvie.

GG has received advisory/speaker honoraria and/or research funding from AbbVie, Almirall, Boehringer Ingelheim, Celgene, Dompè, Eli-Lilly, Galderma, GSK, Janssen, Leo Pharma, Otsuka, Merck-Serono, Maruho, MSD, Novartis and Pfizer.

AA has received consulting fees from Abbvie, Hospira, Lilly, MSD and lecture fees from Abbvie, Chiesi, Ferring, MSD, Nycomed and Otsuka.

AM has received consulting fees and/or speaker fees from Abbvie, Pfizer, Merck, UCB.

RC has been member of advisory boards for Abbvie.

The other authors have no conflicts of interest to declare.

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REVIEW

ADALIMUMAB IN THE TREATMENT OF IMMUNE-MEDIATED DISEASES

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Tumour necrosis factor (TNF) plays an important role in the pathogenesis of immune-mediated inflammatory diseases (IMIDs). TNF inhibition results in down-regulation of abnormal and progressive inflammatory processes, resulting in rapid and sustained clinical remission, improved quality of life and prevention of target organ damage. Adalimumab is the first fully human monoclonal antibody directed against TNF. In this article, we review the role and cost effectiveness of adalimumab in the treatment of IMIDs in adults and children. The efficacy and tolerability of adalimumab has been demonstrated in patients with a wide range of inflammatory conditions, leading to regulatory approval in rheumatoid arthritis (RA), psoriatic arthritis (PsA), plaque psoriasis, inflammatory bowel diseases (Crohn's disease, ulcerative colitis, paediatric Crohn's disease, and intestinal Behçet's disease), ankylosing spondylitis (AS), axial spondyloarthritis (SpA) and juvenile idiopathic arthritis. The major tolerability issues with adalimumab are class effects, such as injection site reactions and increased risk of infection and lymphoma. As with all anti-TNF agents, adalimumab is immunogenic, although less than infliximab, and some patients receiving long-term adalimumab will develop anti-drug antibodies, causing a loss of response. Comparisons of its clinical utility and cost effectiveness have shown it to be a valid treatment choice in a wide range of patients. Recent data from Italian economic studies show the cost effectiveness

Keywords: Adalimumab, tumour necrosis factor (TNF), immune-mediated disorders, anti-TNF therapy

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0394-6320 (2014)

of adalimumab to be below the threshold value for health care interventions for most indications. In addition, analysis of indirect costs shows that adalimumab significantly reduces social costs associated with RA, PsA, AS, Crohn's disease and psoriasis. The fact that adalimumab has the widest range of approved indications, many often presenting together in the same patient due to the common pathogenesis, may further improve the utility of adalimumab. Current clinical evidence shows adalimumab to be a valuable resource in the management of IMIDs. Further research, designed to identify patients who may benefit most from this drug, will better highlight the role and cost-effectiveness of this versatile TNF inhibitor.

Immune-mediated inflammatory disease (IMID) is the designation given to a range of inflammatory disorders that share common pathogenic pathways and a dysregulation of inflammatory cytokines (1). Indeed, some chronic inflammatory disorders share overlapping epidemiological, pathogenic, and genetic features (2, 3), and have been shown to cluster (i.e. the presence of one disease confers an increased risk of developing others) in some patients and families. Examples of these combinations include psoriasis, psoriatic arthritis (PsA) and Crohn's disease (4-6), rheumatoid arthritis (RA) and ulcerative colitis (UC) (7-10), arthropathies and inflammatory bowel disease (IBD; Crohn's disease or UC) (11) and spondyloarthropathies (SpA), PsA and IBD (12).

The cytokine tumour necrosis factor (TNF) plays an important role in the pathogenesis of these chronic inflammatory conditions and immune-mediated disorders (13, 14). The inhibition of TNF results in a down-regulation of the abnormal inflammatory pathways implicated in the pathogenesis and progression of IMIDs (15). Biologic response modifiers targeting TNF – comprising the class of anti-TNF biotechnological drugs – employed as monotherapy or in combination with other immunosuppressive or anti-inflammatory therapies, have been shown to provide rapid and sustained clinical remission, improved quality of life (QoL), prevention of disease progression and, in many cases, resolution of target organ damage under chronic conditions (16, 17).

Inference from the latest EULAR guidelines for treatment of rheumatic diseases with biologic agents suggests that the ideal anti-TNF agent should be effective in alleviating symptoms and preventing radiographic progression of structural damage, and capable of inducing clinical remission (or even reversing the existing damage), with rapid onset of action, persistent effect (no tolerance effect [i.e. low immunogenicity]) and benign tolerability. It should also be convenient and easy to administer, cost effective, and suitable for use in all patient populations, including the elderly, children and those with renal and hepatic impairment (16). Although the ideal anti-TNF drug does not yet exist, among the available anti-TNF agents, adalimumab, the first fully human IgG_1 monoclonal antibody directed against TNF, has many attributes that make it a valid clinical choice for long-term treatment of rheumatic diseases.

Adalimumab binds TNF bivalently, to form multimeric 'antigen-antibody' complexes, thus preventing TNF from activating cell surface TNF receptors, thereby modulating the biological activities regulated by TNF (14). By comparison, infliximab is a chimeric mouse-human IgG_1 monoclonal antibody and golimumab is a fully human IgG_1 monoclonal antibody, and both bind TNF bivalently. Etanercept, on the other hand, is a TNF receptor-IgG fusion protein, which consists of the constant Fc fragment of human IgG_1 connected by a hinge region to two extracellular domains of the human TNF receptor (TNFR) (18), and forms a monovalent bond with TNF. Certolizumab pegol comprises a single IgG_1 Fab' fragment of a humanized monoclonal antibody bound to two 20 kD polyethylene glycol chains, which extend the plasma half-life of the drug (19). Since it is not equipped with an Fc region, certolizumab interacts with TNF in a monovalent fashion (20, 21).

Objective and methodology

The aim of this narrative review is to discuss the place of adalimumab in the treatment of IMIDs in adults and children, as well as to review economic data on its potential to provide a cost effective treatment option compared with other existing treatments, with particular focus on the economics

of its multi-indication role in the treatment of patients with more than one IMID. Combined automated and manual literature searches were performed in PubMed using the search terms 'adalimumab' AND 'immune-mediated disease/disorders' AND ['children' OR pediatric/paediatric' OR 'adolescent' OR 'cross-indication' OR 'disease association' OR 'cost' OR 'economic' or 'pharmacoeconomic']. From the resulting papers, manual searches were performed to find relevant papers on adalimumab in the treatment of immune-mediated disease/disorders.

Current role of adalimumab

Adalimumab was first approved for treatment of RA in 2002 and is now indicated for the treatment of a wide range of IMIDs (Table 1) (22). The efficacy and tolerability of adalimumab has been demonstrated in several pivotal trials in patients with a wide range of inflammatory conditions such as RA (23, 24), AS (25, 26), axial spondyloarthritis (SpA) (27), PsA (26, 28), plaque psoriasis (29, 30), Crohn's disease (31, 32), UC (33, 34) and JIA (12). The clinical data obtained in these trials have been reviewed in another paper in this supplement.

The major safety and tolerability issues with adalimumab include mostly class effects, such as injection site reactions, increased infection risk (serious infections, tuberculosis and opportunistic infections), lymphoma, and other rare events, including demyelinating disease, autoimmune phenomena, hematologic toxicities, and congestive heart failure (35, 36). A large cross-indication analysis of adalimumab safety data from almost 12 years of adalimumab exposure in clinical trials, showed that the most frequently reported serious adverse events (SAEs) were infections, with the greatest incidence reported in studies of patients with RA and Crohn's disease (37). Although the overall malignancy rates were similar to those in the general population, the incidence of lymphoma was increased in patients with RA, and the incidence of non-melanoma skin cancer was raised in RA, psoriasis and Crohn's disease (37).

Immunogenicity

As with all anti-TNF agents, adalimumab is immunogenic, and over time patients develop anti-drug antibodies (ADAs) to adalimumab, which eventually cause tolerance – a reduction in the pharmacological activity leading to a reduced efficacy and a need for dose escalation (38, 39). ADAs, reported particularly with infliximab, are seen to a lesser extent with adalimumab, occurring in approximately 20–28% of patients receiving long-term adalimumab treatment (40). In addition to reduced efficacy, ADAs are also associated with safety issues such as anaphylaxis or vasculitis (41). Combination therapy with non-biologic disease modifying antirheumatic drugs (DMARDs), particularly methotrexate (MTX), seems to reduce the occurrence of ADA formation (40, 42). Studies assessing immunogenicity, to determine optimal treatment regimens and concomitant immunosuppressant therapy to minimize ADA formation or to investigate the use of neutralizing immunotherapy to reduce the likelihood of ADA development, are ongoing (39, 43). In addition to being dependent on the specific anti-TNF agent used, immunogenicity and ADA formation appear to be associated with the mode of administration and regimen used (40, 44, 45). Generally, subcutaneous administration is more immunogenic than intravenous, due to the smaller volumes used, slower distribution and greater variability of interindividual drug exposure (45). The likelihood of ADA formation also appears to be reduced with continuous maintenance therapy compared with intermittent or sporadic treatment (44). ADA formation may also be dependent on the underlying disease, with higher ADA levels observed in RA, Crohn's disease and PsA; although this may simply be due to an increased exposure to biologics or a greater number of clinical studies in these patient populations.

A range of analytical assays, such as enzyme-linked immunosorbent assay (ELISA) and radioimmunoassay (RIA), have been used to detect and measure ADAs; however, the ADA titre can vary according to the type of assay used and is confounded by the presence of circulating anti-TNF antibodies and rheumatoid factor. Accordingly, the reported prevalence of ADAs can vary substantially (44) (Table 2).

IMID cross-indications

Among the available TNF antagonists – etanercept, infliximab, adalimumab, certolizumab

Table 1. *Adalimumab indications according to labelling (21)*

Indication	Approval date (country)	Details
Rheumatoid arthritis (RA)	Dec 2002 (USA) Sept 2003 (Europe)	In combination with MTX: Moderate to severe, active RA in adult patients when the response to DMARDs including MTX has been inadequate Severe, active and progressive RA in adults not previously treated with MTX Can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate
Polyarticular juvenile idiopathic arthritis [JIA]	Feb 2008 (USA) Sept 2008 (Europe)	In combination with MTX: Children and adolescents 4 to 17 years who have had an inadequate response to one or more DMARDs; can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate
Ankylosing spondylitis (AS) and axial spondyloarthritis (AxSp)	AS: Jun 2006 (Europe); Jul 2006 (USA) AxSp: Jul 2012 (Europe)	Adults with severe active AS who have had an inadequate response to conventional therapy Axial spondyloarthritis without radiographic evidence of AS Severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and/or MRI, with inadequate response to, or intolerant to NSAIDs
Psoriatic arthritis	Aug 2005 (Europe) Dec 2005 (USA)	Active and progressive PsA in adults when the response to previous DMARDs has been inadequate
Plaque psoriasis	Dec 2007 (Europe)	Moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, MTX or PUVA
Crohn's disease	Feb 2007 (USA) Jun 20007 (Europe)	Moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies
Paediatric Crohn's disease	Nov 2012 (Europe)	Moderately to severely active Crohn's disease, in children who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or
		have medical contraindications for such therapies
Ulcerative colitis (UC)	April 2012 (Europe) Sept 2012 (USA	Moderately to severely active UC in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies
Intestinal Behçet's disease	May 2013 (Japan)	Intestinal Behçet's disease (Behçet's disease accompanied by intestinal ulcer) in adults refractory to conventional therapies

CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drug; MRI, magnetic resonance imaging; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; PUVA, psoralen-ultraviolet A combination therapy.

Table II. *Frequency of anti-drug antibody (ADA) development reported with anti-tumour necrosis factor (anti-TNF) therapies (44)*

Drug	Indication	Prevalence reported (% patients)
Adalimumab	RA	0.72–87%
	AS	31%
	PsA	18%
	Psoriasis	6–45%
	Crohn's disease	0.04–17%
Infliximab	RA	10–50%
	SpA	15.4–25.5%
	AS	18-29%
	Crohn's disease	6–61%
	PsA	15.4%
	Psoriasis	19.5–51.5%
Etanercept	RA	0–5.6%
	AS	0
	PsA	0
	Psoriasis	1.1–18.3%
Golimumab	RA	0–7%
	AS	1.4–4.1%
	PsA	4.6–4.9%
Certolizumab	RA	5–8.1%
	Psoriasis	4–25%
	Crohn's disease	3.1–17.7%

AS, ankylosing spondylitis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthropathy.

pegol and golimumab – adalimumab has the widest employment, having been approved for use in nine separate IMID indications (RA, PsA, SpA/AS, Crohn's disease, paediatric Crohn's, UC, JIA, psoriasis and intestinal Behçet's disease). Within these indications, IMIDs that have been reported in the same patient include peripheral arthropathies + IBD (46-48), RA + IBD (7-10, 42, 49), RA + paediatric UC + Crohn's disease (50), IBD + psoriasis (4, 6, 49) and PsA + psoriasis + IBD (5).

Table III. *Clinical studies of adalimumab in patients with two or more immune-mediated disorders*

Reference (Study acronym)	Indications	Design	N	Treatment	Endpoints	Efficacy outcomes	Tolerability
Andrisani et al. (42)	Seronegative erosive RA + refractory UC	Case study	1, 54-yr-old female	ADA 160/80 mg wk 0/2, then 40 mg eow	NA	Complete remission after 1 yr	NR
Braun et al. (52) (RHAPSODY)	AS ± psoriasis	P, OL	1250 (148 with psoriasis	ADA 40 mg eow for 12 wks	ASAS40, BASDAI50	ASAS40 46.7% and 54.7% of pts ±psoriasis BASDAI50 58.6% and 57.0% of pts ±psoriasis	No correlation of skin changes with AS efficacy
Kotaniemi et al. (55)	JIA and uveitis	P, OL	94	ADA	Uveitis SUN activity, arthritis activity	SUN 2x reduction (good response) in 28%, moderate 17%, no change 17% and worsening in 13%	NR
Lofberg et al. (46) (CARE)	Moderate-to-severe CD + extraintestinal manifestations (EIMS)	P, OL, MC	945 (497 with EIM)	ADA 160/80 mg wk 0/2, then 40 mg eow	Remission rate HBI <5	Wk 20 CD remission rate 52%; 51% with EIM free of EIM S&S	Serious infections 5%; well tolerated
Moretti et al. (56)	Psoriatic JIA and	Case report	1	ADA	NA	Sustained remission	NR
	uveitis					in JIA and uveitis	
Rudwaleit et al. (53) (RHAPSODY)	AS and peripheral arthritis and enthesitis	P, OL	1250 (686 with enthesitis and 281 with peripheral arthritis)	ADA 40 mg eow for 12 wks	ASAS20, MASES	Improvement in MASES ASAS20 in 66.7–71% of pts	NR
Rudwaleit et al. (47) (RHAPSODY)	AS and uveitis	P, OL	1250 (451 with uveitis or h/o uveitis)	ADA 40 mg eow for 20 wks	Rate of uveitis flares	Wk 20 rate of AU flares reduced by 45–68%	NR
Van der Heijde et al. (58)	AS (some pts with uveitis,	RCT	315 (95 with uveitis, 33 with psoriasis)	ADA (n=208) PBO (n=107)	ASAS20, BASFI, BASDAI, BASMI	ASA20 58.2% with ADA, and 20.6% with PBO	AEs: 75% (ADA) vs 59.8% (PBO) Injection site reactions: 10.1% vs 2.8%
Yildiz et al. (57)	AS and Behçet's	Case study	1, 44-yr-old male	ADA 40 mg eow	NA	Remission of AS and BD	NR
Zannin et al. (54)	JIA and AU	Observational registry	108 (91 with 12-mo follow-up)	ADA (n=43) IFX (n=48)	Change in uveitis course and in number of ocular complications	AU remission 55.3% (ADA 67.4%, IFX 42.8%; p=0.025) Reduction in ocular complications	No SAEs Minor AE in 8.8% (11Aes, 9 with IFX and 2 with ADA)

ADA, adalimumab; AS, ankylosing spondylitis; ASAS20, ≥20% improvement in Assessment of Ankylosing Spondylitis response criteria; AU, anterior uveitis; BASFI, Bath Ankylosing Spondylitis Functional Index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BD, Behçet's disease; CD, Crohn's Disease; DB, double-blind; EIM, extraintestinal manifestations; eow, every other week; HBI, Harvey-Bradshaw Index; h/o, history of; IFX, infliximab; MASES, Maastricht ankylosing spondylitis enthesitis score; MC, multicentre; NA, not applicable; NR, not reported; OL, open-label; P, prospective; PBO, placebo; PC, placebo-controlled; pts, patients; R, randomised; RA, rheumatoid arthritis; RCT, randomised controlled trial; S&S, signs and symptoms; SUN, Standardized Uveitis Nomenclature; UC, ulcerative colitis.

Table IV. *Adalimumab ongoing/unpublished trials in off-label indications [Source: ClinicalTrials.gov]*

ClinicalTrial.gov number (Study acronym)	Indications	Design	Status	Phase	Treatment	Primary endpoint	Estimated N	Estimated study completion date
NCT01138657 VISUAL I	Active uveitis	R, DB, PC, MC	Recruiting	III	ADA Prednisone PBO	Time to treatment failure	250	Nov 2014
NCT01124838 VISUAL II	Inactive uveitis	R, DB, PC, MC	Recruiting	III	ADA Prednisone PBO	Time to treatment failure	250	Oct 2014
NCT01148225 VISUAL III	Non-infectious uveitis	MC, OL	Enrolling by invitation only	III	ADA Prednisone PBO	AEs, Lab parameters and vital signs	400	Mar 2016
NCT00274352	Cutaneous sarcoidosis	R, CO, PC, DB	Completed	II	ADA	Week-12 responders (pts achieved at least a moderate improvement on PGA)	16	Feb 2012 (not yet published)
NCT01166282	Enthesitis-related JIA	R, DB, PC	Active, not recruiting	III	ADA PBO	% change in number of active joints; AEs	45	Dec 2015
NCT01219257 ULSPABIT (extension of NORDMARD study)	Spondyloarthritis	Prospective, observational	Unknown	NR	Anti-TNF	Sensitivity to change of US pathology in joints and entheses	100	Nov 2013
NCT01251614	Juvenile chronic plaque psoriasis	R, DB, PG, MC	Active, not recruiting	III	ADA low dose and standard dose vs MTX	PASI75, PGA, AEs	111	Jan 2015
NCT01497717	Behçet's disease and arthritis	OL	Recruiting	III	ADA	Reduction in DAS28	15	Sept 2016
NCT01960790	Intestinal Behçet's disease	Observational	Recruiting	NR	ADA	AEs	250	May 2017

ADA adalimumab; AE, adverse event; CO, crossover; DAS28, Disease activity score in 28 joints; JIA, juvenile idiopathic arthritis; MC, multicentre; MTX, methotrexate; NR, not reported; OL, open-label; PASI75, the proportion of subjects achieving a Psoriasis Area and Severity Index 75 response; PBO, placebo; PC, placebo-controlled; PG, parallel-group; PGA, physicians' global assessment; R, randomized; US, ultrasound.

Analyses of data from observational studies have also revealed the incidence of some co-occurring IMIDs. The prospective population-based IBSEN study, for example, showed that peripheral arthritis occurs in about 12% of patients with IBD in the first year of IBD diagnosis (51). Association of RA with IBD in the same patient is less common and has been described in a few case studies (9, 42), although a large cross-sectional study showed that IBD patients were more likely to have other inflammatory diseases, including psoriasis and RA (49). In another large study in 174,476 women with psoriasis and PsA, psoriasis was associated with a significantly increased risk of subsequent Crohn's disease, but not UC, with an increased risk of Crohn's disease among women with psoriasis and PsA (6).

Adalimumab clinical data in patients with two or more IMIDs

As a result of several case reports suggesting the efficacy of adalimumab in co-occurring IMIDs (42), clinical trials, such as the RHAPSODY and CARE

studies, have investigated the efficacy and tolerability of adalimumab in co-occurring IMIDs (46, 47). The preliminary evidence from adalimumab clinical and case studies in patients with two or more immune-mediated disorders are summarised in Table 3.

Most data are from the AS RHAPSODY study – a 12-week open-label study of adalimumab in patients with AS. In one analysis, evaluating patients with AS and psoriasis (12% of the cohort), adalimumab treatment resulted in significant improvements in AS clinical parameters (axial disease, peripheral arthritis and enthesitis), but skin changes did not correlate with changes in AS symptoms (52). In addition, among patients with AS, 686 with enthesitis and 281 with peripheral arthritis, adalimumab not only reduced symptoms of active AS but also improved enthesitis and peripheral arthritis (53). In another RHAPSODY analysis in 274 patients with AS and a history of anterior uveitis (AU), adalimumab resulted in a 58% reduction of uveitis flares; this included a 68% reduction in patients with a recent history of AU, 50% reduction in patients with symptomatic AU at baseline and 45% reduction in patients with chronic uveitis (47).

Several papers have reported adalimumab efficacy in patients with JIA and uveitis. The National Italian Registry has evaluated the safety and efficacy of adalimumab (n=43) and infliximab (n=48) in patients with JIA-AU refractory to standard immunosuppressive treatment and treated ≥1 year, showing that AU remission was achieved in 55.3% of patients (67.4% vs 42.8% with adalimumab and infliximab, respectively; p = 0.025) (54).

In a long-term study of the efficacy of adalimumab in 94 patients with JIA and uveitis, adalimumab was effective in the control of JIA and uveitis symptoms, and allowed a reduction in corticosteroid use (55). Adalimumab was also shown to be effective in a patient with psoriatic JIA and uveitis failing NSAID, MTX and etanercept therapy, resulting in remission of both conditions (56) and, in another case report, adalimumab was effective in a patient with AS and Behçet's disease (57).

In a 12-week randomised controlled trial of 208 patients with AS treated with adalimumab, 33% had uveitis and 8% had psoriasis at baseline, although the status of the combined conditions at endpoint was not reported (58). An ASAS20 response (≥20% improvement in Assessment in Ankylosing Spondylitis response criteria) response was achieved in 58.2% of adalimumab-treated patients versus 20.6% with placebo (p<0.001). Other AS parameters (the Bath Ankylosing Spondylitis Functional Index [BASFI], the Bath Ankylosing Spondylitis Disease Activity Index [BASDAI], and the Bath Ankylosing Spondylitis Metrology Index [BASMI], etc.) were also significantly improved with adalimumab versus placebo (58).

Results from the phase IIIb open-label CARE study in 945 patients with moderate-to-severe Crohn's disease and extraintestinal manifestations (EIMs), showed that adalimumab achieved clinical remission and resolution of EIMs in the majority of patients overall and achieved substantial rates even in patients previously failing infliximab (46).

Finally, a case report of successful adalimumab treatment in a patient with refractory UC and seronegative erosive RA, showed that adalimumab resulted in a sustained remission (42). The use of adalimumab in patients with two or more immune-mediated diseases has also shown efficacy in other off-label conditions, but most data are anecdotal and are not the focus of this review. However, this anecdotal evidence has led to a very active Phase III clinical development programme for adalimumab (Table 4).

Adalimumab in paediatric diseases

There is an urgent need for effective and better tolerated treatments in paediatric patients, as IMIDs are often more severe in younger patients and many are not adequately controlled with the available DMARDs. Furthermore, several biologic agents have tolerability issues that make their use problematic in children. The benign tolerability profile of adalimumab has led to its early approved use in children and adolescents (59-61). Indeed adalimumab is currently approved for use in JIA (formerly designated as juvenile rheumatoid arthritis [JRA]) and paediatric Crohn's disease (59-61). However, adalimumab has not been studied in children aged <2 years old, and limited data are available in children weighing less than 15 kg (21).

Juvenile idiopathic arthritis

JIA is a chronic inflammatory disorder defined

as arthritis that persists for ≥6 weeks in children and adolescents aged <16 years without any other identifiable cause (62). The prevalence of significant paediatric arthritis and other rheumatologic conditions has been estimated in the US at approximately 294,000, based on ICD-9-CM estimates (63). As with other IMIDs, treatment for JIA has evolved from symptom-based treatment, to the use of DMARDs such as MTX, corticosteroids, and the biologic drugs etanercept and adalimumab. Adalimumab has shown excellent efficacy and tolerability in patients with JIA. For example in one study in six patients failing MTX, infliximab and etanercept therapy, adalimumab 24 mg/m^2/week plus MTX resulted in a sustained improvement or remission in three children and was well tolerated (64). In a 16-week, single-arm, open-label study of adalimumab in 25 Japanese patients with JIA, the American College of Rheumatology (ACR) Pedi30 (≥30% improvement in ACR pediatric JIA response criteria) response rates at week 16 were 90% and 100% with and without MTX, and the clinical response was maintained up to week 60 in most patients. Of the 25 patients, six patients (all with concomitant MTX therapy) experienced nine serious AEs (65).

Paediatric Crohn's disease

The majority of children with IBD have Crohn's disease, although paediatric UC and indeterminate colitis are also observed. Crohn's disease is a disorder of the young population, with about a quarter of cases presenting in children and young people (66). Complications, such as impaired growth, delayed puberty and low bone density, are caused by malnutrition in children with active Crohn's disease (67). As with adult Crohn's disease, the prevalence has increased in recent years in developed countries, with one US study estimating the prevalence at almost 5 cases per 100,000, which is twice that of paediatric UC (68). The burden of disease is probably increasing due in part to a trend towards an earlier age of onset (69) and partly to improved diagnosis (70).

Conventional treatments, such as corticosteroids, immunosuppressants and non-biological DMARDs, are currently employed, as most biological therapies are not approved for use in children (71). Adalimumab has been shown to be effective and well tolerated in children with Crohn's disease (59, 72-75) and is one of only two anti-TNF agents approved for use in paediatric Crohn's disease (the other being infliximab). The clinical efficacy and tolerability of adalimumab was investigated in the 12-month IMAgINE 1 study – a pivotal trial in 192 children with paediatric Crohn's disease (59). After 2 weeks of open-label induction therapy with subcutaneous adalimumab at weeks 0 and 2 (160/80 mg or 80/40 mg for body weight ≥40 kg or <40 kg, respectively), children were assigned to high (40 or 20 mg) or low dose (20 or 10 mg) adalimumab every other week (eow) for 48 weeks. After 6 months of adalimumab therapy, 33.5% of patients achieved clinical remission and the treatment was well tolerated, with a safety profile similar to that recorded in adults with Crohn's disease (59). In a 12-month study investigating the effect of adalimumab on growth in 36 children with Crohn's disease, remission was achieved in 78% and catch-up growth, occurring in 42% of children with adalimumab, was more likely in those who achieved remission (76).

Pharmacoeconomic considerations

A Health Technology Assessment (HTA) in RA patients failing one anti-TNF inhibitor showed that, compared with DMARDs, the incremental cost-effectiveness ratios (ICERs) were lowest for adalimumab, followed by etanercept and then infliximab (77). A review of eight pharmacoeconomic studies evaluating the cost of adalimumab, etanercept, and infliximab in the management of RA showed that overall, biologic therapies cost considerably more than traditional DMARDs, but produced more quality-adjusted life-years (QALYs) (78).

Pharmacoeconomic studies with a societal perspective that take indirect costs and social outcomes such as work productivity into account, indicate that the benefits provided by adalimumab in terms of improved work productivity, for example, could lend to considerable socio-economic benefits compared with conventional treatment in Crohn's disease (79, 80).

More recently, an Italian group developed two economic evaluation models (81, 82) estimating, in the Social Cost Study (82), the global social cost in terms of lost productivity due to RA, PsA, AS, Crohn's disease, and psoriasis, and, in the COVET

Study (81), estimating the overall economic value of a single multi-indication drug (adalimumab) versus a multi-drug prescription.

Assessment of indirect costs is extremely important when managing chronic diseases. Patients' lost productivity is often overlooked by decision-makers, although it is fundamental for estimation of the true economic impact of disease. Therefore, the Social Cost Study (82) estimated the social savings obtained with adalimumab compared with standard therapies for treatment of RA, PsA, AS, Crohn's disease and psoriasis, in the Italian population. Five different economic models were developed by external consultants to estimate the cost utility of adalimumab versus standard care for each of the five diseases. Both Italian National Health System (direct costs) and social (direct costs + loss of productivity) perspectives were adopted. For each indication, the models calculated the annual loss of productivity per patient with standard therapy and with adalimumab. A sensitivity analysis, based on the variability of model parameters, was performed in order to assess the robustness of the results. In the base-case scenario, the average annual social cost (weighted for prevalence of eligible patients for biologic treatment of each indication) per patient amounted to €1,421 if treated with standard care, compared with €744 with adalimumab. Adalimumab treatment provided an 8.1% (€40 million) reduction in the total social cost, and an annual saving in social costs of 7.0–11.0%, assuming 17% of market penetration for patients eligible for biologic use. The results showed that adalimumab has a significant impact in reducing social costs for all the indications considered. These aspects, often neglected in decision makers' assessments, should be included in the overall evaluation of benefits of innovative technologies such as biologic drugs.

The value of a drug can also be expressed as the cost needed to increase a unit of health (e.g. QALY); however, summarizing the economic value of a molecule with multiple indications is a complex process. The COVET study provided a comprehensive economic evaluation of adalimumab across all five indications approved at the time of the analysis (81). An algorithm was developed to estimate the total economic value of adalimumab. This value was calculated as the sum of ICERs for treating RA, PsA, AS, Crohn's disease, and psoriasis from an Italian National Health System (NHS) perspective. Estimates of the cost per QALY gained for adalimumab versus standard therapy were derived from previously developed economic models. The sum was weighted according to the prevalence of each of the indications considered. Using a systematic literature review, the cost per QALY gained by using other anti-TNF drugs was extrapolated. Subsequently, a Boston matrix was developed to establish the economic cumulative value, i.e. the relationship between demand (i.e., prevalence of patients treatable with biologics for each disease) and supply (e.g., willingness to pay [WTP] threshold of the healthcare authorities), relative to ICER. Using a societal perspective and the highest value of each model, a one-way sensitivity analysis was performed to test the robustness of the results. The total economic value of adalimumab in Italy amounted to €35,854 per QALY. The sensitivity analysis showed that the cost per QALY gained ranged from €27,758 to €40,799. Analysis of the Boston matrix indicated that, with the exception of psoriasis, the cost per QALY gained by using adalimumab instead of standard therapy was below the common WTP threshold. For psoriasis, the cost per QALY for adalimumab was over the WTP threshold, but this is a situation common to all biologic drugs, and adalimumab has the best cost effectiveness ratio. Overall, in comparison with other biologics, the total economic value of adalimumab was positive and sustainable. This should encourage decision makers to facilitate patient access to this cost-effective treatment. The findings may also promote research to develop innovative molecules that are even more cost effective.

Impact on treatment guidelines

Current European and Italian guidelines for management of RA, published by the European League Against Rheumatism (EULAR) (16, 83-86), recommend that biologics should be used as second-line therapy only after MTX (or other DMARD) failure. Biological agents should be administered in combination with MTX, in patients failing to respond to non-biologic DMARD within 6 months and when poor prognostic factors are present (84). ACR guidelines for RA treatment, on the other hand

(87), recommend the use of an anti-TNF, with or without MTX, in patients with early RA (less than 6 months' duration) with high disease activity and poor prognostic features.

Given the benefits demonstrated in early disease (mainly in RA but also in other IMIDs), there is a need for better prognostic indicators and patient risk stratification algorithms to allow identification and selection of those most likely to benefit from first-line adalimumab therapy – either as monotherapy or in combination with MTX. Long-term outcome studies are also needed to provide data for prognostic, predictive and pharmacoeconomic analyses to inform future treatment guidelines.

Although the drug costs of biological agents is considerably higher than that of non-biological DMARDs, many of these extra costs are offset by savings in terms of reduced hospitalisation, reduced number of outpatient visits, etc. In this respect, further research and data are required to demonstrate the overall cost-effectiveness of anti-TNFs from both a healthcare and socioeconomic perspective, the latter taking into account the substantial indirect cost savings resulting from improved work productivity, reduced absenteeism, reduced care costs and assistance with daily living, and improved patient quality of life (88).

The fact that adalimumab has the widest range of approved indications, including many disorders often presenting together in the same patient, may further improve the cost effectiveness of adalimumab, since the use of a multi-indication drug to treat two or more indications in the same patient would decrease considerably the drug burden. This would make adalimumab very valuable for treatment of co-occurring IMIDs.

CONCLUSIONS

Current data demonstrate that adalimumab is a valuable resource in the management of IMIDs. It has proven efficacy and tolerability in a wide range of indications, many of which can be found in the same patient due to their common pathogenesis, and it has been shown also to be suitable in the management of paediatric IMIDs. Comparisons of clinical utility and cost-effectiveness support the view that adalimumab is a valid treatment choice in a wide range of patients. Recent Italian economic studies provide a first indication of the total economic value of adalimumab, showing it to be below the threshold value for health care interventions for all the main indications. In addition, analysis of indirect costs shows that adalimumab significantly reduces societal costs associated with RA, PsA, AS, Crohn's disease and psoriasis.

As a multi-indication drug, adalimumab is expected to have greater pharmacoeconomic benefits in comparison with biologics with a more restricted range of indications, when used to treat two or more indications in the same patient. However, taking all costs into account, the current economic differences appear to be marginal in clinical practice; this may be due to difference in recorded indications. For example, it is unavoidable that the more recently marketed drugs have fewer recorded indications due to their 'youth' in the market. Comparison among indications makes sense only between adalimumab and etanercept, where the lack of effectiveness of etanercept in granulomatous diseases (e.g. Crohn's disease) is certain. However, despite rational aetiopathogenic considerations, information comparing one drug with another in patients with specific disease associations is limited.

Additional research is required to better identify patients who may benefit most from treatments with adalimumab, as well as to expand the range of use of this versatile TNF inhibitor.

ACKNOWLEDGEMENTS

Medical writing assistance was provided by Mary Hines on behalf of HPS, Health Publishing & Services Srl, Milan. The assistance was supported by finding from AbbVie Srl, Italy.

CB has been member of advisory boards for Abbvie.

RC has been member of advisory boards for Abbvie

GG has received advisory/speaker honoraria and/or research funding from AbbVie, Almirall, Boehringer Ingelheim, Celgene, Dompè, Eli-Lilly, Galderma, GSK, Janssen, Leo Pharma, Otsuka, Merck-Serono, Maruho, MSD, Novartis and Pfizer.

AA has received consulting fees from Abbvie, Hospira, Lilly and MSD, and lecture fees from

Abbvie, Chiesi, Ferring, MSD, Nycomed and Otsuka.

AM has received consulting fees and/or speaker fees from Abbvie, Pfizer, Merck, UCB.

The other authors have no conflicts of interest to declare.

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