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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

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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 AxSp without radiographic evidence of AS Severe AxSp 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 (PsA)	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 2. *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 3. *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	Adalimumab 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	Adalimumab 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	Adalimumab	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)	Adalimumab 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 uveitis	Case report	1	Adalimumab	NA	Sustained remission in JIA and uveitis	NR
Rudwaleit et al. (53) (RHAPSODY)	AS and peripheral arthritis and enthesitis	P, OL	1250 (686 with enthesitis and 281 with peripheral arthritis)	Adalimumab 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)	Adalimumab 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)	Adalimumab (n=208) PBO (n=107)	ASAS20, BASFI, BASDAI, BASMI	ASA20 58.2% with Adalimumab, 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	Adalimumab 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)	Adalimumab (n=43) IFX (n=48)	Change in uveitis course and in number of ocular complications	AU remission 55.3% (Adalimumab 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 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; JIA, juvenile idiopathic arthritis

Table 4. *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	Adalimumab Prednisone PBO	Time to treatment failure	250	Nov 2014
NCT01124838 VISUAL II	Inactive uveitis	R, DB, PC, MC	Recruiting	III	Adalimumab Prednisone PBO	Time to treatment failure	250	Oct 2014
NCT01148225 VISUAL III	Non-infectious uveitis	MC, OL	Enrolling by invitation only	III	Adalimumab Prednisone PBO	AEs, Lab parameters and vital signs	400	Mar 2016
NCT00274352	Cutaneous sarcoidosis	R, CO, PC, DB	Completed	II	Adalimumab	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	Adalimumab 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	Adalimumab low dose and standard dose vs MTX	PASI75, PGA, AEs	111	Jan 2015
NCT01497717	Behçet's disease and arthritis	OL	Recruiting	III	Adalimumab	Reduction in DAS28	15	Sept 2016
NCT01960790	Intestinal Behçet's disease	Observational	Recruiting	NR	Adalimumab	AEs	250	May 2017

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 (≥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 produce 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.

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