



NSW Therapeutic Advisory Group
Level 5, 376 Victoria Street
PO Box 766
Darlinghurst NSW 2010
Phone: 61 2 8382 2852
Fax: 61 2 8382 3529
Email: nswtag@stvincents.com.au
www.nswtag.org.au

ADALIMUMAB IN INFLAMMATORY BOWEL DISORDERS

Targeted Literature Review

March 2008

Contents

Summary	3
Introduction	4
Background	4
Methods	4
Current indications and dosage	5
Current subsidy status	5
Ankylosing spondylitis	5
Severe active Psoriatic Arthritis	5
Severe active Rheumatoid Arthritis.....	5
Recent PBAC recommendations	6
Moderate to Severe Crohn Disease.....	6
Summary of evidence of efficacy in ulcerative colitis	6
Safety Issues	6
Injection site reactions and immune response.....	6
Autoimmune disease	7
Malignancy	7
Infection.....	7
Neurologic disorders	8
Use in children	8
Use in the elderly	8
Cost	8
References	9
Acknowledgments	9

Summary

Objective: To review the efficacy and safety of adalimumab in Inflammatory Bowel Disorders

Design: Search for papers using Embase and selected websites.

Results and Conclusion: In Australia, adalimumab is indicated for use in Crohn Disease (CD) but not in Ulcerative Colitis (UC). It is the only biologic drug that may be self administered (subcutaneous [SC] injection). The SC route of administration may provide savings because of fewer hospital visits than for IV infliximab.

In November 2007, The Pharmaceutical Benefits Advisory Committee (PBAC) recommended listing of adalimumab on the Pharmaceutical Benefits Scheme for the treatment of patients with moderate to severe Crohn Disease or in patients with an ileostomy or colectomy due to Crohn disease on a cost-minimisation basis compared with infliximab. There will be no specific listing for the paediatric population as adalimumab has not been trialled in children.

The American Gastroenterological Association (AGA) issued guidelines on the use of biologics in Inflammatory Bowel Disease (IBD). Whilst they suggested it may be used in children with CD, the evidence for this is poor.

Evidence for using adalimumab in UC is lacking and the AGA guidelines state that, currently, there is insufficient data to support its use in UC treatment.

The AGA panel stated that all TNF α inhibitors have similar safety profiles. They increase the risks of infections (such as tuberculosis [TB]). Infusion and injection site reactions occur with all TNF α inhibitors, although rates vary by mode of administration. SC adalimumab can be associated with injection site reactions (2% to 5% of patients), although these are generally less serious in nature than with infliximab. Anti-adalimumab antibodies developed in 0.7% and 2.6% of patients in the CLASSIC I and CLASSIC II studies, respectively. The AGA panel stated that serologic evidence of autoimmunity appears to be less with adalimumab than with infliximab. A recent review found 233 cases of autoimmune diseases among 226 patients given TNF α inhibitor therapy, which included infliximab and adalimumab. Meta-analyses have found that there is an increased risk of malignancy with infliximab or adalimumab in RA patients, especially at high doses. A 2-fold increased risk of serious infections with TNF α inhibitors (regardless of dose) has been estimated in another meta-analysis.

Adalimumab is contraindicated in severe infection (including sepsis, active TB and opportunistic infections), concurrent use with anakinra and in moderate-to-severe heart failure. Precaution is advised if there is other infection (including HBV, latent TB, a demyelinating disorder, immunosuppression, new or worsening congestive heart failure, renal or hepatic impairment, malignancy, latex sensitivity (latex needle cover), and in the elderly, pregnant or lactating females and in children.

Introduction

This *Targeted Literature Review* is not a *Position Statement* and does not represent recommendations from the NSW Therapeutic Advisory Group. It has been derived from papers and website data found in a search of the published literature (see Methods section). Readers should consult the Targeted Literature Review "Infliximab in ulcerative colitis", which was published in August 2007 for comparative information on infliximab and more general information on TNF α inhibitors.

Background

Adalimumab (Humira™) is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. It binds with high affinity and specificity to soluble tumour necrosis factor (TNF α) and neutralises its biological function by blocking its interaction with TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) patients and play an important role in both the pathological inflammation and the joint destruction that are hallmarks of these diseases. Adalimumab also modulates biological responses that are induced or regulated by TNF. In RA patients, adalimumab causes a rapid decrease in levels of acute phase reactants of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate) and serum cytokines. In patients with Crohn's disease (CD), a decrease in CRP levels was observed by week 1. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodelling responsible for cartilage destruction were also decreased after Humira administration. Patients treated with Humira usually experienced improvement in haematological signs of chronic inflammation. (Summarised from MIMS product information.)

The goals of biologic therapy in CD include: induction and maintenance of clinical remissions; induction and maintenance of closure of draining fistulas; mucosal healing; steroid sparing. The ideal situation is that therapy produces corticosteroid-free remission; however, the reality (especially in severely ill or treatment-refractory patients) is that therapeutic success includes varying degrees of efficacy, including corticosteroid reduction or response without frank remission. Ultimately, physicians and patients must define adequate response to biologic therapy in individual patient scenarios.

The goals of biologic therapy in ulcerative colitis (UC) are similar to those in CD. As for CD, the degree of response that is considered success may vary; however, in UC, for which colectomy is an effective and acceptable treatment, continued use of biologics in the face of partial response must be carefully evaluated.¹

Methods

Numerous websites were searched including: ACP Journal Club, the Australian Adverse Drug Reactions Committee (ADRAC), Bandolier, Canadian Agency for Drugs and Technologies in Health (CADTH), Clinical Evidence, Cochrane, European Medicines Agency, Medical Journal of Australia (MJA), Medscape, National Electronic Library for Medicines, National Guideline Clearing House (NGC), National Health and Medical Research Council (NHMRC), National Health Service Health Technology Assessment Programme (NHS HTA Programme), National Institute for Health and Clinical Excellence (NICE), National Library for Health (NLH), National Prescribing Centre (NPC, MeReC), Pharmaceutical Benefits Advisory Committee (PBAC), Scottish Intercollegiate Guidelines Network (SIGN), Scottish Medicines Consortium (SMC), Australian Therapeutic Goods Administration, US Food and Drug Administration.

An Embase search (1996 to 2007 week 50) was also performed using the following terms:
1. ADALIMUMAB; 2. enteritis/ or colon crohn disease/ or crohn disease/ or ulcerative colitis; 3. 1 and 2 combined; 4. clinical study/ or case report/ or case study/ or clinical article/ or community

trial/ or intervention study/ or longitudinal study/ or major clinical study/ or open study/ or prospective study/ or retrospective study/ or case control study/ or hospital based case control study/ or population based case control study/ or clinical trial/ or multicenter study/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/ or randomized controlled trial/; 5. 3 and 4 combined; 6. limit 5 to "review"; 7. 5 not 6. This yielded 192 papers. Selected website information and papers were then used in this review.

Current indications and dosage

The MIMS listing for adalimumab (Humira™) has indications for RA, PsA, AS and CD. With regard to CD, Humira is indicated for the treatment of moderate-to-severe disease in adults to reduce the signs and symptoms and to induce and maintain clinical remission in patients who have had an inadequate response to conventional therapies, or who have lost response to or are intolerant of infliximab (date of TGA approval or last amendment: 26/6/2007).

Humira is the only biologic drug that may be self administered (subcutaneous [SC] injection). The recommended dose in CD for induction is 160mg initial dose (day 0) as four injections, or as two injections on day 0 and two injections on day 1. 80mg second dose (day 14) as two injections. Maintenance dose is 40mg starting day 28 and continuing fortnightly. Aminosalicylates, corticosteroids and/or immunomodulatory agents (eg, 6-mercaptopurine and azathioprine) may be continued during treatment. Patients usually respond within the induction phase; however, if a patient does not show any response, available data do not sufficiently support further Humira treatment. The use of Humira beyond 56 weeks has not been evaluated in controlled studies.

Humira is contraindicated in severe infection (including sepsis, active tuberculosis [TB] and opportunistic infections), concurrent use with anakinra and in moderate-to-severe heart failure. Precaution is advised if there is other infection (including HBV, latent TB, a demyelinating disorder, immunosuppression, new or worsening congestive heart failure, renal or hepatic impairment, malignancy, latex sensitivity (latex needle cover), and in the elderly, pregnant or lactating females and in children (summarised from MIMS product information.)

Current subsidy status

The Schedule of Pharmaceutical Benefits (www.pbs.gov.au) lists the following indications for adalimumab.

Ankylosing spondylitis

From 1 March 2007, under the Pharmaceutical Benefits Scheme (PBS), all patients are able to commence a treatment cycle where they may trial each PBS-subsidised TNF α inhibitor (adalimumab, etanercept or infliximab) without having to experience a disease flare when swapping to the alternate agent. Under these interchangeability arrangements, within a single treatment cycle, a patient may continue to receive long-term treatment with a TNF α inhibitor while they continue to show a response to therapy.

Severe active Psoriatic Arthritis

From 1 August 2006, all patients are able to commence a treatment cycle where they may trial adalimumab, etanercept or infliximab without having to meet the initial treatment criteria, that is they will not need to experience a disease flare, when swapping to the alternate agent. Under these interchangeability arrangements, within a single cycle, patients may receive long-term treatment with a biological agent as long as they sustain a response to therapy.

Severe active Rheumatoid Arthritis

From 1 August 2007, all patients will be able to commence a treatment cycle where they may trial PBS-subsidised biological disease modifying anti-rheumatic drugs (bDMARDs - the TNF α

inhibitors, adalimumab, etanercept, infliximab; the chimeric anti-CD20 monoclonal antibody, rituximab; and the interleukin-1 inhibitor, anakinra) without having to experience a disease flare when swapping to an alternate agent. Under these interchangeability arrangements, within a single treatment cycle, a patient may continue to receive long-term treatment with a bDMARD while they continue to show a response to therapy.

Recent PBAC recommendations

Moderate to Severe Crohn Disease

In November 2007, The Pharmaceutical Benefits Advisory Committee (PBAC) recommended listing of adalimumab on the Pharmaceutical Benefits Scheme for the treatment of patients with moderate to severe Crohn Disease (Crohn Disease Severity Index (CDAI) > 300) or in patients with an ileostomy or colectomy due to Crohn disease on a cost-minimisation basis compared with infliximab. There will be no specific listing for the paediatric population as adalimumab has not been trialled in children. The PBAC considered the equi-effective doses to be adalimumab 160/80mg (week 0, 2), then 40mg every two weeks thereafter and infliximab 5mg/kg (weeks 0, 2, 6 and every 8 weeks thereafter). The full public summary document is available at <http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-adalimumab-nov07>

Summary of evidence of efficacy in ulcerative colitis

The only relevant guidelines/reviews that were found in the literature search were the recent American Gastroenterological Association (AGA) guidelines on the use of biologics in IBD¹ and a 2005 review by the National Horizon Scanning Centre.² NICE is due to publish a review of CD in July 2008. A report by the NHS HTA program on the clinical and cost effectiveness of TNF α inhibitors is expected in late 2008.

Evidence for using adalimumab in UC is lacking and the AGA guidelines state that, currently, there is insufficient data to support its use in UC treatment.¹ There is a 4-week study of adalimumab induction therapy (160mg at wk 0 followed by 80mg at wk 2) in 10 patients with UC who had lost response or become intolerant to infliximab.³ Four patients (40%) benefited from subsequent adalimumab therapy - one achieved remission and 3 had clinical improvement at week 4. Two of the 6 nonresponders subsequently underwent colectomy. The authors remarked that the small advantage of adalimumab in this group of patients needs to be confirmed in RCTs. Another small, open-label study is underway - listed on www.clinicaltrials.gov and due for completion in 2008. The same website also lists two phase 3 RCTs that are recruiting a total of 750 patients with moderate-to-severe active UC to receive adalimumab. Patients from these trials will also be eligible to enter a long-term, open-label extension of this study.

Safety Issues

The AGA panel stated that all TNF α inhibitors have similar safety profiles.¹ They increase the risks of infections (such as TB). Infusion and injection site reactions occur with all TNF α inhibitors, although rates vary by mode of administration.¹

ADRAC has received 319 reports involving TNF α inhibitors since 2000. The more serious of these were: malignant melanoma (3 reports), lymphoma (5), TB (4), pneumonia/lower respiratory tract infections (23), sepsis (10), lupus or lupus-like syndrome (22) and anaphylaxis (9).⁴

Injection site reactions and immune response

SC adalimumab can be associated with injection site reactions, although these are generally less serious in nature than with infliximab. More than 4% of patients in the CHARM trial noted injection site irritation and pain during induction. Injection site reactions were reported in 2% of patients

during induction.⁵ This rate increased up to 4.8% among those treated with a 40mg weekly maintenance regimen.

The development of antibodies against biologic therapies has been correlated with an increased risk of infusion reactions but is not predictive of infusion reactions in a specific individual. Antibody formation against biologic therapies is common but their significance and management are not well defined. They can decrease the degree and duration of response, but this correlation is incomplete.¹ In the clinical trials of adalimumab in CD, 0.7% of patients in CLASSIC I and 2.6% in CLASSIC II developed antiadalimumab antibodies.^{6, 7}

Autoimmune disease

The development of autoantibodies is common with TNFalpha inhibitor therapy. Its clinical relevance is unclear - in contrast to the development of antibodies against the actual biologic drug, it does not reduce the efficacy of TNFα inhibitor therapy and does not cause significant clinical consequences, although occasional lupus-like syndromes have been described. Serologic evidence of autoimmunity appears to be less with adalimumab than with infliximab.¹ A recent review sought to analyse the association of autoimmune diseases with use of TNFα inhibitor therapy.⁸ Their MEDLINE search revealed 233 cases of autoimmune diseases (vasculitis in 113, lupus in 92, interstitial lung diseases in 24, and other diseases in 4) secondary to TNFα inhibitor therapy in 226 patients (the agents were given for RA in 187 (83%) patients, CD 17, AS in 7, PsA 6, juvenile RA in 5, and other diseases in 3 - infliximab in 105 patients, etanercept in 96, adalimumab in 21).

Malignancy

TNFα inhibitors may predispose patients to an increased risk of malignancies or accelerate their development. Australian product information advises caution when prescribing TNFα inhibitors in patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

A meta-analysis of infliximab or adalimumab studies in RA, found that malignancies developed in 29 of 3192 (0.9%) patients treated with infliximab or adalimumab, compared with 3 of 1428 (0.2%) patients given placebo.⁹ The risk of malignancies was not different from placebo with low dose TNFα inhibitors but was 4-fold greater with high doses of infliximab or adalimumab. A pooled OR for malignancy following anti-TNF therapy of 3.3 (95% CI, 1.2 - 9.1) was calculated. The number needed to harm was 154 (95% CI, 91 - 500) for 1 additional malignancy within a treatment period of 6 to 12 months. They concluded there is evidence of a dose-dependent increased risk of malignancies in patients with RA treated with TNFα inhibitors. Similar results were reported in a recent ACP Journal Club analysis.¹⁰ They found that the malignancy risk was greater in RA patients receiving a high dose of TNFα inhibitors compared with placebo (OR 4.3, 95% CI 1.6 - 12) than in those receiving a low dose (OR 1.4, CI 0.3 to 5.7). Direct comparison of high and low dose also showed increased risk for malignancy with high-dose treatment (OR 3.4, CI 1.4 - 8.2).

Infection

ADRAC advises that patients receiving TNFα inhibitors should not receive concurrent vaccination with live vaccines, and that consideration should be given to screening patients for preexisting infections, particularly hepatitis B and TB, prior to use of TNFα inhibitors.⁴

The AGA guidelines state that US postmarketing surveillance data among patients with RA indicated similar rates of TB with different TNFα inhibitors. A broad range of other infections have been reported with infliximab and adalimumab. The reported serious infection rates for infliximab were approximately 4% in the ACCENT I and II trials^{11, 12} whilst 3.6% was reported for adalimumab, administered every other week in the CHARM trial.⁵ A recent ACP Journal Club meta-analysis (2006) found that that serious infection risk with TNFα inhibitors was increased in

patients with RA.¹⁰ A dose effect was not observed for serious infection (high dose vs low dose, OR 1.4, CI 1.0 - 2.0). The Bongartz et al meta-analysis showed a 2-fold increased risk of serious infections with TNF α inhibitors, regardless of dose.⁹ The number needed to harm was 59 (95% CI, 39 - 125) for 1 serious infection within a treatment period of 3 to 12 months. They concluded there is evidence of an increased risk of serious infections in patients with RA treated with TNF α inhibitor therapy.

Adalimumab was well tolerated in CHARM, and its safety profile was consistent with that reported in previous studies with adalimumab and other anti-TNF-alpha agents.⁵ The rate of infections was similar across all 3 treatment arms. An ACG report stated that there was 1 case of TB in each of the adalimumab groups, and none in the placebo patients.¹³

Neurologic disorders

Rare reports of optic neuritis, seizure, and new onset or exacerbation of central nervous system demyelinating disorders, including multiple sclerosis, have been reported with the use of anti-TNFs.¹⁴ The majority of these cases have been reported in association with infliximab, probably because of greater patient exposures, and neurologic complications have emerged with adalimumab use.¹ A case of optic neuritis associated with adalimumab therapy has recently been reported.¹⁵ The AMH advises caution with adalimumab if the patient has a demyelinating disease.

Use in children

Adalimumab has not been studied specifically in children.¹ A case has been reported of its use in a child with refractory CD.¹⁶

Use in the elderly

MIMS states that a total of 519 RA patients ≥ 65 years (including 107 patients ≥ 75 years) received Humira in clinical studies. There was no overall difference in effectiveness between these subjects and younger subjects. The frequency of serious infection and malignancy among Humira treated subjects over age 65 was higher than for those under age 65. Because there is a higher incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly.

Cost

When weighing the risks and benefits of biologic therapy for patients with IBD, physicians must account for the consequences of undertreated IBD. These include the direct costs of hospitalisations and operations for IBD, the direct costs of treatment for side effects associated with chronic, nonbiologic therapies, and indirect costs associated with lost productivity or nonmonetary costs such as quality-of-life decrements.¹

The UK National Horizon Scanning Centre (2005) review was published before full clinical and cost details about adalimumab were known. They remarked that the SC route of administration may provide savings because of fewer hospital visits than for IV infliximab.²

A UK study stated that only a minority of CD and UC sufferers are hospital inpatients but they account for approximately half the direct medical costs of IBD treatment. Drug costs contributed less than a quarter of the total healthcare costs.¹⁷ Lifetime costs for IBD are comparable to a number of major diseases, including heart disease and cancer. They stated that in the next 5 to 10 years, the contribution of drug costs will increase as biological therapies become used more widely. The key economic question is whether the health gains from these drugs will lead to reduced expenditures on hospitalisation and surgery.

References

1. Clark M, Colombel JF, Feagan BC, et al. American Gastroenterological Association Consensus Development Conference on the Use of Biologics in the Treatment of Inflammatory Bowel Disease, June 21-23, 2006. *Gastroenterology* 2007;133(1):312-39.
2. Adalimumab (Humira) for moderate to severely active Crohn's disease. National Horizon Scanning Centre, 2005. (Accessed 21 December, 2007, at <http://www.pcpoh.bham.ac.uk/publichealth/horizon/>.)
3. Peyrin-Biroulet L, Laclotte C, Roblin X, Bigard MA. Adalimumab induction therapy for ulcerative colitis with intolerance or lost response to infliximab: An open-label study. *World Journal of Gastroenterology* 2007;13(16):2328-32.
4. Tumour necrosis factor alpha inhibitors. *Aust Adv Drug Reactions Bull* 2006;25(6):23-4.
5. Colombel J, Sandborn WJ, Rutgeerts P, et al. Adalimumab for Maintenance of Clinical Response and Remission in Patients With Crohn's Disease: The CHARM Trial. *Gastroenterology* 2007;132(1):52-65.
6. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: The CLASSIC-I trial. *Gastroenterology* 2006;130(2):323-32.
7. Sandborn WJ, Hanauer SB, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn's disease: Results of the CLASSIC II trial. *Gut* 2007;56(9):1232-9.
8. Ramos-Casals M, Brito-Zeron P, Munoz S, et al. Autoimmune diseases induced by TNF-targeted therapies: Analysis of 233 cases. *Medicine* 2007;86(4):242-51.
9. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *Jama* 2006;295(19):2275-85.
10. Anti-tumor necrosis factor antibody therapy for rheumatoid arthritis increases risk for serious infection and malignancy. *ACP Journal Club* 2006;145(3):65.
11. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004;350(9):876-85.
12. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;359(9317):1541-9.
13. ACG 2006 - current and emerging strategies in biologic therapy for IBD. Medscape, 2006. (Accessed 14 December, 2007, at www.medscape.com.)
14. Questions and answers on Remicade/FDA action. U.S. Food and Drug Administration. Center for Drug Evaluation and Research., 2006. (Accessed 20 December, 2007, at <http://www.fda.gov/cder/drug/infopage/infliximab/qa.htm>.)
15. Chung JH, Van Stavern GP, Frohman LP, Turbin RE. Adalimumab-associated optic neuritis. *Journal of the Neurological Sciences* 2006;244(1-2):133-6.
16. Mian S, Baron H. Adalimumab, a novel anti-tumor necrosis factor-alpha antibody in a child with refractory Crohn's disease. *Journal of Pediatric Gastroenterology and Nutrition* 2005;41(3):357-9.
17. Luces C, Bodger K. Economic burden of inflammatory bowel disease: A UK perspective. *Expert Review of Pharmacoeconomics & Outcomes Research* 2006;6(4):471-82.

Acknowledgments

Author, data search and collation:

Dr Gordon Mallarkey, Project Officer, NSW Therapeutic Advisory Group Inc

Reviewed by: Editorial Committee members, NSW Therapeutic Advisory Group Inc.

This document is copyright of the NSW Therapeutic Advisory Group Inc and NSW Health Department. Apart from any use as permitted under *the Copyright Act 1968*, no part of this information may be reproduced by any process without written permission. Whilst the information contained in this document has been presented with all due care, and the information is considered to be true and correct at the date of publication, changes in circumstances after publication may impact on the accuracy of the information.

This document is a selected summary of published material and should not be relied on as professional advice other than in this context. The information provided should not be regarded as a substitute for detailed expert advice in individual cases. NSW Therapeutic Advisory Group Inc will accept no responsibility for any loss, claim or damage suffered or caused by any person acting or refraining from action as a result of any material in this document.