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Infliximab in ulcerative colitis

Targeted Literature Review

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Contents

Synopsis

This *Targeted Literature Review* is not a *Position Statement* and does not represent recommendations from the NSW Therapeutic Advisory Group. The Synopsis has been derived from the main points from the reviews, guidelines and articles identified in a search of the published literature. Summaries or abstracts of these reviews, guidelines and articles have been presented in the main text of this document, either verbatim or edited for conciseness or clarity.

Background

Infliximab is a chimeric humanised murine monoclonal antibody that binds to human tumour necrosis factor alpha (TNFα), a proinflammatory and immunoregulatory cytokine that, when overexpressed, mediates chronic inflammation in diseases such as Crohn's disease (CD) and rheumatoid arthritis (RA). Biological activities attributed to TNFα include: induction of proinflammatory cytokines such as IL-1 and IL-6; enhancement of leucocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leucocytes; activation of neutrophil and eosinophil functional activity; and induction of acute phase and other liver proteins (summarised from MIMS product information.)

Current indications and dosage

The MIMS lisiting for Infliximab (Remicade™) has indications for RA, ankylosing spondylitis, CD, refractory fistulising CD, psoriatic arthritis, psoriasis and ulcerative colitis (UC) (Date of TGA Approval or Manufacturer's Last Amendment 11/01/2007). For UC, the treatment is for moderately severe to severe active UC in patients who have had an inadequate response to conventional therapy.

The dosage of infliximab for UC is 5 mg/kg given as an intravenous infusion over a 2 hour period followed by additional 5 mg/kg infusion dose at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. If patients have not responded to the initial 3 treatment infusion regimen at weeks 0, 2 and 6 weeks, then careful consideration should be given before persisting with further treatment. Data supporting readministration, other than every 8 weeks, are not available at this time.

A Cochrane review (2006) recommends a dose of 5 mg/kg but it does not recommend an ideal dosing schedule. The American Gastroenterological Association also recommends this dosage (Lichtenstein et al 2006) infused over 2 hours in an induction regimen of 3 doses at weeks 0, 2, and 6 - followed by maintenance therapy every 8 weeks in patients who respond. They add that for patients with CD who respond and then lose their response, consideration may be given to treatment with 10 mg/kg. In the case of nonresponse to 3 infusions, further treatment with infliximab is not recommended. An attempt to withdraw or taper any concomitant corticosteroid therapy is sensible in patients who achieve remission with infliximab.

Current subsidy status

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

Repatriation Pharmaceutical Benefits

Initial treatment, in combination with methotrexate, of specific accepted war-caused or service-related disability of refractory RA. Continuing treatment, in combination with methotrexate, of specific accepted war-caused or service-related disability of refractory RA.

Section 100 items

Treatment of adult patients with active ankylosing spondylitis, severe active psoriatic arthritis or severe active RA.

Public summary documents

Date of PBAC Consideration: July 2006

This submission sought to extend the Section 100 (Highly Specialised Drug) listing for infliximab to include the treatment of severe plaque psoriasis.The PBAC recommended this listing in patients who meet certain criteria on a cost-minimisation basis with efalizumab.

Date of PBAC Consideration: March 2007
This re-submission requested an extension to the Section 100 Authority Required listing to include the treatment of severe refractory Crohn's disease. The PBAC recommended this listing of infliximab for the treatment of patients with severe Crohn's disease (Crohn's Disease Activity Index ≥ 300) or patients with an ileostomy or colectomy due to Crohn's disease on the basis of high and acceptable cost-effectiveness compared to placebo.

Treatment recommendations

Disease resistant to conventional therapy

A Cochrane review concluded that infliximab is effective in patients with moderate-to-severe UC where the disease is resistant to conventional therapy using corticosteroids and/or immunosuppressive agents. The primary outcome measure was the number of patients achieving remission as defined by the primary studies. Infliximab was shown to induce clinical remission and response, promote mucosal healing and reduce the need for colectomy in the short term. Thukral et al (2006) commented that a significant number of patients who were receiving oral corticosteroids at the start of the 2 main randomized controlled trials (RCTs) (ACT1 and ACT2) remained on corticosteroids despite infliximab therapy. However, the proportions of patients who were in clinical remission and had discontinued corticosteroids at week 30 in both studies (and at week 54 in ACT1) were higher in the infliximab groups than in the placebo groups. Also, the decreases in the median daily corticosteroid doses (20mg at baseline) were greater among patients in the infliximab groups than in the placebo groups.

In the systematic review by Gisbert et al (2007), they agreed that infliximab is more effective than placebo in treating moderate-to-severe UC, with a number needed to treat from 3 to 5 and 40% of patients achieving clinical remission after 9 months. Cottone et al (2006) comment that the long-term effectiveness of infliximab, in comparison to placebo, is not clinically impressive even if it is statistically significant.

The Cochrane review states the evidence is unclear on whether both corticosteroids and immunosuppressive agents should be used prior to infliximab therapy.

Thukral et al (2006) state there is insufficient evidence to recommend the use of infliximab as a first-line agent for UC patients with mild or moderate-to-severe disease.

Disease that is <u>not</u> steroid refactory

Cochrane states there is no evidence to show infliximab is more effective than high-dose corticosteroids in patients who are not steroid-refractory.

Preventing colectomy

The Cochrane review concluded that infliximab helps to avoid colectomy in the short term but that long-term studies are required to determine whether infliximab can prevent colectomy. A recent retrospective cohort study of 30 UC patients treated with infliximab showed that 16 required colectomy after a median of 140 days after first infusion (Jakobovits et al 2007)

Safety

General

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

The Cochrane review stated that serious adverse events with infliximab in UC patients are not common but uncommon adverse events such as anaphylactic reactions and infections may occur. In the systematic review by Gisbert et al (2007), they stated that adverse effects were reported in 83% and 75% of infliximab and placebo-treated patients in UC studies, respectively (odds ratio [OR] = 1.52; 95% confidence interval [CI] 1.03-2.24; number-needed-to-harm was 14).

A review of adverse events in 500 consecutive CD patients treated with infliximab at the Mayo Clinic for a median follow-up of 17 months showed that 43 patients (8.6%) experienced a serious adverse event, of which 30 (6%) were related to infliximab (Colombel et al 2004). Acute infusion reactions occurred in 19 (3.8%), serum sickness-like disease in 19 (attributed to infliximab in 14, 2.8%), drug-induced lupus in 3. Forty-eight patients had an infectious event, of which 41 (8.2%) were attributed to infliximab. Twenty patients had a serious infection. Nine patients had a malignant disorder, 3 of which were possibly related to infliximab. A total of 10 deaths were observed - 5 were possibly related to infliximab.

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.

Early evidence of a potential cancer risk came from a case series in 2002 where a post market surveillance system run by the US Food and Drug Administration found 26 cases of lymphoproliferative disorders following treatment with etanercept (18 cases) or infliximab (8 cases) (Brown et al 2002). Bandolier (2006) summarised the results from a series of observational studies in RA patients (ie, Askling et al papers in this document) using etanercept and infliximab mainly. The relative risk of malignancy was

1.1 (95% CI 0.6 - 2.1) - solid cancers occurred at rates little greater than in the general population.

In the Bongartz et al (2006) meta-analysis of infliximab or adalimumab in RA, it was 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. 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. The Bongartz study calculated a pooled OR for malignancy following anti-TNF therapy of 3.3 (95% CI, 1 2 - 9.1). 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 (2006). 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.

Early evidence of a potential infection risk came from a case series in 2001 where a post-market surveillance system run by the US Food and Drug Administration found 70 cases of TB after treatment with infliximab (Keane et al 2001). The estimated incidence of TB associated with infliximab in RA patients was 1,893 per 100,000 in the year 2000 and 1,113 per 100,000 in the year 2001 in a multicentre active-surveillance report in Spain (Gomez-Reino et al 2003). A prospective cohort study in 83 rheumatoid

patients suggested that older age and high-dose corticosteroid therapy were associated with an increased risk of severe pyogenic infection during infliximab therapy (Maillard et al 2005).

A recent ACP Journal Club meta-analysis (2006) found that that serious infection risk with TNFα inhibitors was increased in patients with RA. 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 (2006) meta-analysis showed a 2-fold increased risk of serious infections with TNFα inhibitors, regardless of dose. 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 TNFα inhibitor therapy.

Use in children

MIMS states that the efficacy and safety of infliximab in paediatric patients have not been established. No notable differences in single dose pharmacokinetics were observed between paediatric and adult CD patients.

Efficacy

The Cochrane review states there is an absence of proper RCTs on the effectiveness of infliximab in the paediatric population. Several non-randomised trials are presented in the *Use in Children* section of this document. Positive efficacy results were reported, but the trials involved small numbers of patients. Infliximab was more effective in acutely ill UC patients than in patients with chronic steroid-dependent disease (Fanjiang et al, 2007). Eight of 12 paediatric UC patients were classified as long-term responders in another study (Eidelwein et al 2005)

Safety

Crandall et al (2003) reported that the rate of infusion reactions in children receiving infliximab is similar to that in adults. Female gender, immunosuppressive use for less

than 4 months and prior infusion reactions were thought to be risk factors for subsequent infusion reactions in children. Jacobstein et al (2005) reported 60 infusion reactions from a total of 1652 infusions given to 243 paediatric inflammatory bowel disease (IBD) patients. Kohlo et al (2007) found that adverse reactions to infliximab infusions were common in children with IBD and that young children seemed to be prone to severe allergic reactions despite azathioprine and conventional glucocorticoid therapy. Candon et al (2006) reported that infliximab therapy induced the appearance of neutralising anti-infliximab antibodies in 10 of 28 paediatric CD patients, which resulted in a loss of response to maintenance infusions.

Use in the elderly

MIMS states that no major differences were observed in the pharmacokinetics of Remicade in elderly (65 to 80 years) RA patients.

Efficacy

Clinical studies of Remicade did not include sufficient numbers of CD patients aged 65 and over to determine whether they respond differently from patients aged 18 to 65.

Safety

Studies have not been performed in patients with liver or renal disease. Since elderly patients have a greater frequency of decreased hepatic, renal and/or cardiac function and a greater frequency of concomitant disease and/or other drug therapy, caution in the treatment of elderly patients is recommended. While changes in the ageing immune system may affect the risk of infection, in a cohort study of 15,597 US Medicare beneficiaries (>65 years), Schneeweiss et al (Arthritis and Rheumatism, 2007 – see Safety section) found no increase in the rate of bacterial infections among TNFα inhibitors compared methotrexate.

Cost

The UK National Horizon Scanning Centre (2005) say it is difficult to estimate the cost impact of infliximab use in UC but it may lead to a net saving due to possible reduction in hospitalisation and surgical procedures. They state that minimal additional training of healthcare professionals will be required because infliximab is already used in CD treatment. A UK study states 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 contribute less than a quarter of the total healthcare costs (Luces & Bodger 2006). Lifetime costs for IBD are comparable to a number of major diseases, including heart disease and cancer. They state that in the next 5 to10 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.

Introduction

This document contains summary data from published reviews, guidelines and articles to help drug and therapeutic committees make decisions about use of infliximab in ulcerative colitis (UC). It is not a *Position Statement* and does not represent recommendations from the NSW Therapeutic Advisory Group.

The data was collated after searching websites of organisations/publications including: ACP Journal Club, ADRAC, Australian Clinical Trials Registry, 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 Heath 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), Therapeutic Goods Administration, US Food and Drug Administration.

An Embase search (1996 to 2007 week 24) was also performed using the following MESH terms:
a. exp Ulcerative Colitis
b. exp INFLIXIMAB
c. a and b combined.
d. "Randomised Controlled Trial"
e. a and d combined.
f. exp evidence based practice or exp evidence based medicine
g. c and f combined.
h. economic evaluation or "cost benefit analysis" or "cost control" or "cost effectiveness analysis" or "cost minimization analysis" or "cost of illness" or "cost utilitiy analysis"
i. c and h combined.
j. exp Adverse Drug Reaction/dt [Drug Therapy]
k. b and j combined.

l. exp Case Control Study or exp Cohort Analysis
m. b and j combined.
n. limit c to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>).

All of the results were assessed, and abstracts of the selected papers are presented in this document.

Summaries of systematic reviews and guidelines are reproduced verbatim where possible, but may have been edited for conciseness. The abstracts of review articles and clinical studies are taken verbatim from Embase (background information may have been deleted) and are presented chronologically (latest studies first). Full citations are given so that readers may consult the full papers if required.

Systematic Reviews, Meta-analyses and Guidelines

Cochrane

Summary:

Efficacy

Seven randomised controlled trials (RCTs) were identified that satisfied the inclusion criteria. Five studies (Rutgeerts 2005 ACT1; Rutgeerts 2005 ACT2; Jarnerot 2005; Probert 2003; Sands 2001) compared infliximab with placebo for the induction of remission of acute UC in patients who had failed to respond to conventional treatment using corticosteroids and immunosuppressants. Two studies (Probert 2003; Sands 2001) failed to show any benefit of infliximab but both had relatively small numbers of patients (n = 43 and 13 respectively). In patients with moderate-to-severe UC whose disease was refractory to conventional treatment using corticosteroids and/or immunosuppressive agents, infliximab (3 intravenous infusions at 0, 2, and 6 weeks) was more effective than placebo in inducing clinical remission (relative risk [RR] 3.22, 95% confidence interval [CI] 2.18 to 4.76); inducing endoscopic remission (RR 1.88, 95% CI 1.54 to 2.28); and in inducing clinical response (RR 1.99, 95% CI 1.65 to 2.41) at 8 weeks. The Jarnerot study showed that a single infusion of infliximab was also more effective than placebo in reducing the need for colectomy within 90 days after infusion (RR 0.44, 95% CI 0.22 to 0.87). However, this was a small study (n = 45) and it remains unclear whether colectomy can be prevented in the long term by infliximab. The studies by Armuzzi and Ochsenkuhn compared infliximab with corticosteroids. They both failed to show any significant difference between infliximab and corticosteroids but both had small numbers of patients.

Safety

Four studies (Jarnerot 2005; Ochsenkuhn 2004; Probert 2003; Sands 2001) reported no serious adverse events or infusion reactions with infliximab, although a few patients receiving infliximab developed pruritis, headache, upper respiratory or urinary tract infection and there was 1 case each of renal calculus, cellulitis, central venous catheter septicaemia and pneumothorax following catheter insertion. One patient treated with placebo (Probert 2003) developed life-threatening sepsis. Five of 7 patients receiving oral prednisolone (Ochsenkuhn 2004) developed Cushing-like symptoms, 2 developed facial acne and 1 developed dysphoria. In 2 studies, Rutgeerts 2005 ACT1 (follow up 54 weeks) and Rutgeerts 2005 ACT2 (follow up 30 weeks), the proportion of patients with adverse events was generally similar in the placebo and 2 infliximab groups. In Rutgeerts 2005 ACT1, one patient treated with infliximab developed tuberculosis (TB) and in Rutgeerts 2005 ACT2, one patient receiving infliximab developed histoplasmosis and died from acute respiratory distress syndrome. The incidence of infusion reactions in the 2 studies ranged from 8% to 12% and was similar in the placebo and infliximab groups. In both studies the occurrence of newly positive results for antinuclear antibodies and double-stranded anti-DNA antibodies occurred more frequently in the infliximab groups than the placebo groups. In Rutgeerts 2005 ACT1, 2 patients developed possible delayed hypersensitivity reactions (1 in placebo & 1 in infliximab group). In Rutgeerts 2005 ACT2, a possible delayed hypersensitivity reaction occurred in 1 patient treated with infliximab.

Implications for practice

Infliximab is effective in patients with moderate-to-severe UC whose disease is resistant to conventional therapy using corticosteroids and/or immunosuppressive agents. In such patients, infliximab was more effective than placebo for inducing clinical and endoscopic remission, clinical response and helping to avoid colectomy in the short term. In the 2 largest studies there was no statistically significant difference

between a dose of 5 mg/kg and 10 mg/kg. The authors recommend an intravenous dose of 5 mg/kg. The schedule of therapy was not consistent between studies. In the 2 largest studies which demonstrated the largest effect, infliximab was given at 0, 2 and 6 weeks to induce remission, but in one study (Jarnerot 2005) a single infusion of infliximab was used as a 'rescue therapy' in patients with acute disease judged to have failed to respond to high dose corticosteroids. There is, therefore, insufficient evidence to provide recommendations on the ideal dosing schedule. The authors did not find any evidence to suggest that infliximab is more effective than high-dose corticosteroids in patients who are not steroid-refractory. Serious adverse events attributable to infliximab were not common in the included studies but physicians should be aware of and be prepared to deal with some of the uncommon adverse events such as anaphylactic reactions and infections. The authors found no evidence to support the use of other tumour necrosis factor alpha (TNFα) inhibitors in acute UC.

Implications for research

It is important for researchers to ensure adequate sample size by performing *a priori* power and sample size calculations. The more recent larger studies clearly demonstrated a benefit for infliximab in patients who had previously received corticosteroids and/or immunosuppressive agents. It is unclear from the results of included studies whether both corticosteroids and immunosuppressive agents should be used prior to infliximab therapy. The question of when it is appropriate to use infliximab in clinical practice should be addressed in future studies. The fact that infliximab is effective in UC does not necessarily mean that other TNFα inhibitors will also be effective, and these agents should be tested in randomised trials. Further long term studies are required to determine whether infliximab can prevent colectomy in the long term, and also to evaluate potential long term adverse events. Future studies should also include assessment of quality of life as an important outcome and such studies should be designed to ensure that there is adequate statistical power to detect any differences between groups with regard to this outcome.

As in CD, there is an absence of proper RCTs on the effectiveness of infliximab in the paediatric population. Well designed clinical trials investigating the use of infliximab in childhood inflammatory bowel disease (IBD) are needed.

Alimentary Pharmacology & Therapeutics

Summary:

This was a systematic review and meta-analysis on the efficacy and tolerance of infliximab in UC. Methods: Selection of studies: evaluating efficacy of infliximab in UC. For the meta-analysis, randomised clinical trials comparing infliximab vs. placebo/steroids. Search strategy: electronic and manual. Study quality: independently assessed by 2 reviewers. Data synthesis: meta-analysis combining the odds ratios (OR). Results: Thirty-four studies (896 patients) evaluated infliximab therapy in UC, with heterogeneous results. Mean short-term (2.3 weeks) response and remission with infliximab was 68% (95% CI 65% - 71%) and 40% (36% - 44%). Mean long-term (8.9 months) response and remission was 53% (49% - 56%) and 39% (35% - 42%). Five RCTs compared infliximab with placebo, the meta-analysis showing an advantage ($P < 0.001$) of infliximab in all endpoints (short/long-term response/remission): ORs from 2.7 to 4.6, and number-needed-to-treat (NNT) from 3 to 5. Similar infliximab response was calculated independently of the indication (steroid refractory/non-steroid refractory) or the dose (5/10 mg/kg). Adverse effects were reported in 83% and 75% of the infliximab and placebo-treated patients (OR = 1.52; 95% CI 1.03-2.24; number-needed-to-harm (NNH) was 14). Conclusion: Infliximab is more effective than placebo, with an NNT from 3 to 5, for the treatment of moderate-to-severe UC, achieving clinical remission in 40% of the patients at approximately 9 months of follow-up. Further studies are

necessary to confirm the long-term efficacy of infliximab in UC.

ACP Journal Club

Anti-tumor necrosis factor antibody therapy for rheumatoid arthritis increases risk for serious infection and malignancy. ACP Journal Club, v145(3):65, November/December, 2006.

Summary:

Question: In patients with RA, does treatment with TNFα inhibitors increase the risk for serious infection and malignancy? Methods: Search of MEDLINE, EMBASE/Excerpta Medica, Cochrane Library (2005), abstracts from scientific meetings of the European League against Rheumatism and the American College of Rheumatology (1996 to 2005), and drug manufacturers. Study selection and assessment: RCTs that compared infliximab or adalimumab with placebo (with or without a traditional disease-modifying antirheumatic drug in each group) in patients with RA, with duration of treatment ≥ 12 weeks (range 12 to 54 wk). 9 RCTs (n = 5014) met the selection criteria. 2 reviewers independently assessed the RCTs for methodological quality, including randomisation, allocation concealment, blinding, intention-to-treat analysis, follow-up, outcome assessment, and attrition. All RCTs were double-blinded. Outcomes: Serious infection (requiring antimicrobial therapy or hospitalisation) and malignancy. Main results: TNFα inhibitor therapy increased risk for both serious infection and malignancy more than placebo. For malignancy, risk was greater in patients receiving a high dose of TNFα inhibitor compared with placebo (OR 4.3, 95% CI 1.6 to 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 to 8.2). A dose effect was not observed for serious infection (high dose vs low dose, OR 1.4, CI 1.0 to 2.0). Conclusion: In patients with RA, treatment with TNFα inhibitor increases risk for serious infection and malignancy.

American Gastroenterological Association Institute

Lichtenstein GR, Abreu MT, Cohen R, et al. American Gastroenterological Association Institute Medical Position Statement on Corticosteroids, Immunomodulators, and Infliximab in Inflammatory Bowel Disease. Gastroenterology 2006;130:935–939.

Summary:

Recommendations in UC

Current indications for infliximab include the treatment of moderately to severely active UC in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent (azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]). These patients are individuals who are resistant to medical therapy (complete and adequate therapy with a corticosteroid or an immunosuppressive agent) or who cannot receive such therapies due to intolerance to medications (corticosteroids or medical contraindications [therapy intolerant]).
The recommended initial dose of infliximab for all IBD indications is 5 mg/kg body wt, administered by intravenous infusion over 2 hours in an induction regimen of 3 doses at weeks 0, 2, and 6. This should be followed by maintenance therapy every 8 weeks in patients who respond. For patients with CD who respond and then lose their response, consideration may be given to treatment with 10 mg/kg. In the case of nonresponse to 3 infusions, further treatment with infliximab is not recommended. The treatment should be administered under the supervision and control of a specialised health care deliverer, with emergency equipment for severe infusion reactions available. A follow-up observation period of approximately 1 hour is advocated. If a patient is on infliximab and achieves remission, an attempt to withdraw or taper any concomitant corticosteroid therapy is sensible.
Although there is evidence-based data to support the use of corticosteroids, immunomodulators, and infliximab in the treatment of patients with IBD, there are

many aspects of therapy with these agents for which the data are lacking or inadequate. Additional prospective data are needed to resolve the areas of controversy. The gastroenterologist who uses these agents must have a clear understanding of the proven benefits and risks of these therapies to provide optimal care to the patient with IBD.

JAMA

Bongartz T, Sutton AJ, Sweeting MJ et al. 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; 295:2275-85

Summary:

This paper assesses the extent to which TNFα inhibitors may increase the risk of serious infections and malignancies in patients with RA by performing a meta-analysis to derive estimates of sparse harmful events occurring in RCTs of TNFα inhibitors. DATA SOURCES: A systematic literature search of EMBASE, MEDLINE, Cochrane Library, and electronic abstract databases of the annual scientific meetings of both the European League Against Rheumatism and the American College of Rheumatology was conducted through December 2005. This search was complemented with interviews of the manufacturers of the 2 licensed TNFα inhibitors. STUDY SELECTION: The authors included RCTs of the 2 licensed TNFα inhibitors (infliximab and adalimumab) used for 12 weeks or more in patients with RA. Nine trials met the inclusion criteria, including 3493 patients who received TNFα inhibitors and 1512 patients who received placebo. DATA EXTRACTION: Data on study characteristics to assess study quality and intention-to-treat data for serious infections and malignancies were abstracted. Published information from the trials was supplemented by direct contact between principal investigators and industry sponsors. DATA SYNTHESIS: The authors calculated a pooled OR (Mantel-Haenszel methods with a continuity correction designed for sparse data) for malignancies and serious infections (infection that requires antimicrobial therapy and/or hospitalisation) in TNFα inhibitor-treated patients vs placebo patients. The authors estimated effects for high and low doses separately. The pooled OR for malignancy was 3.3 (95% confidence interval [CI], 1.2-9.1) and for serious infection was 2.0 (95% CI, 1.3-3.1). Malignancies were significantly more common in patients treated with higher doses compared with patients who received lower doses of TNFα inhibitors. For patients treated with TNFα inhibitors in the included trials, the number needed to harm was 154 (95% CI, 91-500) for 1 additional malignancy within a treatment period of 6 to 12 months. For serious infections, the number needed to harm was 59 (95% CI, 39-125) within a treatment period of 3 to 12 months. CONCLUSIONS: There is evidence of an increased risk of serious infections and a dose-dependent increased risk of malignancies in patients with RA treated with TNFα inhibitors. The formal meta-analysis with pooled sparse adverse events data from RCTs serves as a tool to assess harmful drug effects.

National Horizon Scanning Centre

Infliximab (Remicade) for ulcerative colitis July 2005. Available at: www.pcpoh.bham.ac.uk/publichealth/horizon

Summary:

Infliximab may be welcomed by patients with UC who have had an inadequate response to conventional treatment due to the clinical response, and the induction and maintenance of clinical remission demonstrated in recently reported phase III trials. There are, however, significant side effects associated with therapy with TNFα inhibitors.
The number of infusions required for maximum benefit and long-term response is uncertain at present. It is also unclear at present the number of patients that will receive infliximab initially if successfully licensed for UC. It is therefore difficult to estimate the overall cost impact of infliximab

for the treatment of UC at this time. Treatment with infliximab may lead to a net saving due to a possible reduction in hospitalisation and surgical procedures. Infliximab is already used in the gastrointestinal setting in the treatment of CD and thus minimal additional training of healthcare professionals will be required.

Scottish Medicines Consortium

Infliximab 100 mg powder for intravenous infusion. March 2007. Available at: www.scottishmedicines.org.uk

Summary:

In the absence of a submission from the holder of the marketing authorisation. Infliximab (Remicade) is not recommended for use within NHSScotland for the treatment of moderately to severely active UC in patients who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies. The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication. As a result the authors cannot recommend its use within NHSScotland.

NICE Health Technology Appraisal

Infliximab for ulcerative colitis - final scope. March 2007. Available at: www.nice.org.uk

Summary:

This is the final scope of an appraisal of the clinical and cost effectiveness of infliximab for moderately to severely active UC. A first review is scheduled for August 2007 and the date of the second review has not been set.

Use in Adults

Reviews in IBD

Efficacy and safety reviews

Baumgart DC, Sandborn WJ.
> Inflammatory bowel disease: clinical aspects and established and evolving therapies. Lancet. Vol. 369(9573)(pp 1641-1657), 2007.

Abstract:

This paper critically reviews the evidence for established (5-aminosalicylic acid [5-ASA] compounds, corticosteroids, immunomodulators, calcineurin inhibitors) and emerging novel therapies-including biological therapies-directed at cytokines (eg, infliximab, adalimumab, certolizumab pegol) and receptors (eg, visilizumab, abatacept) involved in T-cell activation, selective adhesion molecule blockers (eg, natalizumab, MLN-02, alicaforsen), anti-inflammatory cytokines (eg, interleukin 10), modulation of the intestinal flora (eg, antibiotics, prebiotics, probiotics), leucocyte apheresis and many more monoclonal antibodies, small molecules, recombinant growth factors, and MAP kinase inhibitors targeting various inflammatory cells and pathways.

D'Haens G.
> Risk and benefits of biologic therapy for inflammatory bowel diseases. Gut. Vol. 56(5)(pp 725-732), 2007.

No abstract available.

Thukral C, Cheifetz A, Peppercorn MA.
> Anti-tumour necrosis factor therapy for ulcerative colitis: Evidence to date. Drugs. Vol. 66(16)(pp 2059-2065), 2006.

Abstract:

ACT1 and ACT2 trials were large, randomised and placebo-controlled, and have shown that infliximab is significantly more efficacious than placebo in treating both corticosteroid-responsive and -refractory moderate-to-severe UC. Data from these 2 studies showed that in patients with moderate-to-severe UC, treatment with infliximab (5 and 10 mg/kg), compared with placebo, led to significantly higher rates of clinical response, clinical remission and mucosal healing. However, a significant proportion of patients who were receiving oral corticosteroids at the start of the trials, remained on corticosteroids despite infliximab therapy. Additionally, the safety profile of the drug was found to be similar to what has been reported in clinical studies of infliximab in patients with CD. On the basis of currently available data, the authors use infliximab as a remission-inducing agent in patients who have moderate-to-severe UC and are either refractory to or intolerant of mesalazine products and immunomodulators. Moreover, infliximab seems to be a reasonable therapeutic modality for remission maintenance in those patients with UC in whom mesalazine products and immunomodulators have failed. Although data are limited, infliximab may be considered as a remission-inducing agent in patients with moderate-to-severe UC which is refractory to oral corticosteroids. However, the role of infliximab in the treatment of UC patients who are dependent on oral corticosteroids is still unclear and, therefore, should be considered only in patients who cannot be successfully transitioned to or are intolerant of oral immunomodulators. Furthermore, infliximab may be an alternative to ciclosporin (cyclosporin) in hospitalised patients with severe to moderately severe but not fulminant UC who do not respond to intravenous corticosteroids. At present, there is insufficient evidence to advocate using infliximab as a first-line agent for UC patients with mild or moderate-to-severe disease. Future randomised, controlled trials with clearly defined patient populations should further help to clarify the definitive role of infliximab in the therapeutic scheme for UC.

Scholmerich J.
> Treatment of inflammatory bowel disease. Schweizerische Rundschau fur Medizin Praxis. Vol. 96(9)(pp 337-343), 2007.

Abstract:

Standard treatment for IBD with 5-ASA, steroids and immunosuppressants is rather effective and currently optimised using combinations of drugs or application routes. Among the biologics only infliximab has reached the therapeutic arsenal for CD - it is also effective in some patients with UC. Early aggressive treatment thus far is not established. Hormones and growth factors may play a role. Probiotics have a place in the treatment in particular for UC.

Collins P, Rhodes J.
> Ulcerative colitis: Diagnosis and management. British Medical Journal. Vol. 333(7563)(pp 340-343), 2006.

No abstract available.

Nakamura K, Honda K, Mizutani T, et al.
> Novel strategies for the treatment of inflammatory bowel disease: Selective inhibition of cytokines and adhesion molecules. World Journal of Gastroenterology. Vol. 12(29)(pp 4628-4635), 2006.

Abstract:

Infliximab has become a standard therapy for CD and it is also likely to be beneficial for UC. Several TNFα inhibitors have been developed but most of them seem to not be as efficacious as infliximab. Adalimumab may be useful for the treatment of patients who lost responsiveness or developed intolerance to infliximab. Antibodies against IL-12 p40 and IL-6 receptor could be alternative new anti-cytokine therapies for IBD. Anti-interferon-gamma and anti-CD25 therapies were developed, but the benefit of these agents has not yet been established. The selective blocking of migration of leukocytes into intestine seems to be a nice approach. Antibodies against a4 integrin and a4beta7 integrin showed benefit for IBD. Antisense oligonucleotide of intercellular adhesion molecule 1 may be efficacious for IBD. Clinical trials of such compounds have been either recently reported or are currently underway. In this article, the authors review the efficacy and safety of such novel biological therapies for IBD.

De La Rue SA, Bickston SJ.
> Evidence-based medications for the treatment of the inflammatory bowel diseases. Current Opinion in Gastroenterology. Vol. 22(4)(pp 365-369), 2006.

Abstract:

This review is an update on several significant analyses that have been published recently. It is intended to raise awareness of the data, helping clinicians to evaluate new treatments and to revisit older treatments with a critical eye.

Cottone M, Mocciaro F, Modesto I.
> Infliximab and ulcerative colitis. Expert Opinion on Biological Therapy. Vol. 6(4)(pp 401-408), 2006.

Abstract:

Despite the fact that the cytokine profiles associated with UC and CD are classically considered different (a Th2 pattern in UC and a Th1 pattern in CD), there are several evidences in vitro and in vivo that TNFα has an important role in UC. Infliximab has been evaluated in different clinical settings both in adults and in children: in moderate-severe steroid-dependent UC, in severe refractory UC as rescue therapy, in active non-steroid-refractory UC, in resistant pouchitis and in maintenance of moderate-severe UC responsive to infliximab. On the basis of the RCTs, it is possible to draw the following conclusions for adults: infliximab seems active in severe steroid-refractory UC, allowing colectomy to be spared even if further controlled trials are needed with a larger sample of patients adopting strict and well-defined inclusion criteria. The drug seems active in inducing remission after 8 weeks in steroid-refractory patients, in patients taking steroids (even if it is not clear at which dosage of steroid dependence the drug is more active) and also in patients failing aminosalicylates therapy. The long-term response of infliximab in comparison to placebo in these subgroups of patients is not clinically impressive even if it is statistically significant. Further trials are warranted in order to establish the role of infliximab in steroid-dependent UC (defined with clear criteria), in maintaining remission after

severe UC, in non-steroid-dependent moderate-severe UC and in refractory pouchitis. For children it is not possible to draw the same conclusions, due to a lack of RCTs, despite the encouraging data coming from open studies, mainly in steroid-refractory UC.

Travassos WJ, Cheifetz AS.
Infliximab: Use in inflammatory bowel disease. Current Treatment Options in Gastroenterology. Vol. 8(3)(pp 187-196), 2005.

Abstract:
Infliximab initially was developed to be used in patients with moderate-to-severe luminal or fistulising CD who are refractory to standard medical therapy. More and more practitioners now are using infliximab as first-line therapy because of its superior efficacy. Infliximab rapidly induces remission in CD, but when given chronically, it can provide long-term maintenance of remission. In addition, there are some data to support its use as a steroid-sparing agent and treatment for various extraintestinal manifestations of IBD and, although used predominantly to treat CD, recent data suggest that infliximab also may have a role in the management of UC. Overall, infliximab represents a clinically useful, cost-effective therapy that works well, even though careful patient monitoring is required to avoid rare but significant toxicities. The hope is that infliximab, together with other biologic agents that currently are in development, will allow us to modify the course of IBD, avoid complications such as strictures and abscesses, and reduce the need for surgery.

Knigge K.
Severe, steroid-refractory ulcerative colitis: Infliximab to the rescue? Evidence-Based Gastroenterology. Vol. 6(4)(pp 110-111), 2005.

No abstract available.

Safety reviews

Blonski W, Lichtenstein GR.
Complications of biological therapy for inflammatory bowel diseases. Current Opinion in Gastroenterology. Vol. 22(1)(pp 30-43), 2006.

Abstract:
This review analyses the complications associated with treatment of IBD with biologic agents. The data concerning biologics' associated toxicity in patients with inflammatory bowel disease are the most robust in the case of infliximab. These data are derived from both prospective, RCTs and from post-marketing experience. In the case of the remaining agents the data concerning safety in inflammatory bowel disease are limited, as these agents were not evaluated in as many trials as infliximab; indeed, some of them included only several patients.

Kamm MA.
Safety issues relating to biological therapies, with special reference to infliximab therapy. Research & Clinical Forums. Vol. 24(1)(pp 79-86), 2002.

Abstract:
The only licensed biological therapy for IBD is infliximab. Acute infusions can be associated with an allergic reaction. Development of human anti-chimeric antibodies is associated with acute infusion reactions, delayed type hypersensitivity reactions, and altered drug pharmacokinetics with a consequent diminuation in clinical efficacy. Ultrasound and MRI studies suggest that the subcutaneous track of subcutaneous fistulae often persist. Mucosal healing can lead to stricture formation. Infliximab increases the risk of infection. The risk of TB has been estimated as approximately 3 per 10,000, and has led to some deaths. CD is associated with an increased cancer risk. Any increased risk from treatment is controversial; long term, large, cohort studies are required. Teratogenicity is not apparent either experimentally or in early clinical data. TNFα inhibitors are dramatically effective in CD, often when other treatments have failed. As with every new treatment, however, its use should be judicious and tempered by data on the long-term benefit, side effects and safety issues.

Reviews of safety – general and in other therapeutic areas

Anonymous.
> Tumour necrosis factor alpha inhibitors. Aust Adv Drug Reactions Bull Volume 25 (Number 6), 23-24, December 2006

Abstract:

Currently, 3 TNFα inhibitors are registered in Australia: infliximab (Remicade) - for the treatment of CD, RA and ankylosing spondylitis (AS); etanercept (Enbrel) - for RA, polyarticular juvenile chronic arthritis, psoriatic arthritis and AS; and adalimumab (Humira) - for RA. ADRAC has received 319 reports involving TNFα inhibitors since 2000. The more serious of these are: 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). According to Medicare Australia statistics, 57,846 prescriptions for the 3 TNFα inhibitors combined have been issued for the treatment of RA since 2000. Given their mechanisms of action, it is possible that the use of TNFα inhibitors may predispose patients to an increased risk of malignancies or accelerate their development. A recent metaanalysis of randomised trials of infliximab or adalimumab in RA found that malignancies developed in 29/3192 (0.9%) patients treated with infliximab or adalimumab, compared with 3/1428 (0.2%) patients given placebo. 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. An increased risk of malignancies has also been reported for etanercept. The Australian Product Information for these medicines advises prescribers that caution should be exercised when considering TNFα inhibitor therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy. The recent meta-analysis also showed a 2-fold increased risk of serious infections with TNFα inhibitors, regardless of dose. Patients receiving TNFα inhibitors should not receive concurrent vaccination with live vaccines and consideration should be given to screening patients for preexisting infections, particularly hepatitis B and TB, prior to their use.

Anonymous.
> Adverse events with TNF antagonists. Bandolier 2006; 249. Available at: http://www.jr2.ox.ac.uk/bandolier/

Abstract:

Fiddling with the immune system brings dangers, including cancer and serious infections. Trying to measure the rate at which these rare events occur, and whether the rates are different with TNFα inhibitors is hard because of limited numbers. New studies provide at least some insight, and highlight the problems. It is probably best to look at the evidence from randomised trials first, then compare it with evidence from observational studies.

RCTs

A systematic review and meta-analysis (Bongartz et al – included in this document) used trials of infliximab and adalimumab in RA (etanercept was excluded because of a somewhat different mechanism of action). It examined published material for serious adverse events, used FDA information, and discussed serious adverse events with trialists and manufacturers for clarification. The denominator was the number of patients with at least one dose of drug, and the numerator patients with at least one serious malignancy or infection. Nine trials lasting at least 12 weeks (8 were 6 months to1 year) randomised 5,014 patients.

Malignancy: There were 29 malignancies in 3,192 patients (0.9%) on infliximab or adalimumab, and 3 in 1,428 (0.2%) on placebo; 6 other lymphomas were detected during follow up, but not included in the analysis. The OR was 3.3 (1.2 to 9.1), and the number of patients who needed to be treated for 6 to 12 months with infliximab or adalimumab for one to be harmed was 154 (91 to 500).

Serious infections: There were 126 serious infections in 3,493 patients (3.6%) on infliximab or adalimumab, and 26 in 1,512 (1.7%) on placebo. The OR was 2.0 (1.3 to 3.1), and the number of patients who

needed to be treated for 6 to 12 months with infliximab or adalimumab for one to be harmed was 59 (39 to 125).

Observational studies

A series of observational studies come from Sweden (see Askling et al papers in this document), where the mix of TNFα inhibitors was predominantly etanercept and infliximab. These used several sources of information, a prevalent cohort of 53,000 RA patients, an incidence cohort of 3,700 RA patients, and one RA cohort of 4,160 patients treated with TNFα inhibitors. These had approximately 300,000, 13,000, and 10,000 person years of follow up respectively, with average follow ups of 6, 3.5 and 2.5 years per patient. Linkage between different registries and cancer and other registries meant that outcomes could be collected. The entire Swedish population served as a control group for calculation of standardised rates.

Malignancies: Haematopoietic malignancies occurred in 507 patients, at rates higher than the general population. When compared with the prevalent and incident RA cohorts not receiving TNFα inhibitors, patients receiving TNFα inhibitors had a RR of 1.1 (95% CI 0.6 to 2.1). Solid cancers occurred in 3,584 patients, at rates little greater than in the general population. When compared with the prevalent and incident RA cohorts not receiving TNFα inhibitors, patients receiving TNFα inhibitors were little different overall, or when analysed by duration of observation.

Serious infections: This is limited by the small number of TB cases in patients treated with infliximab or etanercept (15, 10 of them pulmonary). Only 4 of these were included in a statistical analysis. The best guess is that TB rates are increased in RA patients treated with TNFα inhibitors.

Comment

It is always tempting to dismiss observational studies when they disagree with randomised trials (or meta-analyses of them). This may be hasty, especially when both types of study are well done. It is always worth asking a few questions, especially when dealing with serious, but rare, adverse events. The first question is about size, about the number of events. Because they are rare events, malignancies and serious infections are unlikely to be numerous. If a statistical analysis is based

on a handful of events, potential interference from the random play of chance is possible. One meta-analysis, for instance, had 3 malignancies with placebo, and one observational study used 4 and 2 cases of TB to calculate statistics. While on size, observational studies can involve a lot of patients, and here observational studies had up to 4 times as many patient years of observation than did a meta-analysis of randomised trials. Which brings us to time, especially important for adverse events. Some may occur early with treatment, others late, or they can be constant over time. Comparing short with long duration studies can be problematical.

And finally, what treatments are being used? None of the observational studies seemed to include adalimumab, or any other newer agents. So while meta-analyses concentrated on some agents but not others, observational studies reported on a different mix of agents being used in clinical practice. The question, then, is whether like is being compared with like. If there is a lesson here, it is that for serious but rare adverse events, rushing to judgement may not be prudent. If there is an answer, it is that tinkering with the immune system can produce great benefit, but with a risk of something bad happening. Until it can be said for certain who will benefit and who will be at risk, we have to live with that uncertainty.

Efficacy studies

RCTs

Rutgeerts P, Sandborn WJ, Feagan BG, et al.

> Infliximab for induction and maintenance therapy for ulcerative colitis. New England Journal of Medicine. Vol. 353(23)(pp 2462-2476), 2005.

Abstract:

Two randomised, double-blind, placebo-controlled studies - the Active Ulcerative Colitis Trials 1 and 2 (ACT1 and ACT2, respectively) - evaluated the efficacy of infliximab for induction and maintenance therapy in adults with UC. In each study,

364 patients with moderate-to-severe active UC despite treatment with concurrent medications received placebo or infliximab (5 mg or 10 mg per kilogram of body weight) intravenously at weeks 0, 2, and 6 and then every 8 weeks through week 46 (in ACT1) or week 22 (in ACT2). Patients were followed for 54 weeks in ACT1 and 30 weeks in ACT2. In ACT1, 69% of patients who received 5 mg of infliximab and 61% of those who received 10 mg had a clinical response at week 8, as compared with 37% of those who received placebo ($P<0.001$ for both comparisons with placebo). A response was defined as a decrease in the Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute rectal bleeding subscore of 0 or 1. In ACT2, 64% of patients who received 5 mg of infliximab and 69% of those who received 10 mg had a clinical response at week 8, as compared with 29% of those who received placebo ($P<0.001$ for both comparisons with placebo). In both studies, patients who received infliximab were more likely to have a clinical response at week 30 ($P\leq0.002$ for all comparisons). In ACT1, more patients who received 5 mg or 10 mg of infliximab had a clinical response at week 54 (45% and 44%, respectively) than did those who received placebo (20%, $P<0.001$ for both comparisons). The authoprs concluded that patients with moderate-to-severe active UC treated with infliximab at weeks 0, 2, and 6 and every 8 weeks thereafter were more likely to have a clinical response at weeks 8, 30, and 54 than were those receiving placebo.

Jarnerot G, Hertervig E, Friis-Liby I, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: A randomized, placebo-controlled study. Gastroenterology. Vol. 128(7)(pp 1805-1811), 2005.

Abstract:

This was a randomised double-blind trial of infliximab or placebo in severe to moderately severe UC not responding to conventional treatment. Patients were randomised to infliximab/placebo either on day 4 after the initiation of corticosteroid treatment if they fulfilled the index criteria for fulminant UC on day 3 or on day 6-8 if they fulfilled index criteria on day 5-7 for a severe or moderately severe acute attack of UC. Results were analysed according to the intention-to-treat principle. The primary end point was colectomy or death 3 months after randomisation. Secondary end points were clinical and endoscopic remission at that time in patients who did not undergo operation. Results: Forty-five patients were included (24 infliximab and 21 placebo). No patient died. Seven patients in the infliximab group and 14 in the placebo group had a colectomy ($P =. 017$; OR, 4.9; 95% confidence interval, 1.4-17) within 3 months after randomisation. No serious side effects occurred. Three patients in the placebo group required operation for septic complications. Conclusions: Infliximab 4-5 mg/kg is an effective and safe rescue therapy in patients experiencing an acute severe or moderately severe attack of UC not responding to conventional treatment.

Armuzzi A, De Pascalis B, Lupascu A, et al. Infliximab in the treatment of steroid-dependent ulcerative colitis. European Review for Medical & Pharmacological Sciences. Vol. 8(5)(pp 231-233), 2004.

Abstract:

The authors evaluated the efficacy of infliximab in the management of steroid-dependent UC. They report preliminary data from a randomised, open-label, methylprednisolone-controlled trial of infliximab in the induction and maintenance of remission of patients with moderate-to-severe steroid-dependent UC. Twenty patients received either 3 infusion of infliximab (5 mg/kg) at 0, 2 and 6 weeks and thereafter every 8 weeks (group A) or methylprednisolone (0,7-1 mg/kg) daily for 1 week followed by a tapering regimen up to the minimal dose to maintain a symptom-free condition (group B). Clinical remission was defined as a DAI score less than 3. Results: Ten patients in group A (DAI: 8.9 +/- 1.4) achieved remission after the first infusion (DAI: 1.6 +/- 0,7; p = 0.005) and steroids were progressively discontinued. At present (mean follow-up: 9.8 +/- 1.1 months), 9 out of 10 patients maintain clinical remission, while one patient relapsed at 3 months. Ten patients in group B (DAI:

8.7 +/- 1.4) reached clinical remission at 1 week (DAI: 1.9 +/- 0.3; p = 0.005). Eight out of 10 patients were maintained at a minimal steroid dosage without any relapse at 9.7 +/- 1.0 months follow-up. Two patients relapsed at 6 and 8 months, respectively. Conclusions: Infliximab seems to be as effective as steroids in the management of moderate-to-severe steroid-dependent UC. These preliminary data suggest the potential efficacy of repeated treatment with infliximab for short-term maintenance of remission and steroid withdrawal in glucocorticoid-dependent UC.

Ochsenkuhn T, Sackmann M, Goke B. Infliximab for acute, not steroid-refractory ulcerative colitis: A randomized pilot study. European Journal of Gastroenterology & Hepatology. Vol. 16(11)(pp 1167-1171), 2004.

Abstract:

Infliximab, has shown to be effective in the treatment of steroid-refractory UC in pilot studies. The authors therefore evaluated whether infliximab can achieve remission in patients with acute ulcerative pancolitis who were not steroid-refractory. Methods and design: Patients were eligible if they had acute disease with a modified Truelove and Witts activity score of more than 10 for at least 2 weeks and if they were currently not receiving immunomodulators or more than 10 mg/day prednisolone. Patients were randomly assigned to receive either 3 intravenous infusions of infliximab at 5 mg/kg (group A) or high-dose prednisolone (1.5 mg/ kg body weight) daily for 2 weeks, followed by 1 mg/kg for 1 week, followed by a weekly reduction of 5 mg (group B). Therapy success was defined as clinical response in terms of a decrease of more than 5 points from the baseline score and to less than 10 points total after 3 weeks as well as after 13 weeks. Results: Thirteen patients (7 women, 6 men) were randomised (6 for group A and 7 for group B). The median baseline activity scores were 13.5 (12-18) in group A and 14.0 (11-18) in group B. Five of 6 patients in group A and 6 of 7 patients in group B showed therapy success after 3 weeks as well as after 13 weeks. Conclusions Infliximab could be effective in the treatment of acute moderate or severe

UC. The obtained data call for larger controlled trials.

Probert CSJ, Hearing SD, Schreiber S, et al. Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: A randomised controlled trial. Gut. Vol. 52(7)(pp 998-1002), 2003.

Abstract:

The authors conducted a randomised placebo controlled trial of infliximab (5 mg/kg) in the treatment of glucocorticoid resistant UC. Infusions were given at weeks 0 and 2. Disease activity and quality of life were recorded over 8 weeks of follow up. Remission was defined as an UC symptom score (UCSS) of ≤2 and/or Baron score of 0 at week 6. Patients not in remission were offered open label infliximab 10 mg/kg and reviewed 2 weeks later. Results: After 2 weeks, there was no statistically significant difference between the infliximab and placebo groups in the proportion of patients with a Baron score of 0 (13% (3/23) v 5% (1/19) (95% confidence interval (CI) -9% to 24%); p=0.74). After 6 weeks, remission (UCSS ≤2) rates were 39% (9/23) versus 30% (6/20) (95% CI -19 to 34%; p=0.76). The median improvement in UCSS was 3 for the infliximab group and 2.5 for the placebo group (p=0.82, Mann-Whitney U test). A Baron score of 0 was likely in either group (26% (6/23) v 30% (6/20) (95% CI -30% to 23%); p=0.96). Improvement in the IBDQ and EuroQol was not significantly different between the groups (p=0.22 and 0.3, respectively, Mann-Whitney U test). Twenty eligible patients were given open labelled infusions. Remission was achieved in 3/11 (27%) patients initially treated with infliximab and in 1/9 (11%) patients treated with placebo. Conclusion: These data do not support the use of infliximab in the management of moderately active glucocorticoid resistant UC.

Sands BE, Tremaine WJ, Sandborn WJ, et al. Infliximab in the treatment of severe, steroid-refractory ulcerative colitis: A pilot study. Inflammatory Bowel Diseases. Vol. 7(2)(pp 83-88), 2001.

Abstract:

The authors report the experience of 11 patients (of 60 planned patients) enrolled in a double-blind, placebo-controlled clinical trial of infliximab in patients with severe, active steroid-refractory UC. The study was terminated prematurely because of slow enrollment. Patients having active disease for at least 2 weeks and receiving at least 5 days of intravenous corticosteroids were eligible to receive a single intravenous infusion of infliximab at 5, 10, or 20 mg/kg body weight. The primary endpoint used in this study was treatment failure at 2 weeks after infusion. Treatment failure was defined as 1) unachieved clinical response as defined by a modified Truelove and Witts severity score, 2) increase in corticosteroid dosage, 3) addition of immunosuppressants, 4) colectomy, or 5) death. Safety evaluations included physical examination, clinical chemistry and hematology laboratory tests, and occurrence of adverse experiences. Four of 8 patients (50%) who received infliximab were considered treatment successes at 2 weeks, compared with none of 3 patients who received placebo. Improvement in erythrocyte sedimentation rates and serum concentrations of C-reactive protein and interleukin-6 correlated with the clinical response observed in patients receiving infliximab. Infusion with infliximab produced no significant adverse events. Infliximab was well tolerated and may provide clinical benefit for some patients with steroid-refractory UC.

Non-randomised studies

Jakobovits SL, Jewell DP, Travis SPL. Infliximab for the treatment of ulcerative colitis: Outcomes in Oxford from 2000 to 2006. Alimentary Pharmacology & Therapeutics. Vol. 25(9)(pp 1055-1060), 2007.

Abstract:

Aims: To review the rate of colectomy after infliximab for UC and to identify factors that might predict the need for colectomy. Methods: The authors conducted a retrospective cohort study of patients with active UC treated with infliximab between 2000 and 2006. The primary outcome was colectomy-free survival. Disease and treatment characteristics and complications were documented. Results: Thirty patients were treated with infliximab for refractory UC. Sixteen (53%) came to colectomy a median of 140 days after their first infusion (range 4-607). There was no difference in colectomy between those receiving infliximab for acute severe UC failing intravenous steroids (8/14) and out-patients with steroid-refractory UC (8/16). Only 17% (5/30) achieved a steroid-free remission after a median follow-up of 13 months (range 2-72). Univariate analysis showed that a younger age at diagnosis of colitis was significantly associated with an increased rate of colectomy (27.5 years vs. 38.7 years, P = 0.016). Conclusion: Over half the patients studied came to colectomy. Of those avoiding colectomy, only 5 (17%) sustained a steroid-free remission.

Rossetti S, Actis GC, Fadda M, et al. The use of the anti-tumour necrosis factor monoclonal antibody-infliximab-to treat ulcerative colitis: Implications and trends beyond the available data. Digestive & Liver Disease. Vol. 36(6)(pp 426-431), 2004.

Abstract:

Infliximab has recently been added to the list of off-label therapeutic means for UC. The authors conducted a descriptive analysis of the results from studies on the use of the drug published so far. A total of 187 patients qualified for analysis. They were divided into 4 main categories, including steroid-refractory and responsive adults and children. The median frequencies of an early and a sustained response were 77 and 44.5%. These data suggest that adult non-steroid-refractory, and paediatric patients may respond with the highest frequency. While it is obligatory to wait for the yield of the ongoing controlled trials before any conclusion on these indications is drawn, the data provide seminal ideas to further investigations, including the hypothesis to inaugurate with infliximab a top-down strategy for the treatment of IBD.

Kohn A, Prantera C, Pera A, et al. Infliximab in the treatment of severe ulcerative colitis: A follow-up study.

European Review for Medical & Pharmacological Sciences. Vol. 8(5)(pp 235-237), 2004.

Abstract:

Thirteen patients with severe UC, refractory to therapy with methyl-prednisolone, 60 mg IV daily were treated with a single intravenous infusion of Infliximab 5 mg/kg. Ten out of 13 patients (77%) had a clinical response to therapy defined by a CAI ≤ 10 on 2 consecutive days. Two patients (15%) underwent total colectomy because of clinical worsening; one patient refused surgery and was lost to follow-up. Infusion with Infliximab produced no significant adverse events. The mean time of follow-up was 25.6 months (range 17-24); in this period of time 8 out of 10 patients (80%) maintained clinical remission and were able to discontinue corticosteroids therapy. Infliximab appears to be an effective agent for inducing long standing remission in refractory patients with severe UC.

Gornet J-M, Couve S, Hassani Z, et al. Infliximab for refractory ulcerative colitis or indeterminate colitis: An open-label multicentre study. Alimentary Pharmacology & Therapeutics. Vol. 18(2)(pp 175-181), 2003.

Abstract:

The records of 30 patients treated with infliximab for UC (n = 19) or indeterminate colitis (n = 11) were reviewed. Infliximab was given because of steroid resistance (n = 18), dependence (n = 5) or intolerance (n = 7); 5 patients had failed on cyclosporin; 19 patients had a severe flare-up. Results: Median duration of follow-up was 10 months. In 28 patients with active disease, the response rate was 75% at day 7, with 43% having a complete remission, and 50% at month 1, with 32% having a complete remission. Among the 22 responders, the probability of relapse was 73% at month 6. The probability of complete remission without steroids, taking into account the re-treatment for relapse (n = 11), was 57% (95% confidence interval (CI): 45% to 69%) at month 6. The probability of colectomy was 33% (95% CI: 23% to 43%) at month 12. In indeterminate colitis, response rate was only 50% at day 7 and 30% at month 1. Concomitant use of antimetabolite agents was associated with better results. Conclusions: Infliximab was able to induce a rapid response in some patients with UC or indeterminate colitis refractory to conventional treatment. Long-term results were less favourable, with frequent relapses, and about one-third of the patients required a colectomy.

Kohn A, Prantera C, Pera A, et al. Anti-tumour necrosis factor alpha (Infliximab) in the treatment of severe ulcerative colitis: Result of an open study on 13 patients. Digestive & Liver Disease. Vol. 34(9)(pp 626-630), 2002.

Abstract:

A series of 13 patients with severe UC, refractory to therapy with methyl-prednisolone, 60 mg daily for 7 or more days, were treated with a single intravenous infusion of Infliximab 5 mg/kg. There were 10 patients (77%) who had a clinical response to therapy defined by a clinical activity index ≤ 10 on 2 consecutive days. In 2 patients (15%) total colectomy was necessary on account of clinical worsening whilst one patient refused surgery and was lost to follow-up. All patients who responded showed very rapid clinical improvement, within 2 to 3 days of infusion. Infusion with Infliximab produced no significant adverse events. The mean time of follow-up was 10.1 months (range 5-12); during this time, 9 out of 10 patients (90%) maintained clinical remission and were able to discontinue corticosteroid therapy. Infliximab appears to be an effective agent for inducing long-standing remission in refractory patients with severe UC.

Safety studies

IBD

Atzeni F, Ardizzone S, Sarzi-Puttini P, et al Autoantibody profile during short-term infliximab treatment for Crohn's disease: A prospective cohort study. Alimentary Pharmacology & Therapeutics. Vol. 22(5)(pp 453-461), 2005.

Abstract:

Aim: To determine the frequency and correlation of autoantibody formation in patients with CD treated with infliximab in a routine clinical setting. Methods: Sixty-three patients with refractory/inflammatory (31) and/or fistulising CD (32), received an infliximab infusion at a dose 5 mg/kg in weeks O, 2 and 6, and were evaluated for the development of antinuclear, anti-double-stranded DNA, anti-Sm, anti-RNP, anti-SSA, anti-SSB and antihistone antibodies. The correlates with pharmacological treatments, the response to infliximab and adverse events were evaluated. Results: Antinuclear antibodies were found in 5 of the 63 patients (8%) at baseline and in 26 (42%) after 10 weeks (P < 0.001). Of the 26 antinuclear antibody-positive patients who were further subtyped, 9 of 63 (17%) had anti-double-stranded DNA (P = 0.003), and 1.5% were extractable nuclear antigen (ENA) and antihistone-positive. Five patients were initially positive for anticardiolipin antibodies and 2 more patients became positive during infliximab treatment. New autoantibody formation was more frequent in the patients with inflammatory/refractory disease than in those with fistulising disease (17 vs. 7; P = 0.02). One patient developed drug-induced lupus without major organ damage. Conclusions: Autoantibody formation occurs in 42% of patients (8% of these patients were positive before infliximab treatment) with CD receiving induction treatment with infliximab, but the clinical significance of this remains to be determined.

Blonski W, Kundu R, Lichtenstein GR. Lymphoma risk in inflammatory bowel disease: Role of azathioprine/6- mercaptopurine and infliximab. Practical Gastroenterology. Vol. 29(2)(pp 17-32), 2005.

Abstract:

There has been controversy regarding the prevalence of lymphoma in patients with IBD. Tertiary center studies have reported the increased risk of lymphoma in patients with IBD whereas the majority of population based- studies did not find such a risk when compared to the general population. AZA/6-MP and infliximab are immunomodulatory agents used in the treatment of IBD. This review discusses the relationship between IBD, treatment of IBD (with AZA/6-MP and infliximab) and the risk of lymphoma.

Favalli EG, Varenna M, Sinigaglia L. Drug-induced agranulocytosis during treatment with infliximab in enteropathic spondyloarthropathy. Clinical & Experimental Rheumatology. Vol. 23(2)(pp 247-250), 2005.

Abstract:

The authors describe the case of a 20-year-old Caucasian male affected by enteropathic CD spondyloarthropathy HLA B27 negative, successfully treated with infliximab. After the second infliximab infusion, he was found to have a severe transient neutropenia (0.5 x 10^9/L). Routine serum chemistry and full blood cell count (apart from neutrophil count) were normal. Serology excluded an active infection. Bone marrow needle aspirate showed a normal trilineage differentiation. Autoantibody assessment showed negative ANA, anti-dsDNA, anti-ENA, and ANCA, but positive granulocyte-bound antibodies (GBA) and neutrophil-specific (CD 16+)-bound antibodies (anti-NA). Ten weeks after infliximab infusion, neutrophil count and GBA and anti-NA assay returned spontaneously within normal range and the authors observed the same progress after every successive infliximab infusion they performed. These data indicated that infliximab possibly triggered production of granulocyte and neutrophil autoantibodies with resultant autoimmune agranulocytosis.

Seiderer J, Goke B, Ochsenkuhn T. Safety aspects of infliximab in inflammatory bowel disease patients: A retrospective cohort study in 100 patients of a German University Hospital. Digestion. Vol. 70(1)(pp 3-9), 2004.

Abstract:

The authors reviewed their clinical experience in a retrospective safety study looking upon a single cohort of 100 IBD patients from a large German University Hospital. Methods: 100 patients with severe

CD (n = 92), UC (n = 7) or indeterminate colitis (n = 1) treated with infliximab (5 mg/kg) from January 2000 to December 2003 were retrospectively analysed for acute and subacute adverse events by chart review. Results: Overall, infliximab therapy was generally well tolerated. No fatal complications, malignancies, autoimmune diseases, neurologic or cardiovascular complications were observed in the cohort during the study period. Overall, adverse events were observed in 10 patients: 2 patients showed an acute infusion reaction, 1 patient a serum sickness-like reaction, in 4 patients a bacterial or viral infection occurred, in 1 patient pancytopenia and 2 patients developed surgical complications. Only 6 patients with adverse events required admission to hospital. A case of TB after infliximab was not found. The lack of adverse side-effects was associated with young median age and infrequent comorbidities of the cohort. Conclusion: Regarding its strong immunomodulating capacity, infliximab appears to be an efficient and relatively safe therapeutic option for patients with severe IBD. However, the use of infliximab requires careful screening and close patient monitoring to identify patients at risk and the infrequent, but sometimes serious complications of infliximab.

Ljung T, Karlen P, Schmidt D, et al. Infliximab in inflammatory bowel disease: Clinical outcome in a population based cohort from Stockholm County. Gut. Vol. 53(6)(pp 849-853), 2004.

Abstract:

Aim: To assess the use of infliximab in IBD in a population based cohort, with special emphasis on the occurrence of severe adverse events and mortality. Patients: All patients with IBD treated with infliximab between 1999 and 2001 in Stockholm County were evaluated. Methods: Prospective registration of clinical data was carried out. Retrospective analyses were made of possible adverse events occurring in relation to infliximab treatment. Adverse events requiring pharmacological treatment or hospitalisation were defined as severe. Clinical response was assessed as remission, response, or failure. Results: A cohort comprising 217 patients was assembled: 191 patients had CD, and infliximab was used off label for UC in 22 patients. Four patients were treated for indeterminate colitis (IC). Mean age was 37.6 (0.9) years (range 8-79). The mean number of infliximab infusions was 2.6 (0.1) (range 1-11). Forty 2 severe adverse events were registered in 41 patients (CD, n = 35). Eleven of the severe adverse events occurred postoperatively (CD, n = 6). Three patients with CD developed lymphoma (of which 2 were fatal), opportunistic infections occurred in 2 patients (one with UC, fatal), and 2 patients with severe attacks of IBD died due to sepsis (one with CD, one postoperatively with UC). One additional patient with UC died from pulmonary embolism after colectomy. Mean age in the group with fatal outcome was 62.7 years (range 25-79). The overall response rate was 75% and did not differ between the patient groups. Conclusions: Infliximab was efficacious as an anti-inflammatory treatment when assessed in a population based cohort of patients with IBD. However, there appear to be a significant risk of deleterious and fatal adverse events, particularly in elderly patients with severe attacks of IBD. Off label use of infliximab in UC and IC should be avoided until efficacy is proven in randomised controlled trials. The underlying risk of developing malignancies among patients with severe or chronically active CD in need of infliximab treatment is not known but the finding of a 1.5% annual incidence of lymphoma emphasises the need for vigilant surveillance with respect to this malignant complication.

Marchal L, D'Haens G, Van Assche G, et al. The risk of post-operative complications associated with infliximab therapy for Crohn's disease: A controlled cohort study. Alimentary Pharmacology & Therapeutics. Vol. 19(7)(pp 749-754), 2004.

Abstract:

Background: By temporarily suppressing the immune response, infliximab may increase the risk of peri-operative complications. Aim: To test this hypothesis for intestinal resection in a cohort of 313 CD patients

treated with infliximab. Forty received one or more infusions prior to intestinal resection (31/40 within 12 weeks). Methods: The post-operative events of these patients were compared with those of a control group (infliximab naive) of 39 patients adjusted for age, gender and surgical procedure. Early (10 days) and late (3 months) major or minor complications were identified. Results: The incidence of early minor (15.0% vs. 12.8%) and major (12.5% vs. 7.7%) and late minor (2.5% vs. 5.1%) and major (17.5% vs. 12.8%) complications and the mean hospital stay after surgery (10.3 +/- 4.0 days vs. 9.9 +/- 5.5 days) were similar in both groups. A trend towards an increased early infection rate was found in infliximab pre-treated patients (6 vs. 1: $P = 0.10$), but more patients in this group received corticosteroids and/ or immunosuppressives (29 vs. 16 patients; $P < 0.05$). Conclusion: The use of infliximab before intestinal resection does not prolong the hospital stay and does not increase the rate of post-operative complications.

Colombel J-F, Loftus Jr EV, Tremaine WJ, et al.
> The Safety Profile of Infliximab in Patients with Crohn's Disease: The Mayo Clinic Experience in 500 Patients. Gastroenterology. Vol. 126(1 SUPPL. 1)(pp 19-31), 2004.

Abstract:

The medical records of 500 consecutive patients treated with infliximab at the Mayo Clinic were reviewed and abstracted for demographic features and adverse events. The likelihood of a causal relationship to infliximab for each adverse event was determined by calculating an intrinsic likelihood (imputability) score. Results: The 500 patients received a median of 3 infusions and had a median follow-up of 17 months. Forty-three patients (8.6%) experienced a serious adverse event, of which 30 (6%) were related to infliximab. Acute infusion reactions occurred in 19 of 500 patients (3.8%). Serum sickness-like disease occurred in 19 of 500 patients and was attributed to infliximab in 14 (2.8%). Three patients developed drug-induced lupus. One patient developed a new demyelination disorder. Forty-eight patients had an infectious event, of which 41 (8.2%)

were attributed to infliximab. Twenty patients had a serious infection: 2 had fatal sepsis, 8 had pneumonia (of which 2 cases were fatal), 6 had viral infections, 2 had abdominal abscesses requiring surgery, one had arm cellulitis, and one had histoplasmosis. Nine patients had a malignant disorder, 3 of which were possibly related to infliximab. A total of 10 deaths were observed. For 5 of these patients (1%), the events leading to death were possibly related to infliximab. Conclusions: Short- and long-term infliximab therapy is generally well tolerated. However, clinicians must be vigilant for the occurrence of infrequent but serious events, including serum sickness-like reaction, opportunistic infection and sepsis, and autoimmune disorders.

Stallmach A, Giese T, Schmidt C, et al.
> Severe anaphylactic reaction to infliximab: Successful treatment with adalimumab - Report of a case. European Journal of Gastroenterology & Hepatology. Vol. 16(6)(pp 627-630), 2004.

Abstract:

Treatment with infliximab is highly effective in the treatment of refractory and fistulising CD. Infliximab has been tolerated well, with minimal and short-lived adverse effects. The likelihood of severe reactions to infliximab, such as acute and delayed hypersensitivity infusion reactions, is small; nevertheless, if they do occur, they are life-threatening. The authors report a case of an anaphylaxis-like reaction in a 22-year-old female with long-standing CD. The patient was treated successfully with adalimumab. Follow-up demonstrated mucosal healing and normalisation of elevated pro-inflammatory cytokine transcripts.

Cheifetz A, Smedley M, Martin S, et al.
> The incidence and management of infusion reactions to infliximab: A large center experience. American Journal of Gastroenterology. Vol. 98(6)(pp 1315-1324), 2003.

Abstract:

A total of 165 consecutive patients who received 479 infliximab infusions in the Division of Clinical Immunology Infusion

Center at Mount Sinai Medical Center from July, 1998 to January, 2001 were evaluated. Specific treatment protocols for initial and subsequent acute infusion reactions were followed and the outcomes documented. RESULTS: The overall incidence of infusion reactions to infliximab was 6.1% (29 of 479) of infusions, affecting 9.7% (16 of 165) of patients. Mild, moderate, or severe acute reactions occurred in 3.1% (15 of 479), 1.2% (6 of 479), and 1.0% (5 of 479) of infliximab infusions, respectively. Use of treatment protocols resulted in rapid resolution of all acute reactions to infliximab. With the prophylaxis protocol, all patients who experienced an initial mild or moderate acute reaction were able to receive additional infusions. Four patients experienced a total of 5 severe acute reactions. Three patients were retreated: 2 patients had no further problems, whereas one patient had a second severe acute reaction that rapidly resolved with treatment. Suggesting that acute infusion reactions are not type I hypersensitivity reactions, in 11 patients who experienced 14 acute infusion reactions, serum tryptase levels were normal. Delayed infusion reactions occurred in 0.6% (3 of 479) of infusions. CONCLUSIONS: Infliximab infusions were accompanied by acute reactions in approximately 5% of infusions. These reactions did not seem to be true IgE-mediated type I hypersensitivity events. Using appropriate treatment protocols, these reactions were effectively treated and prevented upon retreatment in nearly all patients. Delayed reactions were rare, occurring in <1% of infusions.

Baert F, Noman M, Vermeire S, et al.
Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. New England Journal of Medicine. Vol. 348(7)(pp 601-608), 2003.

Abstract:
In a cohort of 125 consecutive patients with CD who were treated with infliximab infusions, The authors evaluated the concentrations of infliximab and of antibodies against infliximab, clinical data, side effects (including infusion reactions), and the use of concomitant medications before and 4, 8, and 12 weeks after each infusion. RESULTS A mean of 3.9 infusions (range, 1 to 17) per patient were administered over a mean period of 10 months. Antibodies against infliximab were detected in 61% of patients. The presence of concentrations of 8.0 mug per milliliter or greater before an infusion predicted a shorter duration of response (35 days, as compared with 71 days among patients with concentrations of less than 8.0 mug per milliliter; P<0.001) and a higher risk of infusion reactions (relative-risk, 2.40; 95% confidence interval, 1.65 to 3.66; P<0.001). Infliximab concentrations were significantly lower at 4 weeks among patients who had had an infusion reaction than among patients who had never had an infusion reaction (median, 1.2 vs. 14.1 mug per milliliter; P<0.001). Patients who had infusion reactions had a median duration of clinical response of 38.5 days, as compared with 65 days among patients who did not have an infusion reaction (P<0.001). Concomitant immunosuppressive therapy was predictive of low titers of antibodies against infliximab (P<0.001) and high concentrations of infliximab four weeks after an infusion (P<0.001). CONCLUSIONS The development of antibodies against infliximab is associated with an increased risk of infusion reactions and a reduced duration of response to treatment. Concomitant immunosuppressive therapy reduces the magnitude of the immunogenic response.

Lobel EZ, Korelitz BI, Warman JI.
Red man syndrome and infliximab [5]. Journal of Clinical Gastroenterology. Vol. 36(2)(pp 186), 2003.

No abstract available.

Hommes DW, Parlevliet W, Sterringa GJ, et al.
Infliximab therapy in patients with Crohn's disease; experience with 132 patients. Nederlands Tijdschrift voor Geneeskunde. Vol. 146(25)(pp 1187-1191), 2002.

Abstract:
The aim of this study was to report the experience with infliximab treatment for a large cohort of CD patients in the

Netherlands. Design. Descriptive. Method. All l34 CD patients receiving infliximab infusions in the Amsterdam Medical Centre, the Netherlands, after the drug's registration in the Netherlands in l999 were followed prospectively (study period: l November l999-3l January 2002). Reliable follow-up data were absent in 2 patients. Clinical response, adverse effects, laboratory findings, the number of infusions and the interval between infusions were assessed for both active luminal disease and fistulous disease. The costs associated with the infliximab therapy were also calculated. Results. A total of 592 infusions were administered to l34 patients. The mean number of infusions was 4.4 per patient and the mean interval between infusions was 45 days. The response rate was 78% in active luminal CD and 89% in fistulous disease. Adverse effects were recorded in l7% (n = 22) of the patients, including 3 with serious allergic reactions. No TB or malignancies were observed during the study period. The cost per treatment per patient was between 2000 and 2800 euro. Conclusion. Infliximab was safe and effective for both the induction of remission and the maintenance therapy of active luminal and fistulous CD.

Rheumatoid conditions

Schneeweiss S, Setoguchi S, Weinblatt ME, et al
> Anti-tumor necrosis factor alpha therapy and the risk of serious bacterial infections in elderly patients with rheumatoid arthritis. Arthritis & Rheumatism. Vol. 56 (pp1754-64), 2007.

Abstract:

The objective was to assess the association between the initiation of TNFα inhibitor therapy and the risk of serious bacterial infections in routine care. This was a cohort study of patients with RA in whom specific disease-modifying antirheumatic drugs (DMARDs) were initiated. Patients were Medicare beneficiaries ages 65 years and older (mean age 76.5 years) who were concurrently enrolled in the Pharmaceutical Assistance Contract for the Elderly provided by the state of Pennsylvania. A total of 15,597 RA patients in whom a DMARD was initiated between January 1, 1995 and December 31, 2003 were identified using linked data on all prescription drug dispensings, physician services, and hospitalizations. Initiation of TNFα inhibitor therapy, cytotoxic agents other than MTX, noncytotoxic agents, and glucocorticoids was compared with initiation of MTX. The main outcome measure was serious bacterial infections that required hospitalization. The incidence of serious bacterial infections was, on average, 2.2 per 100 patient-years in this population (95% CI 2.0-2.4). Glucocorticoid use doubled the rate of serious bacterial infections as compared with MTX use, independent of previous DMARD use (rate ratio [RR] 2.1 [95% CI 1.5-3.1]), with a clear dose-response relationship for dosages >5 mg/day (for ≤5 mg/day, RR 1.34; for 6-9 mg/day, RR 1.53; for 10-19 mg/day, RR 2.97; and for ≥20 mg/day, RR 5.48 [P for trend < 0.0001]). Adjusted models showed no increase in the rate of serious infections among initiators of TNFα inhibitor therapy (RR 1.0 [95% CI 0.6-1.7]) or other DMARDs as compared with initiators of MTX. Thus, in a large cohort of patients with RA, no increase in serious bacterial infections among users of TNFα inhibitor therapy compared with users of MTX was found. Glucocorticoid use was associated with a dose-dependent increase in such infections.

Baraliakos X, Listing J, Rudwaleit M, et al
> Safety and efficacy of readministration of infliximab after longterm continuous therapy and withdrawal in patients with ankylosing spondylitis. Journal of Rheumatology. Vol. 34(3)(pp 510-515), 2007.

Abstract:

Objective. To analyse the safety and efficacy of infliximab in patients with AS after discontinuation of long-term therapy over 1 year and readministration, using clinical and laboratory assessments including serum levels of antibodies to infliximab (ATI). Methods. Altogether 42/43 patients with AS in a 3-year multicenter trial discontinued therapy after continuous treatment with infliximab (5 mg/kg/6 wks). Infliximab was only readministered in case of a clinical relapse [judged by Bath AS Disease Activity

Index (BASDAI) and physician global assessment > 4]. ATIwere measured at different timepoints. The primary outcome was safety, and efficacy outcomes were secondary. Results. One patient dropped out after the eighth infusion after retreatment due to repeated local infections. ATI were detected in this patient only. No other relevant adverse events were observed. One patient remained in clinical remission without therapy for more than 1 year. The other 40 patients (97.6%) were reinfused because of clinical relapse. There was no correlation between ATI and clinical measures. BASDAI 50% responses were seen in 25 (63%) and partial remission in 12 (30%) patients. The mean (+/- SD) BASDAI score dropped from 6.0 +/- 1.4 at the time of relapse to 2.6 +/- 2.0, and the median C-reactive protein from 11.2 to 1.8 mg/1 after 1 year (all p < 0.05). Conclusion. Readministration of infliximab after discontinuation of longterm treatment was generally safe and efficacious. Ongoing remission after discontinuation was rare. There was only one patient with relevant adverse events. ATI were detected only in this patient, but there was no correlation to clinical data. Formation of ATI seems to be rare after long-term infliximab therapy in AS.

Den Broeder AA, Creemers MCW, Fransen J, et al.

> Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: A large retrospective study. Journal of Rheumatology. Vol. 34(4)(pp 689-695), 2007.

Abstract:

Objective. To identify risk factors for surgical site infection (SSI) in patients with RA with special attention for TNFα inhibitors. Methods. All patients with RA who had undergone elective orthopedic surgery since introduction of TNFα inhibitors were included in a retrospective parallel-cohort study with a1-year followup. Primary endpoint was a SSI according to the 1992 Centers for Disease Control and Prevention criteria and/or antibiotic use. Cohort 1 did not use TNFα inhibitors, cohort 2 used TNFα inhibitors but had either stopped (2A) or continued TNFα inhibitors preoperatively (2B), the cutoff point being set at 4 times the half-life time of the drug. Infection rates were compared between cohorts, and logistic regression analysis was performed to examine risk factors. Results. In total, 1219 (768 patients) procedures were included, and crude infection risks were 4.0% (41/1023), 5.8% (6/104), and 8.7% (8/92) in cohorts 1, 2A, and 2B, respectively. Elbow surgery (OR 4.1,95% CI 1.6-10.1), foot/ankle surgery (OR 3.2,95% CI 1.6-6.5), and prior skin or wound infection (OR 13.8, 95% CI 5.2-36.7) were associated with increased risk of SSI, whereas duration of surgery (OR 0.42,95% CI 0.23-0.78) and sulfasalazine use (OR 0.21,95% CI 0.05-0.89) were associated with decreased risk. Perioperative use of TNFα inhibitors was not significantly associated with an increase in SSI rates (OR 1.5,95% CI 0.43-5.2). Conclusion. The most important risk factor for SSI is history of SSI or skin infection. Although the study was not powered to detect small differences in infection rates, perioperative continuation of TNFα inhibitors does not seem to be an important risk factor for SSI.

Spanakis E, Sidiropoulos P, Papadakis J, et al.

> Modest but sustained increase of serum high density lipoprotein cholesterol levels in patients with inflammatory arthritides treated with infliximab. Journal of Rheumatology. Vol. 33(12)(pp 2440-2446), 2006.

Abstract:

The authors assessed whether TNFα inhibitors modify the unfavorable lipid profile induced by chronic inflammatory arthritides. Methods. Sixty patients (24 with RA, 26 AS, and 10 psoriatic arthritis) receiving infliximab because of ongoing disease activity despite disease modifying drugs (DMARD) were prospectively studied for 6 months. Lipid profile, total cholesterol/high density lipoprotein cholesterol (TC/HDL-C), and low density lipoprotein cholesterol (LDL-C)/HDL-C ratios, as well as disease activity indices (DAS28 and BASDAI), were assessed. Results. A sustained increase of serum HDL-C was observed [mean increase (95% CI)] 5 (3-7) mg/dl, 3.5 (1-6) mg/dl, and 3 (1-5) mg/dl at 1, 3, and 6 months, respectively

(p < 0.01). Compared to nonresponders, HDL-C increased significantly more in EULAR or BASDAI responders (0.8 vs 5.8 mg/dl; p = 0.05). Serum TC was significantly increased [11 (4-8) mg/dl; p = 0.001] only after the first month of treatment. TC/HDL-C and LDL-C/HDL-C decreased only after the first month [0.3 (0.1-0.4), p < 0.01, and 0.2 (0.1-0.4), p < 0.01, respectively]. For patients with baseline LDL-C > 130 mg/dl, LDL-C/HDL-C decreased (p < 0.05) during the whole study period and TC/HDL-C decreased (p < 0.05) at 1 and 3 months. Conclusion. TNFα inhibitors in patients with chronic inflammatory arthritides induces a modest, but sustained, increase in serum HDL-C levels, which may have a favorable effect in reducing the cardiovascular risk in these patients.

Dixon WG, Watson K, Lunt M, et al. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: Results from the British Society for Rheumatology Biologics Register. Arthritis & Rheumatism. Vol. 54(8)(pp 2368-2376), 2006.

Abstract:

Objective. To determine whether the rate of serious infection is higher in TNFα inhibitor-treated RA patients compared with RA patients treated with traditional disease-modifying antirheumatic drugs (DMARDs). Methods. This was a national prospective observational study of 7,664 TNFα inhibitor-treated and 1,354 DMARD-treated patients with severe RA from the British Society for Rheumatology Biologics Register. All serious infections, stratified by site and organism, were included in the analysis. Results. Between December 2001 and September 2005, there were 525 serious infections in the TNFα inhibitor-treated cohort and 56 in the comparison cohort (9,868 and 1,352 person-years of followup, respectively). The incidence rate ratio (IRR), adjusted for baseline risk, for the TNFα inhibitor-treated cohort compared with the comparison cohort was 1.03 (95% confidence interval 0.68-1.57). However, the frequency of serious skin and soft tissue infections was increased in TNFα inhibitor-treated patients, with an adjusted IRR of 4.28 (95% confidence interval 1.06-17.17). There was no difference in infection risk between the 3 main TNFα inhibitors. Nineteen serious bacterial intracellular infections occurred, exclusively in patients in the TNFα inhibitor-treated cohort. Conclusion. In patients with active RA, TNFα inhibitor therapy was not associated with increased risk of overall serious infection compared with DMARD treatment, after adjustment for baseline risk. In contrast, the rate of serious skin and soft tissue infections was increased, suggesting an important physiologic role of TNF in host defense in the skin and soft tissues beyond that in other tissues.

Konttinen L, Honkanen V, Uotila T, et al. Biological treatment in rheumatic diseases: Results from a longitudinal surveillance: Adverse events. Rheumatology International. Vol. 26(10)(pp 916-922), 2006.

Abstract:

The objective of this study was to assess the long-term safety and tolerability of biologicals in a clinical setting. Data on adverse events (AEs) have been collected over a 5-year period by means of detailed reports sent in to the National Register of Biological Treatment in Finland (ROB-FIN) and validated by information collected by the National Agency for Medicines. Three hundred and 8 reports on AEs were filed, concerning a total of 248 patients; this corresponds to 17% of all patients in the ROB-FIN register who started biological treatments. Skin reactions and infections comprised 35 and 28% of the AEs, respectively. Some cases of TB and other infections, heart failure and demyelinating conditions were seen. This work demonstrates no unexpected AEs in a Finnish patient cohort consisting of RA and spondylarthropathy patients, although many of them were treated with combination treatments in common use in Finland. Biological treatment appears safe in the hands of the Finnish rheumatologists.

Uthman I, Touma Z, El-Sayyad J, Zaitoun F. Successful retreatment with infliximab in patients with prior severe infusion reactions. Clinical

Rheumatology. Vol. 25(4)(pp 540-541), 2006.

Abstract:

Infusion of infliximab can be associated with the development of severe infusion reactions (IR) during retreatment. The authors present the case of 2 RA patients with a history of severe acute IR to infliximab who subsequently underwent successful infusion using a prophylactic treatment with a combination of H1 and H2 receptor blockers, hydrocortisone, and diphenhydramine.

Mori S, Imamura F, Kiyofuji C, et al. Development of interstitial pneumonia in a rheumatoid arthritis patient treated with infliximab, an anti-tumor necrosis factor a-neutralizing antibody. Modern Rheumatology. Vol. 16(4)(pp 251-255), 2006.

Abstract:

Infliximab was introduced to a 66-year-old woman with MTX-resistant RA. Although the TNFα inhibitor therapy was successful, she developed noninfectious interstitial pneumonia (IP) after a second infusion of infliximab. In most cases reported previously, infliximab-associated noninfectious IP occurred after a second or third infusion of infliximab, and this type of IP was more fatal in comparison with cases associated with MTX treatment alone. Keeping a sharp lookout on IP development during this period is crucial to the success of infliximab treatment. After MTX discontinuation and steroid pulse therapy, this patient made a dramatic recovery from IP.

Tubach F, Salmon-Ceron D, Ravaud P, et al. The RATIO observatory: French registry of opportunistic infections, severe bacterial infections, and lymphomas complicating anti-TnFa therapy. Joint, Bone, Spine: Revue du Rhumatisme. Vol. 72(6)(pp 456-460), 2005.

Abstract:

The RATIO observatory collects nationwide data on opportunistic infections, severe bacterial infections, and lymphomas in patients with a past or present history of TNFα inhibitor treatment in France. The cases are validated by a committee of experts, and the capture-recapture method is used to check and to improve case ascertainment. A nested case-control comparison is carried out to identify risk factors for the events of interest. The registry differs from other biological registries in that the inclusion criterion is occurrence of the event (infection or lymphoma) instead of administration of the treatment. This method ensures collection of a far larger number of cases. The RATIO observatory is a remarkable example of a 3-way partnership of learned societies, pharmaceutical companies, and institutions (the French research institute INSERM and the French drug safety agency AFSSAPS). Over 100 events were reported in the first 16 months, a large increase compared to European registries of fixed patient cohorts monitored for 4 to 5 years. This result validates this original approach, which will probably need to be extended to other biotherapies for inflammatory joint disease and to other potential adverse events. The strong commitment of rheumatologists in France, who are the main prescribers of TNFα inhibitors, and of the French Society for Rheumatology explain the high case-ascertainment and must continue to ensure that answers are rapidly provided to the drug safety questions that are vital to patients.

Listing J, Strangfeld A, Kary S, et al. Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis & Rheumatism. Vol. 52(11)(pp 3403-3412), 2005.

Abstract:

Objective. To estimate the incidence rates of serious and nonserious infections in patients with RA who start treatment with a biologic agent, and to compare these rates with those in patients with RA who receive conventional treatment. Methods. Patients enrolled in the German biologics register between May 2001 and September 2003

were included. Treating rheumatologists assessed adverse events and serious adverse events. All adverse events and serious adverse events experienced within 12 months after study entry were analysed. Propensity score methods were applied to estimate which part of a rate increase was likely to be attributable to differences in patient characteristics. Results. Data were available for 512 patients receiving etanercept, 346 patients receiving infliximab, 70 patients receiving anakinra, and 601 control patients treated with disease-modifying antirheumatic drugs. The total number of adverse events per 100 patient-years was 22.6 (95% CI 18.7-27.2) among patients receiving etanercept, 28.3 (95% CI 23.1-34.7) among patients receiving infliximab, and 6.8 (95% CI 5.0-9.4) among controls (P < 0.0001). Significant differences in the rate of serious adverse events were also observed. For patients receiving etanercept, those receiving infliximab, and controls, the total numbers of serious adverse events per 100 patient-years were 6.4 (95% CI 4.5-9.1), 6.2 (95% CI 4.0-9.5), and 2.3 (95% CI 1.3-3.9), respectively (P = 0.0016). After adjusting for differences in the case patient mix, the RRs of serious adverse events were 2.2 (95% CI 0.9-5.4) for patients receiving etanercept and 2.1 (95% CI 0.8-5.5) for patients receiving infliximab, compared with controls. Conclusion. Patients treated with biologic agents have a higher a priori risk of infection. However, the data suggest that this risk is increased by treatment with TNFα inhibitor.

Askling J, Fored CM, Brandt L, et al. Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. Annals of the Rheumatic Diseases. Vol. 64(10)(pp 1421-1426), 2005.

Abstract:

Background: Existing studies of solid cancers in RA reflect cancer morbidity up until the early 1990s in prevalent cohorts admitted to hospital during the 1980s. Objective: To depict the cancer pattern of contemporary patients with RA, from updated risk data from prevalent and incident RA populations. To understand the risk of solid cancer after TNFα inhibitor treatment by obtaining cancer data from cohorts treated in routine care rather than trials. Methods: A population based study of 3 RA cohorts (one prevalent, admitted to hospital 1990-2003 (n = 53 067), one incident, diagnosed 1995-2003 (n = 3703), and one treated with TNFα inhibitors 1999-2003 (n = 4160)), which were linked with Swedish nationwide cancer and census registers and followed up for cancer occurrence through 2003. Results: With 3379 observed cancers, the prevalent RA cohort was at marginally increased overall risk of solid cancer, with 20-50% increased risks for smoke related cancers and +70% increased risk for non-melanoma skin cancer, but decreased risk for breast (-20%) and colorectal cancer (-25%). With 138 cancers, the incident RA cohort displayed a similar cancer pattern apart from non-decreased risks for colorectal cancer. TNFα inhibitor-treated patients displayed solid cancer (n = 67) risks largely similar to those of other patients with RA. Conclusion: The cancer pattern in patients treated with TNFα inhibitors mirrors those of other contemporary as well as historic RA cohorts. The consistent increase in smoking associated cancers in patients with RA emphasises the potential for smoking cessation as a cancer preventive measure in RA.

Askling J, Fored CM, Baecklund E, et al. Haematopoietic malignancies in rheumatoid arthritis: Lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. Annals of the Rheumatic Diseases. Vol. 64(10)(pp 1414-1420), 2005.

Abstract:

Background: Patients with RA are at increased risk of malignant lymphomas, and maybe also of leukaemia and multiple myeloma. The effect of TNFα inhibitors on lymphoma risk and characteristics is unclear. Objective: To assess expected rates and RRs of haematopoietic malignances, especially those associated with TNFα inhibitors, in large population based cohorts of patients with RA. Methods: A population based cohort study was performed of patients with RA (one prevalent cohort (n = 53 067), one incident

cohort (n = 3703), and one TNFα inhibitor-treated cohort 1999 through 2003 (n = 4160)), who were linked with the Swedish Cancer Register. Additionally, the lymphoma specimens for the 12 lymphomas occurring in patients with RA exposed to TNFα inhibitors in Sweden 1999 through 2004 were reviewed. Results: Study of almost 500 observed haematopoietic malignancies showed that prevalent and incident patients with RA were at increased risk of lymphoma (SIR =1.9 and 2.0, respectively) and leukaemia (SIR = 2.1 and 2.2, respectively) but not of myeloma. Patients with RA treated with TNFα inhibitors had a tripled lymphoma risk (SIR = 2.9) compared with the general population. After adjustment for sex, age, and disease duration, the lymphoma risk after exposure to TNFα inhibitors was no higher than in the other RA cohorts. Lymphomas associated with TNFα inhibitors had characteristics similar to those of other RA lymphomas. Conclusion: Overall, patients with RA are at equally increased risks for lymphomas and leukaemias. Patients with RA treated with TNFα inhibitors did not have higher lymphoma risks than other patients with RA. Prolonged observation is needed to determine the long term effects of TNFα inhibitors on lymphoma risk.

Jacobsson LTH, Turesson C, Gulfe A, et al. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. Journal of Rheumatology. Vol. 32(7)(pp 1213-1218), 2005.

Abstract:

Objective. To investigate the risk of cardiovascular disease (CVD) in patients with RA treated with TNFα inhibitors, compared to a standard RA population. Methods. Patients were recruited from a regional register, which includes over 90% of patients with RA started on TNFα inhibitors in 1999 or later, and a local community based cohort of RA patients, established in 1997. Of a total of 983 patients in the combined cohort, 531 received treatment with etanercept or infliximab during the study period. The total cohort (n = 983) was linked with national registers for inpatient care and cause of death through December 31, 2001. CVD was defined as the first inpatient care or death from CVD without inpatient care for CVD prior to study entry. First CVD events in those treated versus not treated with TNFα inhibitors were estimated, using age and sex adjusted incidence density computations with treatment and disease severity markers as time-dependent covariates. Results. In the TNFα inhibitor-treated patients, the age-sex adjusted incidence rate of first CVD event was 14.0/1000 person-years at risk (95% CI 5.7-22.4), compared with 35.4/1000 person-years (95% CI 16.5-54.4) in those not treated. Controlling for disability, the age-sex adjusted rate ratio was 0.46 (95% CI 0.25-0.85, p = 0.013) in TNFα inhibitor-treated versus not treated. Conclusion. These findings suggest that the risk of developing CVD is lower in patients with RA treated with TNFα inhibitors. This is compatible with the hypothesis that inflammation contributes to the development of cardiovascular events.

Maillard H, Ornetti P, Grimault L, et al. Severe pyogenic infections in patients taking infliximab: A regional cohort study. Joint, Bone, Spine: Revue du Rhumatisme. Vol. 72(4)(pp 330-334), 2005.

Abstract:

Objective. - To evaluate the prevalence and risk factors of severe pyogenic infections in rheumatology patients taking infliximab in everyday practice. Methods. - Regional prospective cohort study of patients taking infliximab for RA or AS with data collection on standardised forms. The medical records of patients with severe pyogenic infections were subjected to a detailed retrospective review. Patients with and without severe pyogenic infections were compared. Results. - The cohort included 83 patients (55 women and 28 men). Severe pyogenic infections occurred in 5 (6%) patients (3 women and 2 men), all of whom had acute or underlying risk factors. Higher values were found in these 5 patients for mean age (65.8 +/- 12 vs. 53.9 +/- 13 years, P = 0.04) and mean daily glucocorticoid dosage (15.5 +/- 9 vs. 6.9 +/- 7 mg/day prednisone-equivalent, P = 0.036), as compared to the other patients. Conclusion. - Older age and

high-dose glucocorticoid therapy are associated with an increased risk of severe pyogenic infection during infliximab therapy. Caution is in order when starting and monitoring infliximab therapy in patients with risk factors. The data also emphasise the need for a careful search for risk factors before each infliximab infusion.

Askling J, Fored CM, Brandt L,et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. Arthritis & Rheumatism. Vol. 52(7)(pp 1986-1992), 2005.

Abstract:

This study sought to determine the risk of TB among Swedish patients with RA. Methods. Using data from Swedish nationwide and population-based registers and data from an ongoing monitoring program of TNFα inhibitors, the RRs of TB in patients with RA (versus the general population) and of TB associated with TNFα inhibitors (versus RA patients not treated with biologics) were determined by comparing the incidence of hospitalisation for TB in 3 RA cohorts and 2 general population cohorts from 1999 to 2001. The authors also reviewed the characteristics of all reported cases of TB in RA patients treated with TNFα inhibitors in Sweden and calculated the incidence of TB per type of TNFα inhibitor between 1999 and 2004. Results. During 1999-2001, RA patients who were not treated with TNFα inhibitors were at increased risk of TB versus the general population (RR 2.0, 95% confidence interval [95% CI] 1.2-3.4). RA patients treated with TNFα inhibitors had a 4-fold increased risk of TB (RR 4.0, 95% CI 1.3-12) versus RA patients not treated with TNFα inhibitors. The reported TB cases during 1999-2004 in RA patients exposed to TNFα inhibitors (9 infliximab, 4 etanercept, 2 both) were predominantly pulmonary. TB occurred up to 3 years following the start of treatment. Conclusion. Irrespective of whether TNFα inhibitors are administered, Swedish patients with RA are at increased risk of TB. During 1999-2001, TNFα inhibitors were associated with an increased risk of TB, up to 4-fold in magnitude. This increased risk

may persist over time during treatment and is related to both infliximab and etanercept.

Elkayam O, Burke M, Vardinon N, et al. Autoantibodies profile of rheumatoid arthritis patients during treatment with infliximab. Autoimmunity. Vol. 38(2)(pp 155-160), 2005.

Abstract:

The authors aim was to prospectively analyse a wide array of autoantibodies in RA patients before and 14 weeks after starting infliximab. Material and methods: In this study, 26 consecutive active RA patients participated. All treated with infliximab at a dosage of 3 mg/kg on week 0, 2, 6 and every 8 weeks, along with weekly low dose MTX. Patients were evaluated at week 0 and 14. Clinical assessment included the number of tender and swollen joints, duration of morning stiffness, adverse events (AE) (including SLE-like) and ESR. Sera were collected before the 1st infusion of infliximab at week 0 and 14. The autoantibodies studied were: fluorescent ANA, anti-double-stranded-DNA (anti-ds-DNA), IgG and IgM anti-cardiolipin (ACA), anti-histone-H1 and C (H1, H2A, H2B, H3, H4), anti-SSA, -SSB, -ENA, -scleroderma 70, -thyroid peroxidase (TPO) and -neutrophilic cytoplasmatic (ANCA) antibodies. Results: Of 26 patients, 17 were women. A significant decrease in duration of morning stiffness, number of tender and swollen joints and ESR were observed between week 0 and 14. During follow up (mean of 20.5 +/- 7.3 months), 9 patients stopped infliximab due to inefficacy or AE (most of them after the 4th infusion). Two patients developed lupus-like phenomena. ANA was found positive at baseline in 7 out of 26 patients. In 5 of them, an increase in the titer of ANA was observed at week 14. ANA negative turned positive for 8 patients. A significant increase of anti-cardiolipin (ACA)-IgM levels was observed in 8 patients and of ACA-IgG in 6, in parallel with ANA seroconversion. The mean level of anti-double-stranded-DNA (anti-ds-DNA) -IgG significantly increased from 66 +/- 33 to 93 +/- 68 IU/ml, in 4 patients to pathological levels. Four patients demonstrated an increase in anti-histone H1. Levels of ANCA, anti-ENA, -SSA, -SSB, -RNP, -scleroderma70 and -thyroid peroxidase

(TPO) were negative in all patients and remained unchanged during the study. Cessation of treatment with infliximab was found to be associated with the appearance of ANA. Conclusion: An increased titer or a new appearance of ANA was observed in 12 out of 26 patients. The main autoantibodies found were anti-ds-DNA, ACA-IgM and -IgG and anti-histone. In this cohort, the appearance of some autoantibodies seemed to predict late cessation of treatment.

Vissers WHPM, De Jong EMGJ, Flendrie M, et al.
Infliximab (Remicade) induced skin reaction in a patient with rheumatoid arthritis. Nederlands Tijdschrift voor Dermatologie & Venereologie. Vol. 15(5)(pp 213-214), 2005.

Abstract:

An 87-year-old patient with RA was admitted to the inpatient department because of a severely itching skin rash after starting treatment with the TNFα inhibitor infliximab. Skin rashes on TNFα inhibitors occur frequently and are described in case-reports. Recently, a cohort study was performed at the department of rheumatology and dermatology comparing the RA patients on TNFα inhibitors with RA patients in a control group. The frequency and nature of the skin disorders was recorded.

Chavez-Lopez MA, Delgado-Villafan~a J, Gallaga A, et al.
Severe anaphylactic reaction during the second infusion of infliximab in a patient with psoriatic arthritis. Allergologia et Immunopathologia. Vol. 33(5)(pp 291-292), 2005.

Abstract:

A 33-year-old woman with no history of atopy, diagnosed of psoriatic arthritis, received 200 mg I.V. infliximab, with previous oral administration of loratadine and betamethasone, that was well tolerated. Two minutes after a second infusion 2 weeks later, with the same pretreatment, the patients suffer dyspnea, laryngeal spasm, generalised tremor, vomiting, hypotension, sinusal tachycardia, anxiety and hyposemia. She recovered in 45 minutes, after the

administration of I.V. hydrocortisone, chloropyramine, adrenaline and oxigene. Several reports of infliximab-induced anaphylactic reactions have been published, especially in patients with CD, that have been attributed to a type I (acute or delayed) hypersensitivity reaction mechanism.

Sugiura F, Kojima T, Oba M, et al.
Anaphylactic reaction to infliximab in two rheumatoid arthritis patients who had previously received infliximab and resumed. Modern Rheumatology. Vol. 15(3)(pp 201-203), 2005.

Abstract:

The authors report on 2 cases of anaphylactic reaction following infliximab infusion in patients with active RA. Both individuals had received infliximab treatment during a clinical trial approximately 2 years prior to further therapy; subsequent infusion of this agent led to anaphylactic reactions in both cases. In light of these findings, the authors recommend that future treatments with infliximab in RA patients who have previously received this agent should be carefully monitored.

Grange L, Nissen MJ, Garambois K, et al.
Infliximab-induced cerebral thrombophlebitis [5]. Rheumatology. Vol. 44(2)(pp 260-261), 2005.

No abstract available.

Wolfe F, Michaud K.
Lymphoma in rheumatoid arthritis: The effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. Arthritis & Rheumatism. Vol. 50(6)(pp 1740-1751), 2004.

Abstract:

Objective. The risk of lymphoma is increased in patients with RA, and spontaneous reporting suggests that MTX and TNFα inhibitor therapy might be associated independently with an increased risk of lymphoma. However, data from clinical trials and clinical practice do not provide sufficient evidence concerning these issues because of small sample sizes and

selected study populations. The objective of this study was to determine the rate of and standardised incidence ratio (SIR) for lymphoma in patients with RA and in RA patient subsets by treatment group. Additionally, the authors sought to determine predictors of lymphoma in RA. Methods. The authors prospectively studied 18,572 patients with RA who were enrolled in the National Data Bank for Rheumatic Diseases (NDB). Patients were surveyed biannually, and potential lymphoma eases received detailed followup. The SEER (Survey, Epidemiology, and End Results) cancer data resource was used to derive the expected number of cases of lymphoma in a cohort that was comparable in age and sex with the RA cohort. Results. The overall SIR for lymphoma was 1.9 (95% confidence interval [95% CI] 1.3-2.7). The SIR for biologic use was 2.9 (95% CI 1.7-4.9) and for the use of infliximab (with or without etanercept) was 2.6 (95% CI 1.4-4.5). For etanercept, with or without infliximab, the SIR was 3.8 (95% CI L9-7.5). The SIR for MTX was 1.7 (95% CI 0.9-3.2), and was 1.0 (95% CI 0.4-2.5) for those not receiving MTX or biologics. Lymphoma was associated with increasing age, male sex, and education. Conclusion. Lymphomas are increased in RA. Although the SIR is greatest for TNFα inhibitors, differences between therapies are slight, and confidence intervals for treatment groups overlap. The increased lymphoma rates observed with TNFα inhibitors may reflect channeling bias, whereby patients with the highest risk of lymphoma preferentially receive TNFα inhibitors. Current data are insufficient to establish a causal relationship between RA treatments and the development of lymphoma.

Godinho F, Godfrin B, El Mahou S, et al.
Safety of leflunomide plus infliximab combination therapy in rheumatoid arthritis. Clinical & Experimental Rheumatology. Vol. 22(3)(pp 328-330), 2004.

Abstract:

Objective. To analyse the safety of leflunomide plus infliximab combination therapy, in adult RA patients. Patients. A retrospective study of 17 adult patients with active RA (DAS 28 = 5.94 +/- 0.88 at baseline) who were treated with a combination of leflunomide plus infliximab after failure of treatment with other DMARDs. 13 patients were treated for a minimum of 3 months with leflunomide without toxicity before beginning infliximab. Treatment was begun simultaneously with both drugs in 4 patients. Side effects (clinical and biological) and efficacy (DAS 28) were evaluated at each infliximab infusion (3 mg/kg at week 0, 2, 6 and then every 8 weeks). Results. Thirteen patients experienced 20 types of side effects and 8 of them stopped the combination therapy. The causes of discontinuation were congestive heart failure (1 case), hypertension with thoracic pain (2 cases), eczematous skin patches (2 cases) and neutropenia (3 cases). No death was registered. Nine RA patients continuted the therapy with a median follow-up of 22 weeks. Only 4 of them experienced no side effects. Eight patients were positive for antinuclear antibodies (ANA) and 1 for double-stranded DNA (dsDNA) antibodies at study entry. After treatment, 13 and 5 patients tested positive respectively for ANAs and dsDNA antibodies. There was no relationship between discontinuation and ANA/dsDNA positivity. Conclusion. In this cohort, adverse events were not very different from those seen in patients on either treatment alone and the combination of leflunomide plus infliximab did not appear to be as badly tolerated as described in a previous study.

Gomez-Reino JJ, Carmona L, Rodriguez Valverde V, et al.
Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in TB risk: A multicenter active-surveillance report. Arthritis & Rheumatism. Vol. 48(8)(pp 2122-2127), 2003.

Abstract:

Objective. The long-term safety of therapeutic agents that neutralise TNF is uncertain. Recent evidence based on spontaneous reporting shows an association with active TB. The authors undertook this study to determine and describe the long-term safety of 2 of these agents, infliximab and etanercept, in rheumatic diseases based on a national active-surveillance

system following the commercialisation of the drugs. Methods. The authors analysed the safety data actively collected in the BIOBADASER (Base de Datos de Productos Biologicos de la Sociedad Espan~ola de Reumatologia) database, which was launched in February 2000 by the Spanish Society of Rheumatology. For the estimation of TB risk, the annual incidence rate in patients treated with these agents was compared with the background rate and with the rate in a cohort of patients with RA assembled before the era of TNFα inhibitor treatment. Results. Seventy-one participating centers sent data on 1,578 treatments with infliximab (86%) or etanercept (14%) in 1,540 patients. Drug survival rates (reported as the cumulative percentage of patients still receiving medication) for infliximab and etanercept pooled together were 85% and 81% at 1 year and 2 years, respectively. Instances of discontinuation were essentially due to adverse events. Seventeen cases of TB were found in patients treated with infliximab. The estimated incidence of TB associated with infliximab in RA patients was 1,893 per 100,000 in the year 2000 and 1,113 per 100,000 in the year 2001. These findings represent a significant increased risk compared with background rates. In the first 5 months of 2002, after official guidelines were established for TB prevention in patients treated with biologies, only 1 new TB case was registered (in January). Conclusion. Therapy with infliximab is associated with an increased risk of active TB. Proper measures are needed to prevent and manage this adverse event.

Mikuls TR, Moreland LW.
Benefit-risk assessment of infliximab in the treatment of rheumatoid arthritis. Drug Safety. Vol. 26(1)(pp 23-32), 2003.

Abstract:

Recent reports have highlighted several potential serious adverse effects associated with infliximab (and other TNFα inhibitors), including infusion reactions, congestive heart failure, drug-induced lupus, and CNS demyelination. In addition, recent reports have cited the potential for reactivation of mycobacterial and fungal infection in patients receiving infliximab, mandating appropriate TB screening prior to drug initiation. Although the frequency of serious drug-related toxicity (requiring discontinuation of the agent) appears to be quite low, these reports underscore the need for caution and close surveillance with the administration of TNFα inhibitors, particularly given that strategies aimed at preventing toxicity remain unproven. Despite its potential for toxicity, infliximab remains a valuable alternative for patients with RA.

Favalli EG, Sinigaglia L, Varenna M, et al.
Drug-induced lupus following treatment with infliximab in rheumatoid arthritis. Lupus. Vol. 11(11)(pp 753-755), 2002.

Abstract:

The authors report a case of a 69-year-old female with a 5 year history of RA, who was successfully treated with low-dose MTX and infliximab (initially 3 mg/kg and from the fourth infusion 5 mg/kg) for 23 weeks. Before the sixth infusion, she was diagnosed with DIL by both clinical features (fever > 38 degrees C, recurrence of active synovitis, myalgia, erythematous rash and general malaise) and laboratory findings (antinuclear antibodies 1:160, anti-double-stranded DNA positive by ELISA assay, decreased serum complement C3 and C4, hypergammaglobulinaemia, increased erythrocyte sedimentation rate). After discontinuation of treatment and therapy with oral prednisone, lupus resolved within 8 weeks.

Brown SL, Greene MH, Gershon SK, et al.
Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. Arthritis Rheum 2002; 46:3151-8.

Abstract:

Relevant data in the MedWatch postmarket adverse event surveillance system run by the US Food and Drug Administration were reviewed. RESULTS: The authors identified 26 cases of lymphoproliferative disorders following treatment with etanercept (18 cases) or infliximab (8 cases). The majority

of cases (81%) were non-Hodgkin's lymphomas. The interval between initiation of therapy with etanercept or infliximab and the development of lymphoma was very short (median 8 weeks). In 2 instances (1 infliximab, 1 etanercept), lymphoma regression was observed following discontinuation of TNFα inhibitors, in the absence of specific cytotoxic therapy directed toward the lymphoma. CONCLUSION: Although data from a case series such as this cannot establish a clear causal relationship between exposure to these medications and the risk of lymphoproliferative disease, the known predisposition of patients with RA and CD to lymphoma, the known excess of lymphoma in other immunosuppressed populations, and the known immunosuppressive effects of the TNFα inhibitors provide a biologic basis for concern and justification for the initiation of additional epidemiologic studies to formally evaluate this possible association.

Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 2001; 345:1098-104.

Abstract:

The authors analysed all reports of TB after infliximab therapy that had been received as of May 29, 2001, through the MedWatch spontaneous reporting system of the Food and Drug Administration. RESULTS: There were 70 reported cases of TB after treatment with infliximab, for a median of 12 weeks. In 48 patients, TB developed after 3 or fewer infusions. Forty of the patients had extrapulmonary disease (17 had disseminated disease, 11 lymph node disease, 4 peritoneal disease, 2 pleural disease, and 1 each meningeal, enteric, paravertebral, bone, genital, and bladder disease). The diagnosis was confirmed by a biopsy in 33 patients. Of the 70 reports, 64 were from countries with a low incidence of TB. The reported frequency of TB in association with infliximab therapy was much higher than the reported frequency of other opportunistic infections associated with this drug. In addition, the rate of reported cases of TB among patients treated with infliximab was higher than the available background rates. CONCLUSIONS: Active TB may develop soon after the initiation of treatment with infliximab. Before prescribing the drug, physicians should screen patients for latent TB infection or disease.

Use in Children

Reviews in IBD

Efficacy and safety reviews

Greifer MK, Markowitz JF.
> Update in the treatment of paediatric ulcerative colitis. Expert Opinion on Pharmacotherapy. Vol. 7(14)(pp 1907-1918), 2006.

Abstract:

UC is an important disease in the paediatric population. UC is one of the chronic IBDs, and is medically incurable. However, the arsenal of medications has grown as knowledge of the pathogenesis of this disease advances. This review looks at the classical treatments for children with UC, including the 5-ASAs, corticosteroids and imunomodulators, as well as biological therapy and other, newer modalities.

Safety reviews

No reviews found.

Reviews of safety – general and in other therapeutic areas

No reviews found.

Efficacy studies

RCTs

No studies found.

Non-randomised studies

Fanjiang G, Russell GH, Katz AJ.
> Short- and long-term response to and weaning from infliximab therapy in pediatric ulcerative colitis. Journal of Pediatric Gastroenterology & Nutrition. Vol. 44(3)(pp 312-317), 2007.

Abstract:

The authors reviewed the charts of 27 paediatric patients with UC who were treated with infliximab instead of undergoing a colectomy. Patients with new-onset UC refractory to intravenous steroids for 5 to 10 days and patients with non-steroid-dependent UC with an acute exacerbation were classified as acutely ill (n = 16); patients with chronic steroid-dependent UC were classified as chronically ill (n = 11). The Lichtiger Colitis Activity Index (LCAI) was measured for all patients at baseline and at 1 and 2 months after treatment with infliximab was initiated. Patients were regarded as successfully treated if they remained off steroids and avoided colectomy. RESULTS: The acutely ill group had a mean LCAI score of 11.4 at induction and 0.3 after 2 months. The chronically ill group had a mean LCAI score of 11.2 at induction and 5.5 after 2 months. Treatment with infliximab was successful in 75% of acutely ill patients and in 27% of chronically ill patients. Infliximab was discontinued in 80% of successfully treated patients (83% of acutely ill, 67% of chronically ill). These patients had an average of 10 infusions and a mean follow-up time of 10 months from their last infliximab infusion. CONCLUSIONS: These results suggest that infliximab is more effective in acutely ill UC patients than in patients with chronic steroid-dependent UC. In addition, some patients treated with infliximab can be weaned from infliximab and maintain remission.

Cucchiara S, Latiano A, Palmieri O, et al.
> Polymorphisms of tumor necrosis factor-a but not MDR1 influence response to medical therapy in pediatric-onset inflammatory bowel disease. Journal of Pediatric Gastroenterology & Nutrition. Vol. 44(2)(pp 171-179), 2007.

Abstract:

The authors investigated the contribution of variants of TNFα and MDR1 genes in the predisposition and response to medical therapy in a large paediatric cohort of patients with Crohn disease and UC. PATIENTS AND METHODS: In this study, 200 patients with CD, 186 patients with UC, 434 parents (217 trios), and 347 healthy

unrelated controls were investigated. Single-nucleotide polymorphisms -G308A and -C857T of the TNFα gene and C3435T of the MDR1 gene were investigated and correlated with clinical subphenotypes and efficacy of medical therapy. RESULTS: The frequency of the -308A allele of the TNFα gene was significantly increased in both patients with CD (15%; OR = 2.79; P < 0.01) and patients with UC (11%; OR = 1.96; P < 0.003) compared with controls (6%). Carriers of this allele were 27% in CD (OR = 2.94; P < 0.01) and 19% in UC (OR = 1.86; P = 0.015) compared with 11% in healthy controls. No significant difference was found for both the -C857T and C3435T single-nucleotide polymorphisms. With the genotype/phenotype analysis, no correlation in patients with UC with the MDR1 gene was found. CD carriers of the -308A allele had a higher frequency of surgical resection (35% vs 20%; OR = 2.1; P = 0.035) and more frequent resistance to steroids (22% vs 8%; OR = 0.29; P = 0.032) compared with noncarriers. These findings were confirmed by stepwise logistic regression. CONCLUSIONS: In this paediatric cohort, the promoter -308A polymorphism of TNFα but not the MDR1 gene is significantly involved in the predisposition to both CD and UC. This polymorphism carries a significant reduction in response to steroid therapy, probably leading to a more frequent need for surgical resection.

Akobeng AK.
> Infliximab for induction and maintenance therapy for ulcerative colitis. Journal of Pediatric Gastroenterology & Nutrition. Vol. 42(5)(pp 589-590), 2006.

No abstract available.

Erzin Y, Cosgun S, Dobrucali A, et al.
> Complicated granulomatous colitis in a patient with Hermansky-Pudlak syndrome, successfully treated with infliximab. Acta Gastroenterologica Belgica. Vol. 69(2)(pp 213-216), 2006.

Abstract:
The bowel disease of the Hermansky-Pudlak syndrome (HPS) is a unique type of IBD with clinical features suggestive of idiopathic UC and pathologic features suggestive of CD. The authors report a patient with HPS which was complicated by granulomatous colitis with perineal and rectovaginal fistulas refractory to antibiotics and AZA but dramatically responded to repeated infusions of infliximab.

Eidelwein AP, Cuffari C, Abadom V, et al.
> Infliximab efficacy in pediatric ulcerative colitis. Inflammatory Bowel Diseases. Vol. 11(3)(pp 213-218), 2005.

Abstract:
All paediatric patients with UC who received infliximab between July 2001 and November 2003 at the Johns Hopkins Children's Center were identified. Short- and long-term outcomes and adverse reactions were evaluated. Results: Twelve paediatric patients with UC received infliximab for treatment of fulminant colitis (3 patients), acute exacerbation of colitis (3), steroid-dependent colitis (5), and steroidrefractory colitis (1). Nine patients had a complete short-term response, and 3 had partial improvement. The mean per patient dose of corticosteroid after the first infliximab infusion decreased from 45 mg/day at the first infusion to 22.2 mg/day at 4 weeks (P = 0.02) and 7.8 mg/day at 8 weeks (P = 0.008). Eight patients were classified as long-term responders with a median follow-up time of 10.4 months. Of the 4 long-term nonresponders, 3 underwent colectomy, and the fourth has ongoing chronic symptoms. Three of 4 long-term nonresponders were steroid-refractory compared with 1 of 8 longterm responders. Patients receiving 6-MP had a better response to infliximab. Conclusion: Infliximab should be considered in the treatment of children with symptoms of acute moderate-to-severe UC.

Mamula P, Markowitz JE, Brown KA, et al.
> Infliximab as a novel therapy for pediatric ulcerative colitis. Journal of Pediatric Gastroenterology & Nutrition. Vol. 34(3)(pp 307-311), 2002.

Abstract:

The authors collected data on all consecutive paediatric patients with UC who received infliximab at The Children's Hospital of Philadelphia until July 2001. The primary measured outcome was clinical response at 2 days and 2 weeks after infliximab infusion, as measured by the Lichtiger colitis activity index (LCAI) score and the Physician Global Assessment (PGA). Tolerance of the infusions and adverse events were recorded. Results: Nine patients qualified for clinical response analysis. The median Lichtiger colitis activity index score decreased from 11 before the infusion to 1 at 2 days and 2 weeks after the infusion, respectively (P = 0.01 for 2 days and 2 weeks). Seven of 9 (77%) patients had decreased activity of their disease measured by the Physician Global Assessment. Corticosteroid therapy was discontinued in 6 (66%) patients. An infusion reaction developed (generalised pruritus and facial flushing) in 2 patients and an elevated anti-nuclear antibody (ANA) titer of 1:1280 developed in one patient. Conclusion: Infliximab is associated with short-term clinical improvement in children and adolescents with moderate-to-severe UC.

Serrano M-S, Schmidt-Sommerfeld E, Kilbaugh TJ, et al.
Use of infliximab in pediatric patients with inflammatory bowel disease. Annals of Pharmacotherapy. Vol. 35(7-8)(pp 823-828), 2001.

Abstract:

This was a retrospective review of data regarding 18 paediatric and adolescent patients with active CD (n = 15) and UC (n = 3) poorly controlled with conventional therapy. All patients received 1 to 6 intravenous infusions of infliximab 5 mg/kg, while receiving their usual medications. RESULTS: All patients experienced clinical improvement, including decrease in the frequency of stooling and resolution of extraintestinal symptoms such as arthropathy, malaise, and skin manifestations after treatment with infliximab. All but one patient had a documented decrease in the erythrocyte sedimentation rate. Prednisone dosage was tapered in all but 2 patients, and discontinued in 7 patients. Intravenous infusion of infliximab was well tolerated. One patient developed a rash several days after the infusion. A patient who received 6 infliximab infusions developed recurrent Staphylococcus aureus infections, as well as septic arthritis and chronic osteomyelitis during the follow-up period, raising the issue of the long-term safety of infliximab. CONCLUSIONS: Treatment of patients with refractory CD and UC with infliximab was associated with remarkable clinical improvement. Although the drug may have an important role in their management, further assessment of long-term safety and efficacy is needed.

Safety studies

IBD

Kolho K-L, Ruuska T, Savilahti E.
Severe adverse reactions to infliximab therapy are common in young children with inflammatory bowel disease. Acta Paediatrica. Vol. 96(1)(pp 128-130), 2007.

Abstract:

Since 2000 the authors have introduced 141 infliximab infusions to 23 children with severe IBD. A total of 7 severe adverse reactions occurred in 26% (6 of 23) of the children. Four reactions were acute (anaphylaxis n = 2; allergic reaction n = 2) and 3/4 of these children were younger than 10 years of age. Two children developed an abscess and one child had septicaemia and brain lesions related to progressive multifocal leucoencephalopathy. Conclusion: adverse reactions to infliximab infusions are common. Young children seem to be prone to severe allergic reactions although they are on AZA and conventional glucocorticoid therapy.

Candon S, Mosca A, Ruemmele F, et al.
Clinical and biological consequences of immunization to infliximab in pediatric Crohn's disease. Clinical Immunology. Vol. 118(1)(pp 11-19), 2006.
Infliximab therapy induces the appearance of neutralising anti-infliximab antibodies. In

the paediatric cohort the authors analysed (n = 28) sensitisation occurred in 35.7% patients and was associated with a loss of response to maintenance infusions. In 2 patients presenting high titers of anti-infliximab antibodies, severe infusion reactions were observed, possibly IgE-mediated, precluding further use of the medication. Serum concentrations of TNFα and infliximab were influenced by the presence of anti-infliximab antibodies. The authors propose that surveillance of circulating infliximab and/or TNFα concentration during maintenance therapy represents an indirect but reliable method to monitor anti-infliximab immunisation.

Jacobstein DA, Markowitz JE, Kirschner BS, et al.
> Premedication and infusion reactions with infliximab: Results from a paediatric inflammatory bowel disease consortium. Inflammatory Bowel Diseases. Vol. 11(5)(pp 442-446), 2005.

Abstract:

The authors studied the proportion of paediatric patients receiving infliximab for IBD that developed infusion reactions (IRs) and the potential effects of premedication on IR. Methods: Uniformly collected data from a cohort of paediatric patients with IBD enrolled between January 2000 and May 2003 at 6 paediatric centers were analysed. Data were retrospectively reviewed and analysed. Results: A total of 1652 infusions given to 243 patients in 6 centers was analysed. Overall, 60 IRs were recorded in 40 patients (3.6% of infusions, 16.5% of patients). Thirty-three of 243 patients received premedication before the first IR (group 1). Two hundred ten patients did not receive premedication until the development of IRs, if at all (group 2). IRs were more common among patients in group 1 than in group 2 (12/33 versus 28/210, P < 0.01). Of the 28 patients in group 2 with IRs, 10 began receiving premedication with each subsequent infusion, 12 continued without premedications, and 6 had no further infusions recorded. Two of 10 who began receiving premedication had a subsequent IR versus 6 of 12 who did not receive premedication (P = 0.15). Conclusions: IRs occur in a small proportion of infusions among paediatric patients receiving infliximab for IBD. Premedication does not seem to prevent the development of IRs; however, once an IR has occurred, premedication may be indicated to prevent subsequent IRs.

Crandall WV, Mackner LM.
> Infusion reactions to infliximab in children and adolescents: Frequency, outcome and a predictive model. Alimentary Pharmacology & Therapeutics. Vol. 17(1)(pp 75-84), 2003.

Abstract:

This was a retrospective review of all infliximab infusions performed at Columbus Children's Hospital from December 1998 through September 2001. Results: Fifty-7 children received 361 infusions. Three hundred and fifty-five of the 361 infusions (98.3%) were completed. Fifty children had 304 repeat infusions. There were a total of 35 infusion related reactions. Female gender and the use of immunosuppressive medications for less than 4 months were risk factors for a reaction to infusion number 2. A reaction to infusion 2 and immunosuppressive use for less than 4 months were risk factors for infusion number 3. Conclusions: The rate of infusion reactions in children receiving infliximab is similar to that in adults. Female gender, immunosuppressive use for less than 4 months and prior infusion reactions may be risk factors for subsequent infusion reactions in children.

Predictors of response

Ferrante M, Vermeire S, Katsanos KH, et al.
Predictors of early response to infliximab in patients with ulcerative colitis. Inflamm Bowel Dis. Vol 13(2)(pp 123-8), 2007.

Abstract:

The objective was to report the outcome of infliximab in UC patients from a single center and to identify predictors of early clinical response. METHODS: The first 100 UC patients (45 female; median age, 37.9 years) who received infliximab at a single center were included. Eighty-four patients received 5 mg/kg infliximab, and 37 patients received a 3-dose infliximab induction at weeks 0, 2, and 6. The Mayo endoscopic subscore, assessed by sigmoidoscopy before inclusion, was 1, 2, and 3 in 5%, 52%, and 43% of patients, respectively. Sixty percent had pancolitis, 63% were on concomitant immunosuppressive therapy, 9% were active smokers, 64% had C-reactive protein ≥5 mg/dL, and 44% were pANCA+/ASCA-. Five patients received infliximab because of severe acute colitis refractory to intravenous corticosteroids. RESULTS: Early complete and partial clinical responses were observed in 41% and 24% of patients. Patients with early clinical response were significantly younger than nonresponders (median age, 35.7 versus 41.6 years, $P = 0.041$). Patients who were pANCA+/ASCA- had a significantly lower early clinical response (55% versus 76%; odds ratio [OR] = 0.40 (0.16-0.99), $P = 0.049$). Concomitant immunosuppressive therapy and the use of an infliximab induction scheme did not influence early clinical response. Only 1 of 5 patients who received infliximab for acute steroid-refractory colitis required colectomy within 2 months. CONCLUSIONS: infliximab is an efficient therapy in UC, as shown by 65% early clinical response. A pANCA+/ASCA- serotype and an older age at first infliximab infusion are associated with a suboptimal early clinical response.

Health economics, resources, risk/benefit

Luces C, Bodger K.
Economic burden of inflammatory bowel disease: A UK perspective. Expert Review of Pharmacoeconomics & Outcomes Research. Vol. 6(4)(pp 471-482), 2006.

Abstract:

IBDs are chronic, relapsing conditions that have no permanent drug cure, may occur for the first time in early life and have the potential to produce long-term morbidity. In the era of emerging biological drug therapies, the costs associated with IBD have attracted increased attention. This review considers the available information on the macroeconomics of UC and CD. In relation to direct medical costs, the consistent findings are: hospital (in-patient) costs are incurred by a minority of sufferers but account for approximately half the total cost; and drug costs contribute less than a quarter of the total healthcare costs. Data for levels of costs associated with lost productivity are more variable, but some studies have estimated that 'indirect' costs falling on society exceed medical expenditures. Lifetime costs for IBD are comparable to a number of major diseases, including heart disease and cancer. Over the next 5-10 years, the contribution of drug costs to the overall profile of cost-of-illness will change significantly as biological therapies play an increasing role. A key economic question is whether the health gains realised from exciting new drugs will also lead to reduced expenditures on hospitalisation and surgery.

Acknowledgments