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Evidence on the use of Infliximab in Crohn's Disease

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Introduction

TAGNet has identified the use of infliximab in Crohn's disease as an important issue. There is good evidence of efficacy; however, PBAC has not approved subsidy for this indication.

Rather than add infliximab to the Position Statement schedule, and thus delay the provision of information on this subject, TAG has produced this document with the aim of presenting a collation of data from published guidelines and articles to assist TAGNet members make decisions about use of infliximab in Crohn's disease. TAG has not performed a critical evaluation of the data or made any recommendations.

Readers may use this document to gain a consensus of information on the subject (ie, from the review sections on pages 3-9) or they may also consult the Clinical Studies section for details of recent studies from 2002 onwards.

The guidelines and articles were collated after searching the published literature. This included searches on Cochrane, NICE, SIGN, CCOHTA, National Guideline Clearing House and Medscape (October 2006) as well as selection of articles from Embase searches (*Crohn & *infliximab = 277 results; *infliximab & [case control study or cohort analysis] = 51 results; 21 November 2006). The systematic reviews by CCOHTA and NICE were published in 2002 and included articles from 2001 and earlier. The Cochrane review on induction of remission featured articles up to June 2003. The Embase search was conducted from 2002 onwards to provide latest reviews and clinical trials on infliximab in Crohn's disease.

Summaries of systematic reviews are either verbatim or have been edited for conciseness. The abstracts of review articles and clinical studies are taken verbatim from Embase.

Systematic Reviews

National Guideline Clearing House

Source: (www.guideline.gov published in:Lichtenstein GR, Abreu MT, Cohen R, Tremaine W. American Gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology* 2006 Mar;130(3):935-9.

Recommendations for Infliximab Use (extract from complete summary)

The recommended initial dose of infliximab for all IBD indications is 5 mg/kg body weight, 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. The treatment should be administered under the supervision and control of a specialized health care deliverer, with emergency equipment for severe infusion reactions available. A follow-up observation period of approximately 1 hour is advocated. Current indications for infliximab include the following:

1. Treatment of moderately to severely active CD or UC in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent (AZA, 6-MP, or methotrexate). 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]).

- For induction therapy, the administration of infliximab at time 0 and 2 and 6 weeks is recommended; in the case of nonresponse to 3 infusions, further treatment with infliximab is not recommended.
 - Withdrawal or tapering of concomitant corticosteroid therapy: if a patient is on infliximab and achieves remission, an attempt to withdraw or taper any concomitant corticosteroid therapy is sensible.
 - Patients who respond to induction therapy should receive maintenance therapy with infusions every 8 weeks.
2. Treatment of CD with fistulas in patients who have not responded despite complete and adequate therapy with conventional treatments (including antibiotics, surgical drainage with examination under anesthesia, and/or immunosuppressive therapy): the use of infliximab should be avoided in patients with known hypersensitivity to infliximab, active infections, demyelinating disorders, severe congestive heart failure, and current or recent malignancy. Appropriate screening for latent and active tuberculosis should be performed on all patients before administration of infliximab.

COCHRANE

Source:

www.mrw.interscience.wiley.com/cochrane
Akobeng AK, Zachos M. Tumor necrosis factor-alpha antibody for induction of remission in Crohn's disease. *Cochrane Database of Systematic Reviews* 2003, Issue 4. Art. No.: CD003574.

Summary of main findings:

The objective was to conduct a systematic review to evaluate the effectiveness of TNF- α blocking agents in inducing remission in

patients with active Crohn's disease. The authors searched MEDLINE (1966-June 2003), EMBASE (1984-June 2003), the Cochrane Central Register of Controlled Trials from the Cochrane Library (Issue 2, 2003) and the IBD Review Group Specialized Trials Register. They included only randomised controlled trials in which patients with active Crohn's disease (defined by a validated Crohn's disease activity index) were randomly allocated to receive a TNF- α blocking agent in the treatment arm, or to receive placebo or another treatment in the comparison arm. Ten studies were identified of which 4 met the inclusion criteria. There is evidence from one randomised controlled trial that suggests that a single intravenous infusion of infliximab may be effective for induction of remission in Crohn's disease (Targan et al *N Engl J Med* 1997; 337:1029-35). There was no difference in response rates among infliximab doses of 5, 10 or 20 mg/kg. Thus, a single infusion of infliximab may be effective for induction of remission in Crohn's disease. Based on this study, the authors recommend a dose of 5 mg/kg. The period of follow up for the patients in these studies was probably too short to allow adequate assessment of recently reported serious adverse effects such as tuberculosis and lymphoma.

CCOHTA

Source: www.cadth.ca Marshall J, Blackhouse G, Goeree R, et al. *Infliximab for the Treatment of Crohn's Disease: A Systematic Review and Cost-Utility Analysis*. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2002. Technology report no 24. (See also Mitton and Hilsden reviews below, which discuss this paper.)

Summary of main findings:

Treatment of fistulizing CD: Three infusions of infliximab (5 or 10 mg/kg) at Weeks 0, 2 and 6 were superior to placebo in achieving partial (62% vs. 26%, $p=0.002$) and complete (46% vs. 13%, $p=0.001$) closure of fistulas over 18 weeks. No significant dose response was observed, although numerically higher closure rates were seen with 5mg/kg.

Treatment of active CD resistant to conventional medical therapy: The results show that a single intravenous infusion of infliximab is superior to placebo in inducing clinical response (65% vs. 16%, $p<0.001$) and clinical remission (33% vs. 4%, $p=0.005$) at four weeks. The gains in response (41% vs. 12%, $p=0.008$) and remission (24% vs. 8%, $p=0.31$) were attenuated by 12 weeks. Again, no dose-response was observed, with numerically greater treatment effects at 5 mg/kg than 10 or 20 mg/kg. Among subjects who responded to a blinded infliximab infusion or an open-label re-infusion (10 mg/kg), re-infusions of 10 mg/kg at eight-week intervals yielded significantly higher rates of clinical remission (44% vs. 20%, $p=0.013$) and numerically higher rates of clinical response (62% vs. 37%, $p=0.16$) at Week 44. Preliminary results from a larger trial evaluating maintenance strategies for subjects who achieve clinical response two weeks after infliximab infusion also suggest that repeat infusions of infliximab (5 mg/kg or 10 mg/kg) every eight weeks are numerically superior to placebo in providing clinical response (55% vs. 27%) or remission (42% vs. 21%) at Week 30 (significance testing not reported). Full results of this trial are awaited.

No clinical subgroups in which infliximab consistently offers preferential benefit have been identified. In controlled clinical trials of CD, treatment with infliximab has been tolerated well, with mild and self-limited infusion reactions in three to seven percent of patients. Increased rates of acute respiratory infection were observed. With rare cases of reactivated tuberculosis reported in post-marketing surveillance, screening for tuberculosis is now recommended among candidates for infliximab treatment. The long-term risks of infliximab, including malignancy and autoimmune disease, are currently unknown.

Economic Analysis and Review: Six previous economic analyses of infliximab and two observational studies of infliximab-associated resource utilization were identified. Four evaluations, submitted by industry, generated favourable results for treatment of fistulizing and active CD, and suggested it to be cost-saving. A cost-utility analysis of single-dose infliximab for the

treatment of active CD estimated its incremental cost-utility ratio (ICUR) to range from US \$14,200/QALY to US \$40,000/QALY, but it has been published only in abstract form with limited information on methods and assumptions. The only analysis to be published in a peer-reviewed journal concluded that the ICUR of primary treatment with infliximab for fistulizing CD, relative to usual care, was US \$355,450/QALY.

The authors undertook a cost-utility analysis of infliximab for active CD resistant to conventional therapy. From the perspective of a Canadian provincial ministry of health, no strategy was dominant in the base-case analysis. Usual care yielded the fewest QALY and incurred the lowest costs over one year. A single-infusion of infliximab was estimated to yield 0.01524 additional QALY for incremental direct medical costs of C \$2,762 (ICUR C \$181,201/QALY). Re-treatment of responders further improved outcomes (ICUR C \$480,111/QALY) while adding maintenance therapy for responders provided the best outcome (ICUR C \$696,078/QALY).

Infliximab appears to be clinically effective for the treatment of fistulizing CD and active CD resistant to conventional therapy. While more information on the long-term consequences of infliximab therapy is needed, its short-term safety profile is acceptable. A cost-utility analysis of infliximab in treatment-resistant active CD suggests the incremental costs per additional quality-adjusted life year exceed traditional benchmarks for cost per QALY.

NICE

Source: www.nice.org.uk The clinical effectiveness and cost effectiveness of infliximab for Crohn's Disease, March 2002

Summary (verbatim):

NICE has recommended that infliximab should be used to treat people with severe Crohn's disease provided that all three of the following conditions are fulfilled:

1. The person has severe active Crohn's disease. People with severe active Crohn's disease will be in very poor general health. They will have severe symptoms of the disease such as

weight loss, severe pain and frequent diarrhoea. In addition to symptoms such as these, new fistulas may be developing and the disease may be affecting parts of the body away from the intestines. The doctor can measure the severity of the disease by comparing a patient's symptoms with a standard checklist that can be used to calculate a severity 'score'. Two 'scoring measures' that are often used are the Crohn's Disease Activity Index (or CDAI) and the Harvey-Bradshaw Index. Severe active Crohn's disease would usually have a score of 300 or more on the Crohn's Disease Activity Index or at least 8 to 9 on the Harvey-Bradshaw Index.

2. Treatment with immunomodulators and corticosteroids has not worked, or has caused side effects that make it impossible or unsafe for the person to take them.
3. Because of the person's condition, surgery would not be the right form of treatment.

Infliximab treatment can be repeated for someone who matched criteria 1-3 (above) for treatment with infliximab and who responded to the initial treatment but whose condition then got worse. The doctor should explain the likely risks and benefits of repeating the treatment with infliximab before a decision is made about whether to give another round of treatment.

Reviews

Vader J-P, Froehlich F, Juillerat P, et al. Appropriate treatment for Crohn's disease: Methodology and summary results of a multidisciplinary international expert panel approach - EPACT. *Digestion* 2006;73:237-48.

Background/Aims: For many therapeutic decisions in Crohn's disease (CD), high-grade evidence is lacking. To assist clinical decision-making, explicit panel-based appropriateness criteria were developed by an international, multi-disciplinary expert panel. **Methods:** 10 gastroenterologists, 3 surgeons and 2 general practitioners from 12 European countries assessed the appropriateness of therapy for CD using the RAND Appropriateness Method. Their assessment was based on the study of a recent literature review of the subject, combined with their own expert clinical judgment. Panelists rated clinical indications and treatment options using a 9-point scale (1 = extremely inappropriate; 9 = extremely appropriate). These scenarios were then discussed in detail at the panel meeting and re-rated. Median ratings and disagreement were used to aggregate ratings into three assessment categories: appropriate (A), uncertain (U) and inappropriate (I). **Results:** 569 specific indications were rated, dealing with 9 clinical presentations: mild/moderate luminal CD (n = 104), severe CD (n = 126), steroid-dependent CD (n = 25), steroid-refractory CD (n = 37), fistulizing CD (n = 49), fibrostenotic CD (n = 35), maintenance of medical remission of CD (n = 84), maintenance of surgical remission (n = 78), drug safety in pregnancy (n = 24) and use of infliximab (n = 7). Overall, 146 indications (26%) were judged appropriate, 129 (23%) uncertain and 294 (52%) inappropriate. Frank disagreement was low (14% overall) with the greatest disagreement (54% of scenarios) being observed for treatment of steroid-refractory disease. **Conclusions:** Detailed explicit appropriateness criteria for the appropriate use of therapy for CD were developed for the first time by a European expert panel. Disease location, severity and previous treatments were the main factors taken into account. User-friendly access to EPACT criteria is available via an Internet

site, www.epact.ch, allowing prospective evaluation and improvement of appropriateness of current CD therapy.

De La Rue SA, Bickston SJ. Evidence-Based Medications for the Treatment of the Inflammatory Bowel Diseases. *Curr Opin Gastroenterol.* 2006;22(4):365-369. Available at www.medscape.com

Infliximab is a chimeric mouse-human IgG1 monoclonal antibody that binds to tumor necrosis factor (TNF)- α , and has played a significant role in the management of Crohn's disease since it was approved for use in 1998. The precise mechanism of action of infliximab has yet to be elucidated, but it activates complement and promotes cell apoptosis, which may lead to some of the positive clinical effects.^[1,2] There is extensive evidence supporting the utility of infliximab as an induction agent for Crohn's disease, which is summarized in a recent Cochrane review.^[3] An analysis of patients from the ACCENT (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen 1) phase III clinical trial demonstrated that patients that enter remission with infliximab have fewer hospitalizations and surgeries, increased employment, and improved quality of life.^[4] This supports the concept that infliximab may truly change the course of the disease.

1. Van den Brande JM, Braat H, van den Brink GR, *et al.* Infliximab but not etanercept induces apoptosis in lamina propria T-lymphocytes from patients with Crohn's disease. *Gastroenterology* 2003; 124:1774-1785.
2. Zimmermann-Nielsen E, Agnholt J, Thorlacius-Ussing O, *et al.* Complement activation in plasma before and after infliximab treatment in Crohn disease. *Scand J Gastroenterol* 2003; 38:1050-1054.
3. Akobeng AK, Zachos M. Tumor necrosis factor-alpha antibody for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2004; CD003574.
4. Lichtenstein GR, Yan S, Bala M, Hanauer S. Remission in patients with Crohn's disease is associated with improvement in employment and quality of life and a decrease in

hospitalizations and surgeries. Am J Gastroenterol 2004; 99:91-96.

Mahadevan U. Clinical Trial Design and Endpoints in Biologic Therapy for Crohn's Disease: Interpretation of the Results. Medscape Gastroenterology. 2006;8(2).

Available at www.medscape.com.

In ACCENT 1,^[1] 573 patients with a CDAI > 220 received a 5-mg/kg infusion of infliximab at week 0. Those patients with clinical response, defined as a CDAI reduction of ≥ 70 points and a ≥25% reduction in CDAI score from baseline (n = 335 patients [58%]), were randomized to receive either placebo (group 1) at week 2, week 6, and every 8 weeks; infliximab 5 mg/kg (group 2) at week 2, week 6, and every 8 weeks; or infliximab 5 mg/kg at weeks 2 and 6 and then 10 mg/kg (group 3) every 8 weeks. The coprimary endpoints, by ITT analysis, were the proportion of patients who responded at week 2 and were in remission (CDAI = 150) at week 30, and the time to loss of response up to week 54 in patients who responded. Loss of response was defined as an increase in CDAI of ≥ 70 points from the qualifying score, with a total ≥ 175, an increase in CDAI of 35% or more from the baseline score, or the introduction of a new treatment for active Crohn's disease. At week 30, 21% of group 1 patients were in remission compared with 39% of patients in group 2 (*P* = .003) and 45% of patients in group 3 (*P* = .0002). The median time to loss of response was 38 weeks for group 2 and > 54 weeks for group 3, compared with 19 weeks for group 1. ACCENT 1 demonstrated that among initial responders, infliximab maintained remission, allowed the discontinuation of steroids, and maintained response for longer than patients receiving placebo.

1. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomized trial. Lancet 2002;359:1541-9 (see "Efficacy" section below).

Tilg H, Knoflach P, Petritsch W, Vogelsang H, Reinisch W. Infliximab in the treatment of Crohn's disease - A practical approach - Consensus statement of the Working Group on

Chronic Inflammatory Crohn's Diseases of the OGGH. [German]. Zeitschrift fur Gastroenterologie 2004; 42:1256-1263. No abstract available.

Panaccione R, Fedorak RN, Aumais G, et al. Canadian association of gastroenterology clinical practice guidelines: The use of infliximab in Crohn's disease. Canadian Journal of Gastroenterology 2004; 18:503-508. No abstract available.

Mitton CR. Funding the new biologics - A health economic critique of the CCOHTA report: Infliximab for the treatment of Crohn's disease. Canadian Journal of Gastroenterology 2002; 16:873-876.

The report of the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) on the use of infliximab in the treatment of refractory Crohn's disease stated that the medication did not meet 'conventional standards of cost-effectiveness'. It had several methodological weaknesses, however, including the derivation of the quality-adjusted life-years (QALYs) gained and the interpretation of the incremental cost utility ratios (ICURs). The validity of economic analyses is highly dependent on the underlying assumptions that are made about the implications of health care states and treatments. The authors of the report mapped utilities from three health states, taken from an American study, onto the nine health states that were considered in their economic analysis. The QALYs that were derived might not have been sensitive to small changes in health outcomes. Moreover, the indirect costs of Crohn's disease and its complications were ignored. Therefore, it is possible that the benefits of infliximab therapy were underestimated. The high ICURs that were quoted in the report do not necessarily mean that infliximab is not valuable, because opportunity costs were not considered. Instead of calculating the ICUR, a preferable approach would be to determine the benefit of this therapy, compared with that which could be derived from alternative uses of the same amount of health care resources. A 'balance sheet' approach would allow decision-makers to determine whether the

additional cost of infliximab therapy would be justified by the health care gains that it produces. It is inappropriate to assign an arbitrary cut-off point to cost effectiveness, as defined by ICURs, especially when considering new and expensive treatments for severely ill patients who have few other therapeutic alternatives. Because only a small number of patients would require infliximab, the overall expenditure that would be required to make it available may be manageable.

Hilsden R. Funding the new biologics - What can we learn from infliximab? The CCOHTA report: A gastroenterologist's viewpoint. *Canadian Journal of Gastroenterology* 2002; 16:865-868.

The treatment of severe Crohn's disease is difficult, and approximately 20% of patients do not respond to conventional therapy, including corticosteroids and immunosuppressives. Infliximab is one of the only treatments of proven efficacy in this group. Awareness of its benefits and risks is incomplete, because the drug has only recently been introduced and published research data are relatively sparse. Economic analyses help to evaluate the value of interventions that are both effective and expensive, but their validity is compromised by input data that involve questionable assumptions. They should not, therefore, be the only basis for funding decisions. Patients with severe Crohn's disease are frequently unable to be gainfully employed and thus incur significant indirect costs. In a recent study by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA), infliximab was deemed to not meet commonly accepted standards of cost effectiveness. This economic analysis did not incorporate indirect costs, and thus was inherently flawed and likely underestimated infliximab's value. The CCOHTA report also used population data from a period of time during which treatment of Crohn's disease was undergoing major transition. The study population was based in Minnesota and thus might not be applicable to Canada. Although they are routinely used in cost effectiveness models, quality-adjusted life-years gained are difficult to translate into practice, and the health care resources required to induce

remission (or some other clinically meaningful result) might be a preferable measure. The CCOHTA report also did not include concomitant therapy with immunosuppressives, despite growing evidence for its benefit. Instead, it considered 'usual care', but, given the lack of effective treatment for many patients with Crohn's disease, such an option constitutes 'no care' and continued suffering. Economic analyses should not be the only basis on which decisions regarding the funding of infliximab, or other new agents, are made.

Keating GM, Perry CM. Infliximab: An updated review of its use in Crohn's disease and rheumatoid arthritis. *Biodrugs* 2002; 16:111-148.

Infliximab is a chimeric monoclonal antibody that binds to tumour necrosis factor- α (TNF α) and neutralises its effects. TNF α plays an important role in the development of both Crohn's disease and rheumatoid arthritis. In a large, double-blind, randomised study involving patients with active, refractory Crohn's disease, significantly more recipients of intravenous infliximab, compared with placebo, achieved a clinical response after 4 weeks' follow-up. Moreover, infliximab administration was associated with a rapid improvement in endoscopic and histological findings in clinical trials involving patients with active, refractory Crohn's disease. The results of the A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen (ACCENT) I study showed that maintenance infliximab therapy prolonged response and remission in patients with moderate to severe Crohn's disease. In patients with enterocutaneous fistulae associated with Crohn's disease who were involved in a double-blind, randomised study, significantly more patients who received multiple infusions of infliximab, compared with placebo, experienced a $\geq 50\%$ reduction from baseline in the number of draining fistulae at ≥ 2 consecutive study visits. In patients with active rheumatoid arthritis refractory to treatment with methotrexate who were enrolled in a large, double-blind, randomised study [the Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) study], American College of Rheumatology (ACR) 20, 50 and 70%

response rates were seen in significantly more patients who received multiple infusions of infliximab plus methotrexate, compared with methotrexate plus placebo, after 30 and 54 weeks' treatment. Moreover, the ACR 20% response rate was maintained after 102 weeks' treatment. In addition, significantly less radiographic progression was seen in infliximab plus methotrexate, compared with methotrexate plus placebo, recipients after 54 weeks' treatment. Infliximab therapy was also associated with improvements in health-related quality of life in patients with Crohn's disease or rheumatoid arthritis. Infliximab was generally well tolerated in clinical trials with the most common adverse events including upper respiratory tract infection, headache, nausea, coughing, sinusitis and diarrhoea. Infliximab therapy may be associated with an increased risk of reactivation of tuberculosis in patients with latent disease. In conclusion, infliximab is an important treatment option in patients with active Crohn's disease who have not responded to conventional therapy and in patients with Crohn's disease who have fistulae. Moreover, infliximab plus methotrexate is effective in patients with active rheumatoid arthritis who have not responded adequately to traditional disease-modifying antirheumatic drugs, in terms of reducing symptoms and signs, improving physical function and delaying the progression of structural damage.

Clinical Studies

Efficacy

M LE, Mary J, Duclos B, et al. Infiximab Plus Azathioprine for Steroid-Dependent Crohn's Disease Patients: A Randomized Placebo-Controlled Trial. *Gastroenterology* 2006; 130:1054-1061.

Background & Aims: The aim of this study was to evaluate the usefulness of short-term infiximab combined with azathioprine (AZA) or 6-mercaptopurine (6-MP) in steroid-dependent Crohn's disease patients.

Methods: Patients with active disease despite prednisone given for more than 6 months were eligible and were stratified as follows: the failure stratum consisted of patients receiving AZA/6-MP at a stable dose for more than 6 months, and the naive stratum consisted of patients not treated previously with AZA/6-MP. Patients were randomized to infiximab 5 mg/kg or placebo at weeks 0, 2, and 6. All patients were treated with AZA/6-MP maintained at a stable dose throughout the 52 weeks of the study. The primary end point was remission off steroids at week 24. **Results:** Among the 113 enrolled patients (55 in the failure stratum), 57 were assigned to infiximab. At week 24, the success rate (intent-to-treat analysis) was higher in the infiximab group than in the placebo group (57% vs 29%; $P = .003$); at weeks 12 and 52, the corresponding rates were 75% vs 38% ($P < .001$) and 40% vs 22% ($P = .04$), respectively. In each stratum, the success rate was significantly higher in the infiximab group at weeks 12 and 24, and a trend was found at week 52. In the failure stratum, only 27% of the patients in the infiximab group were still in remission off steroids, compared with 52% in the naive stratum. Steroid resistance was less common and the cumulative dose of prednisone was lower in the infiximab group. **Conclusions:** Infiximab plus AZA/6-MP is more effective than AZA/6-MP alone in steroid-dependent Crohn's disease patients.

Poupardin C, Lemann M, Gendre JP, et al. Efficacy of infiximab in Crohn's disease. Results of a retrospective multicenter study with a 15-month

follow-up. *Gastroenterologie Clinique et Biologique* 2006; 30:247-252.

Objectives - To evaluate prescription practices and response to infiximab treatment for Crohn's disease (CD). **Patients and methods -** The files of CD patients treated with at least one infusion of infiximab treated in gastroenterology units belonging to university teaching hospitals of the Parisian hospitals group (Assistance Publique-Hopitaux de Paris (AP-HP) during the year 2000 were analyzed retrospectively. **Results -** One hundred and thirty-seven patients (36.0 +/- 12.7 years, 92 females) from 12 centers were studied. **Indication for treatment** was fistulae or perianal disease in 39% of patients, active Crohn's disease in 45% and mixed conditions in 16%. Mean follow-up was 15.2 +/- 7.2 months. The overall response rate was 85%. No predictive factor of sustained remission could be identified. The mean time to relapse was to 3.9 +/- 3.1 months. Thirty-eight patients were on maintenance therapy at the end of the follow up; 37% exhibiting progressive lost of response to treatment. Immunosuppressive therapy was added to infiximab in 78% of cases but response to infiximab was not modified by addition of immunosuppressive drugs. **Adverse events**, most frequently minor, were noted in 23% of the patients. **Conclusion -** This retrospective study confirms the efficacy and safety of infiximab in CD.

Markowitz J, Hyams J, Mack D, et al. Corticosteroid Therapy in the Age of Infiximab: Acute and 1-Year Outcomes in Newly Diagnosed Children With Crohn's Disease. *Clinical Gastroenterology & Hepatology* 2006;4:1124-9.

Background & Aims: The aim of this study was to describe 3-month and 1-year outcomes of children with Crohn's disease (CD) treated with corticosteroids within 30 days of diagnosis, with particular emphasis on the influence of infiximab on these outcomes. We also aimed to determine whether there are clinical or laboratory characteristics associated with corticosteroid therapy outcomes. **Methods:** Data from 109 children were drawn from a multicenter observational registry that was started in 2002. **Clinical characteristics and data on**

corticosteroid and other therapies were recorded prospectively. Corticosteroid therapy outcomes at 3 months were defined as complete acute response, partial response, or corticosteroid resistance. At 1 year, corticosteroid responsiveness, dependence, and surgical rates were determined. Infliximab's influence on short- and long-term outcomes also was investigated. Results: At 3 months, 65 of 109 (60%) patients had a complete acute response to corticosteroids, 26 (24%) had a partial response, and 18 (17%) were corticosteroid resistant. At 1 year, 61% were corticosteroid responsive, 31% were corticosteroid dependent, and 8% required surgery. Irrespective of the duration of corticosteroid treatment, 16 of 24 of corticosteroid-dependent/resistant patients rapidly discontinued corticosteroids after starting infliximab. No clinical or laboratory characteristics at diagnosis predicted short-term outcome. Growth impairment at diagnosis increased risk for corticosteroid dependence or surgery at 1 year. Conclusions: At 3 months, 84% of children had a complete or partial response to corticosteroids. However, despite concomitant immunomodulators, at 1 year 31% were corticosteroid dependent and 8% required surgery. Infliximab improves outcomes of corticosteroid-dependent/resistant patients because the duration of corticosteroid use can be controlled by initiating treatment with infliximab.

Duburque C, Lelong J, Iacob R, et al.
Successful induction of tolerance to infliximab in patients with Crohn's disease and prior severe infusion reactions. *Alimentary Pharmacology & Therapeutics* 2006;24:851-8.

Aim: To appraise the tolerance and efficacy of an induction of tolerance protocol to infliximab permitting the re-administration of the drug to patients with Crohn's disease having had infusion reactions requiring suspension of treatment. Methods: Fourteen patients were included in the induction of tolerance protocol. Each infusion of infliximab (5 mg/kg) was divided into 11 escalating 15 min increments over a 3-h time period. The induction of tolerance procedure was repeated for subsequent infusions. Results: Ten patients (71.4%)

received all the three infusions for the induction treatment. Nine (64.3%) had a significant response and six (48.8%) still benefited from infliximab infusions. Seven patients (50%) achieved a complete remission, after a mean of 2.5 (two to three) infusions. Four patients (28.6%) had no response and the protocol was stopped. Three patients (21.4%) experienced mild immediate hypersensitivity reactions, which were controlled, two patients (14.2%) experienced severe immediate hypersensitivity reactions, leading to interruption of the treatment and one patient developed a delayed hypersensitivity reaction. Conclusion: Our induction of tolerance protocol allows some patients who have experienced severe or repetitive infusion reactions to infliximab to be safely retreated with the drug in a hospitalized setting, with a clinical response achieved in a majority of these patients.

Abreu MT, Geller JL, Vasiliauskas EA, et al.
Treatment with infliximab is associated with increased markers of bone formation in patients with Crohn's disease. *Journal of Clinical Gastroenterology* 2006;40:55-63.

OBJECTIVE: Osteoporosis is a common complication of Crohn's disease (CD). Glucocorticoid use and detrimental effects of inflammatory cytokines including tumor necrosis factor-alpha (TNF-a) can lead to osteoporosis. The aim of this study was to assess the ability of treatment with the TNF-a antagonist infliximab to increase bone formation as measured by surrogate markers of bone turnover in patients with active CD. METHODS: Sera from 38 prospectively enrolled CD patients were examined for levels of bone alkaline phosphatase (BAP), N-telopeptide of type I collagen (NTX), immunoreactive parathyroid hormone (iPTH), calcium, and pro-inflammatory cytokines at baseline and 4 weeks following infliximab infusion. Crohn's Disease Activity Index (CDAI), Inflammatory Bowel Disease Questionnaire (IBDQ), and glucocorticoid dose also were collected. RESULTS: In this cohort, CDAI and IBDQ scores were significantly improved at week 4 ($P < 0.001$). Infliximab therapy was associated with an increase in BAP, a marker of bone formation ($P = 0.010$), whereas NTX, a marker of bone resorption,

was not increased ($P = 0.801$). Among 22 patients who were taking glucocorticoids, mean glucocorticoid dose decreased 36% ($P < 0.001$; -7.9 mg). **CONCLUSIONS:** Treatment with infliximab was associated with increased markers of bone formation (BAP) without increasing bone resorption (NTX). This effect may be due to a beneficial effect of TNF- α blockade on bone turnover, a beneficial effect on CD activity resulting in decreased glucocorticoid dose, or both. Studies of longer duration are needed to assess the effect of infliximab on bone mineral density.

Tomecki R, Bartnik W, Butruk E, et al.
Assessment of the efficacy, tolerance and safety of infliximab (Remicade) in the treatment of Crohn's disease - Results of an open, multicentre clinical trial. *Gastroenterologia Polska* 2004; 11:537-542.

Introduction: Infliximab is a chimeric anti-TNF- α antibody registered as the first biological drug effective in the treatment of Crohn's disease. **Objectives:** The aim of the study was assessment of the effectiveness, safety and tolerance of infliximab therapy in patients with Crohn's disease. **Material and method:** The treated group included 30 patients: 16 with clinically active CD and 14 with fistulae complicating the inflammatory disease. Infliximab was administered in dose 5 mg/kg body weight, in intravenous infusion lasting two hours. In cases with active CD the patients were given the drug in single dose. In the group with fistulae the preparation was given thrice in weeks 0, 2, and 6 also in dose 5 mg/kg body weight. **Results:** Remission was achieved in 12 and improvement in one out of 16 treated patients, what accounted for 81% of positive responses to the therapy. In most cases the improvement occurred immediately after drug administration leading to complete remission in week 8 of the follow-up. In the group of 14 patients with fistulae, complete closure of the fistulae was obtained in three cases while healing of at least 50% of the fistulae was observed in five cases 56.7% of the patients with this form of Crohn's disease benefited from infliximab therapy. Healing of the fistulae progressed rapidly between week 6 and week 10 and the favourable clinical effect vanished between

week 10 and week 14 after the first administration of the drug. The tolerance of intravenous infusions of anti-TNF- α antibodies was very good in all cases. No significant immediate reactions were observed. In four patients between week 4 and week 24 after drug administration infectious complications developed. In two cases they were easily controllable bacterial infections of the urinary system, lungs and subcutaneous tissue. In two cases severe pulmonary and lymphonodular-pulmonary tuberculosis developed. Two cases of tuberculosis in our material may be the evidence of higher-than-average risk of such complication in the Polish population. **Conclusions:** The performed study conducted good tolerance and high effectiveness of infliximab in the treatment of the main forms of Crohn's disease.

Witthoft T, Ludwig D. Effectiveness and tolerability of repeated treatment with infliximab in patients with Crohn's disease: A retrospective data analysis in Germany. *International Journal of Colorectal Disease* 2005; 20:18-23.

Aim: The aim was to evaluate the efficacy and safety of repeated treatment with infliximab in patients with chronic active Crohn's disease under routine conditions in clinics and private practices. **Methods:** Patients with active Crohn's disease were treated with a total of 567 infusions (420 re-infusions) of infliximab. The treatment schedule was at the discretion of the treating physician. Efficacy and tolerability were documented by a standardized questionnaire. **Results:** There were indications for therapy in 46% of patients with chronic active disease, fistulas in 15% and combined symptoms in 38%. The mean disease duration was 9.4 years. At the beginning of therapy, 76% of patients were on corticosteroids, 67% received 5-aminosalicylates and 48% azathioprine. The average dose of infliximab administered was 300 mg; the mean interval between individual infusions was 8.7 weeks. Following treatment with infliximab, steroids could be withdrawn in 47% and reduced in 33% of patients, whereas the dosage of 5-aminosalicylates and azathioprine mostly remained unchanged. The efficacy and tolerability of infliximab were judged by the

physicians as being very good or good in 73.4 and 88.4% of patients respectively. Further treatment with the anti-TNF α antibody was planned for 61% of patients. Improvement of Crohn's Disease Activity Index (CDAI), white blood cell (WBC) and C-reactive protein (CRP) levels was noted in almost all patients. Conclusion: Infliximab used in an individually adapted regimen induced a significant clinical response in the majority of patients with refractory and fistulating Crohn's disease. In nearly 80% of patients corticosteroids could be withdrawn or reduced and the majority of patients were on azathioprine at the end of follow-up procedures.

Arslan S, Kav T, Besisik F, et al. Clinical outcome of Crohn's disease treated with infliximab. *Hepato Gastroenterology* 2003; 50:952-956.

Background/Aims: Controlled studies in humans have shown the role of antibodies to tumor necrosis factor- α in the treatment of both fistulizing and inflammatory Crohn's disease. The aim of this study is to report the results of a multicenter clinical trial to evaluate efficacy of infliximab in Crohn's disease patients who are refractory to conservative drugs or fistulizing Crohn's disease. Methodology: This trial was carried out at 5 university and community hospitals, in Turkey. A total of 25 patients with Crohn's disease that were unresponsive to conventional medical therapy, participated; 17 of the 25 were in the fistulizing disease group and 8 were in the inflammatory disease group. Clinical response was classified according to fistula drainage, diarrhea as positive response or no response. Results: Overall response rate was 92% (23/25), regardless of the disease group, after first infusion of infliximab. Sixteen out of 17 patients in the fistulizing disease group had a positive response. Fourteen of the 16 positive responders later relapsed. Median duration of response was 8 weeks (range, 2-35 wk). Active inflammatory disease patients had a positive response rate of 75% (6/8) and two of the patients were nonresponders. A further two patients relapsed at week 14. Two patients in both arms of the study were still in remission at the end of the study. Major adverse events were: pneumonia in one patient, skin infections in two patients,

pulmonary thromboembolism and death in one patient. Conclusions: Infliximab treatment seems to be more effective in Crohn's disease patients especially in those with fistulizing disease than those with nonfistulizing, inflammatory disease. It is evident that maintenance of remission might be achieved with ongoing maintenance therapy. We suggest maintenance of infliximab therapy.

Kinney T, Rawlins M, Kozarek R, France R, Patterson DJ. Immunomodulators and 'on demand' therapy with infliximab in Crohn's disease: Clinical experience with 400 infusions. *American Journal of Gastroenterology* 2003; 98:608-612.

OBJECTIVES: Infliximab has been proven effective for treatment of active Crohn's and fistulizing Crohn's disease. We reviewed our experience with infliximab in patients with Crohn's disease to determine if its combination with immunomodulators leads to better response and longer periods of disease quiescence. METHODS: We performed a retrospective chart review of 122 patients with Crohn's disease who received infliximab infusions. Data were collected on patient demographics, clinical response to infliximab, fistula response, prednisone dose, infusion reactions/side effects, concomitant immunomodulator therapy, and time intervals between infliximab infusions. RESULTS: Of 122 patients receiving infliximab infusions, 117 completed more than 2 wk of follow-up (400 infusions), and five patients had no follow-up. Co-therapies included azathioprine (AZA) in 47 (40.2%) patients, 6-mercaptopurine (6-MP) in 11 (9.4%), methotrexate (MTX) in 23 (19.7%), prednisone in 64 (54.7%), mesalamine in 51 (43.6%), and antibiotics in 16 (13.7%). Mean follow-up was 52 wk (14-864 days). Overall response rate to infliximab was similar between patients receiving immunomodulators (AZA/6-MP 87.9%, MTX 82.6%) and patients receiving infliximab alone (75%), although there was a trend toward higher response with AZA/6-MP ($p = 0.10$). More frequent drug reactions/side effects occurred in the infliximab alone group (22.2%) compared with patients receiving MTX (13.0%) and AZA/6-MP (13.8%), but this was not statistically

significant. Prednisone dosage was reduced from a mean of 19.5 mg to 7.5 mg per day overall ($p < 0.05$). Fistula response and dosing intervals were not affected by concomitant immunosuppression.

CONCLUSIONS: Concomitant use of immunomodulators with infliximab in patients with Crohn's disease did not improve patient response to several parameters measured, including clinical response rate, dose reduction of prednisone, fistula response, and mean intervals between infliximab infusions.

Doubremelle M, Bourreille A, Zerbib F, et al. Treatment of Crohn's disease with anti-TNF alpha antibodies (infliximab): Results of a multicentric and retrospective study. [French]. *Gastroenterologie Clinique et Biologique* 2002; 26:973-979.

Objective - To evaluate the results of infliximab therapy, an anti-TNF- α antibody, in patients with severe and refractory Crohn's disease or with fistulas, treated outside the setting of a therapeutic trial.
Methods - All Crohn's disease patients treated at the Departments of Gastroenterology of the University Hospitals of Bordeaux, Nantes, Poitiers, Rennes and Tours were retrospectively analyzed.
Results - Sixty-nine patients were treated with a total of 170 infusions of infliximab, 32 patients being treated for refractory Crohn's disease and 37 for fistulas. The median follow-up was 8 months (extremes 1-20). An objective response was observed in 79% of refractory Crohn's disease patients and 78% of fistulizing patients. A remission was observed in 72% and 70% of the patients respectively. Forty-five percent of patients had relapsed within 4 months (extremes 2-7). Immunosuppressive therapy was associated with a lower relapse rate (18% with versus 56% without, $P = 0.004$). Infliximab resulted in a steroid-sparing effect in 73% of patients. Forty adverse events, none of severe grade, were observed in 22% of the patients, without any influence of steroids or immunosuppressive therapy.
Conclusion - This study confirms that infliximab is very effective in steroid-dependent and fistulizing Crohn's disease. Infliximab has a steroid-sparing effect and immunosuppressive therapy is associated with a reduced relapse rate. Although the

tolerance is good in the short term, long term safety remains to be established by further studies.

Ardizzone S, Colombo E, Maconi G, et al. Infliximab in treatment of Crohn's disease: The Milan experience. *Digestive & Liver Disease* 2002; 34:411-418.

Background. Efficacy of infliximab in treatment of patients with moderate-to-severe refractory and fistulizing Crohn's disease has been shown in controlled clinical trials. Moreover, audit data from North America and North Europe have confirmed efficacy in clinical practice comparable to that in clinical trials. **Aim.** To report clinical experience using infliximab in treatment of Crohn's disease in Italy, comparing efficacy and safety with those reported in clinical trials and other published series. **Patients and Methods.** The study population comprised 63 patients (31 males and 32 females, median age 33 years) treated with infliximab for refractory/inflammatory (31 patients) and/or fistulizing Crohn's disease (32 patients). All patients received an infusion of infliximab at a dose of 5 mg/kg at weeks 0, 2 and 6. After the first infusion, clinical and laboratory assessments were repeated at weeks 2, 6 and 10. For refractory inflammatory Crohn's disease, clinical remission was defined as a Crohn's Disease Activity Index of ≤ 150 at each scheduled visit, clinical response as a reduction in the Crohn's Disease Activity Index score of ≥ 70 points in comparison to baseline. For fistulizing Crohn's disease, a complete response was defined as closure of any draining fistulae at week 10. A fistula was defined as closed when it no longer drained despite gentle finger pressure. A partial response was defined as reduction in number, size or drainage of fistulae, at the same visit. **Results.** According to an intention-to-treat evaluation on the 31 patients with refractory/inflammatory Crohn's disease, at week 2, 42.5% (14 patients) had a clinical response and 31.3% of patients (10 patients) were in clinical remission. At week 10 (4 weeks after the end of third infusion), 80.6% (25 patients) had a clinical response and 71% (22 patients) were in clinical remission and 14/19 (74%) had discontinued steroid treatment. Of the 32 patients with fistulizing Crohn's Disease, 15

(46.9%) had a complete response, 8 (25%) a partial response, and 9 (28.1%) no response at week 10 check-up. The incidence of side-effects was low (16%) and not influenced by concurrent immunomodulatory therapy. Conclusion. The present experience with infliximab in clinical practice confirms its efficacy, in particular in inflammatory/refractory Crohn's disease and its safety, at least, in short-term follow-up.

Hommes DW, Parlevliet W, Sterringa GJ, Hermans M, Bartelsman J, Van Deventer SJH. Infliximab therapy in patients with Crohn's disease; experience with 132 patients. [Dutch]. *Nederlands Tijdschrift voor Geneeskunde* 2002; 146:1187-1191.

Objective. The aim of this study was to report the experience with infliximab treatment for a large cohort of Crohn's disease (CD) patients in the Netherlands. Design. Descriptive. Method. All 134 CD patients receiving infliximab infusions in the Amsterdam Medical Centre, the Netherlands, after the drug's registration in the Netherlands in 1999 were followed prospectively (study period: 1 November 1999-31 January 2002). Reliable follow-up data were absent in two 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 134 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 Crohn's disease and 89% in fistulous disease. Adverse effects were recorded in 17% (n = 22) of the patients, including three with serious allergic reactions. No tuberculosis 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 Crohn's disease.

Sample C, Bailey RJ, Todoruk D, et al. Clinical experience with infliximab for Crohn's disease: The first 100 patients in Edmonton, Alberta. *Canadian Journal of Gastroenterology* 2002; 16:165-170.

Objective: To determine whether the clinical efficacy and safety of infliximab in diverse clinical referral practices was similar to that seen in the randomized, controlled clinical trials. Methods: Data were gathered from a review of charts of 109 consecutive patients with inflammatory and/or fistulizing Crohn's disease who received infliximab infusions. Responses were recorded based on the physician's global clinical assessment and classified as complete, partial or nonresponse. Results: One hundred nine patients were treated with one to nine infusions of infliximab at a dose of 5 mg/kg and followed up for a median of 24 weeks (range one to 40 weeks). Fifty-four patients were treated for inflammatory disease, 38 for fistulizing disease and 17 for both. Clinical response occurred in 73% (17% complete response, 55% partial response). The clinical response rate did not vary relative to patient demographics, disease distribution, indication for infliximab, or the concomitant use of corticosteroids or immune modifiers. For those taking concomitant immune modifiers, the response rate was 75%. The median time to response was two weeks (range one to six weeks). The median duration of response was 12 weeks (range six to 88 weeks). Reduction or cessation of steroids was possible in 17 of 32 patients. Adverse events related to infliximab occurred in 7% of patients. These events were characterized as mild and did not require stoppage of infliximab therapy, except in one patient who had a treatable anaphylactic-like infusion reaction. Conclusions: The patient group in the present study realized significant clinical benefit, with minimal adverse effects, following treatment with infliximab. Clinical response rates paralleled those previously described in placebo controlled trials and retrospective clinical practice reviews. Nevertheless, the complete response rate (ie, remission) in this patient group was lower than that previously described.

Maintenance therapy

Kevans D, Keegan D, Mulcahy HE, O'Donoghue DP. Influximab therapy in Crohn's disease: A pragmatic approach? *Alimentary Pharmacology & Therapeutics* 2006; 24:351-359.

Background: Influximab is recognized as an effective therapy in unresponsive luminal and fistulating Crohn's disease. The use of maintenance or 'on demand' therapy thereafter is controversial. Aim: To assess the need for maintenance influximab therapy in a clinical setting where immunomodulatory agents are widely used and where episodic therapy is used in preference to maintenance therapy. Methods: Ninety-three patients with Crohn's disease receiving influximab; 72 with unresponsive luminal disease and 21 with fistulous disease. Data collected included disease site and duration, surgical and smoking history, initial response rates, duration of response maintenance and concomitant medications. Results: Fifty-six of 72 (78%) patients with luminal disease and 11 of 21 (52%) with fistulous disease achieved an initial response. Ten of 67 responders required conversion to maintenance influximab infusions, while 31 remain in remission. Patients with luminal disease and those who had not taken previous surgery had higher response rates to influximab. Younger patients and those with small bowel disease had higher relapse rates following initial response. Three patients developed allergic reactions to influximab and one patient died of progressive pulmonary disease 6 weeks after their first infusion. Conclusions: Many patients with Crohn's disease can be maintained successfully with an episodic influximab regimen.

Rutgeerts P, Diamond RH, Bala M, et al. Scheduled maintenance treatment with influximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. *Gastrointestinal Endoscopy* 2006; 63:433-442.

Background: The endoscopic substudy of the ACCENT I (A Crohn's Disease Clinical Trial Evaluating Influximab in a New Long-term Treatment Regimen) Crohn's disease

trial examined the effects of influximab on mucosal inflammation and mucosal healing, and assessed their impact on outcomes. Design: ACCENT I was a randomized, double-blind, parallel group study. Setting: This study took place at multiple centers in North America, Europe, and Israel. Main Outcome Measurements: Ileocolonoscopy examinations were performed at weeks 0, 10, and 54. Complete mucosal healing was defined as the absence of all mucosal ulcerations. The end point of principal interest was the proportion of patients randomized as responders with mucosal healing at week 10. The proportion of responders who demonstrated mucosal healing at week 54 or at both weeks 10 and 54 is also summarized. Changes in Crohn's disease endoscopic index of severity (CDEIS) scores from baseline to week 10 and 54 were calculated for all patients in this substudy. Results: Complete mucosal healing by week 10 occurred in significantly more week 2 responders who had received 3 doses of influximab compared with a single dose (31% vs. 0%, $p = 0.010$). A significantly higher proportion of week 2 responders in the combined scheduled maintenance group had complete mucosal healing at week 54 compared with the episodic group (50% vs. 7%, $p = 0.007$). The results for all patients are consistent with those for week 2 responders only. Significantly greater improvement in the CDEIS occurred with scheduled maintenance compared with episodic treatment at week 10 ($p \leq 0.001$) and week 54 ($p = 0.026$). Notably, no strong relationship between clinical remission and complete mucosal healing was found. Overall, mucosal healing appeared to correlate with fewer hospitalizations, although these results were not statistically significant. Conclusions: Scheduled influximab maintenance therapy resulted in more improvement in mucosal ulceration and in higher rates of mucosal healing. There was a numerical trend for patients with better mucosal healing to have a lower rate of Crohn's disease-related hospitalizations.

Geboes K, Rutgeerts P, Opendakker G, et al. Endoscopic and histologic evidence of persistent mucosal healing and correlation with clinical

improvement following sustained infliximab treatment for Crohn's disease. *Current Medical Research & Opinion* 2006; 21:1741-1754.

Objectives: the long-term effect of infliximab on endoscopic and histologic disease activity and expression of inflammatory markers was assessed in Crohn's disease patients who received infliximab as episodic or scheduled maintenance therapy over 54 weeks (ACCENT I). **Methods:** All patients received infliximab 5 mg/kg at week 0 and at week 2 were then randomized as responders or nonresponders to placebo or infliximab (5 or 10 mg/kg). Patients received placebo or infliximab 5 mg/kg at weeks 2 and 6 followed by placebo or infliximab (5 or 10 mg/kg) every 8 weeks or episodically on loss of response. Crohn's Disease Activity Index (CDAI), Crohn's Disease Endoscopic Index of Severity (CDEIS), Inflammatory Bowel Disease Questionnaire (IBDQ), and colonic and ileal Global Histologic Disease Activity (CGHAS and IGHAS) scores were determined at weeks 0, 10, and 54. Tumor necrosis factor- α (TNF- α), gelatinase B, infliximab, tenascin, clusters of differentiation marker 68 (CD68), and intercellular adhesion molecule-1 (ICAM-1) were detected in mucosal biopsies by immunohistochemistry. **Results:** At baseline, CDEIS significantly correlated with CGHAS only. Further at baseline, both CDEIS and the worst CGHAS or IGHAS, were significantly correlated with CD68, ICAM-1, and gelatinase B expression. At week 10, improvement in CGHAS only, correlated significantly with better CDAI, CDEIS, and IBDQ scores. Improvements in CDEIS and GHAS at week 10 correlated with reductions in gelatinase B and CD68, whereas only GHAS improvement correlated with decreased TNF- α expression. At week 54, decreased gelatinase B expression continued to correlate with improved CDEIS and GHAS while decreased CD68 and TNF- α expression correlated with GHAS and CDEIS improvement, respectively. **Conclusions:** Endoscopic and histologic evidence of mucosal healing was associated with a sustained reduction in the expression of inflammatory markers. Infliximab-induced improvement in the clinical signs and symptoms of Crohn's disease was associated with endoscopic and histologic evidence of sustained mucosal healing.

Bernstein M, Irwin S, Greenberg GR. Maintenance infliximab treatment is associated with improved bone mineral density in Crohn's disease. *American Journal of Gastroenterology* 2005; 100:2031-2035.

OBJECTIVES: Diminished bone mineral density (BMD) is a recognized complication of Crohn's disease (CD). The mechanisms underlying bone loss are unclear but may include a direct effect of inflammatory cytokines related to disease activity. Because tumor necrosis factor alpha (TNF- α) plays a central role in the pathogenesis of CD inflammation, we evaluated the effect on BMD of maintenance treatment with infliximab in patients with CD. **METHODS:** BMD of the lumbar spine (L2-L4) and proximal left femur (neck and trochanter) were measured at baseline and 1 yr in 46 CD patients treated with infliximab (5 mg/kg) at 6-8 wk intervals for 1 yr. Thirteen patients received concurrent prednisone at a mean dose of 10 mg/day (range: 5-15). **RESULTS:** At baseline, reduced BMD (T-score \leq 1) occurred in 43% of patients at the lumbar spine and 46% at the left femur. Between baseline and 1 yr, mean BMD increased at the lumbar spine by 2.4% \pm 0.7% ($p=0.002$), at the femoral trochanter by 2.8% \pm 1.2% ($p=0.03$), and at the femoral neck by 2.6% \pm 0.7% ($p=0.001$). BMD gain at the lumbar spine and the left femur between the groups without and with osteopenia were not different. Changes in BMD were not correlated with concurrent corticosteroid therapy, calcium supplementation, or changes in C-reactive protein (CRP). **CONCLUSIONS:** Maintenance treatment with infliximab improves BMD in patients with CD and this effect is independent of corticosteroid administration. The BMD response after infliximab suggests that TNF- α plays a role in the bone loss associated with CD.

Menachem Y, Avidan B, Lavy A, et al. Increasing the infliximab dose is beneficial in Crohn's disease patients who responded to a lower dose and relapsed. *Digestion* 2005; 72:124-128.

Background: Relapse after an initial response to infliximab therapy poses a

problem for maintenance treatment. Aim: To assess the effects of increasing the infliximab dosage in Crohn's disease (CD) patients who initially responded but flared during maintenance therapy. Methods: This was an observational study. Twelve CD patients with both inflammatory and fistulizing manifestations were included. All patients initially responded to 5 mg/kg of infliximab, relapsed during maintenance therapy, and were treated with 10 mg/kg. The Harvey-Bradshaw index, the fistula activity, and steroid use were assessed before and after treatment with the increased dose of infliximab. Results: The mean Harvey-Bradshaw index score after flare-up during treatment with 5 mg/kg of infliximab was 13.5 +/- 3.7. Treatment with 10 mg/kg, in a mean of 3.3 infusions, decreased the activity score to a mean of 8.8 +/- 2.5. Two patients were weaned off prednisone, and a reduced dose was possible in the other steroid-treated patients. Conclusions: Increasing the infliximab dose may be beneficial in CD patients who initially responded to therapy, but relapsed during maintenance with the lower dosage.

Sands BE, Anderson FH, Bernstein CN, et al. Infliximab Maintenance Therapy for Fistulizing Crohn's Disease. *New England Journal of Medicine* 2004; 350:876-885.

BACKGROUND: Infliximab, a monoclonal antibody against tumor necrosis factor, is an effective maintenance therapy for patients with Crohn's disease without fistulas. It is not known whether infliximab is an effective maintenance therapy for patients with fistulas. **METHODS:** We performed a multicenter, double-blind, randomized, placebo-controlled trial to evaluate the efficacy of infliximab maintenance therapy in 306 adult patients with Crohn's disease and one or more draining abdominal or perianal fistulas of at least three months' duration. Patients received 5 mg of infliximab per kilogram of body weight intravenously on weeks 0, 2, and 6. A total of 195 patients who had a response at weeks 10 and 14 and 87 patients who had no response were then randomly assigned to receive placebo or 5 mg of infliximab per kilogram every eight weeks and to be followed to week 54. The primary analysis was the time to the loss of response among patients who had a

response at week 14 and underwent randomization. **RESULTS:** The time to loss of response was significantly longer for patients who received infliximab maintenance therapy than for those who received placebo maintenance (more than 40 weeks vs. 14 weeks, $P < 0.001$). At week 54, 19 percent of patients in the placebo maintenance group had a complete absence of draining fistulas, as compared with 36 percent of patients in the infliximab maintenance group ($P = 0.009$). **CONCLUSIONS:** Patients with fistulizing Crohn's disease who have a response to induction therapy with infliximab have an increased likelihood of a sustained response over a 54-week period if infliximab treatment is continued every 8 weeks.

Rutgeerts P, Feagan BG, Lichtenstein GR, et al. Comparison of Scheduled and Episodic Treatment Strategies of Infliximab in Crohn's Disease. *Gastroenterology* 2004; 126:402-413.

Background & Aims: This analysis of Crohn's disease patients treated with infliximab in ACCENT I compared episodic and scheduled treatment strategies under conditions that simulate clinical practice. **Methods:** After 5 mg/kg infliximab at week 0, 573 patients were randomized to infusions at weeks 2 and 6 and every 8 weeks until week 46 of placebo (episodic), infliximab 5 mg/kg at weeks 2 and 6 followed by 5 mg/kg (5 mg/kg scheduled) every 8 weeks, or infliximab 5 mg/kg at weeks 2 and 6 followed by 10 mg/kg (10 mg/kg scheduled) every 8 weeks. At or after week 14, treatment could be given with a dose of infliximab 5 mg/kg higher upon loss of response. **Results:** The efficacy of scheduled infliximab therapy was better than episodic treatment. Crohn's Disease Activity Index (CDAI) scores were consistently significantly better in the 10 mg/kg scheduled maintenance group from weeks 10 to 54, and response and remission rates (combined scheduled) were significantly higher from weeks 10 to 30. A greater proportion of patients achieved complete mucosal healing at week 54 ($P = 0.041$). A lower proportion developed antibodies to infliximab in the scheduled groups than in the episodic group (9% [5 mg/kg], 6% [10 mg/kg], 28% [episodic], respectively). Scheduled strategy patients

had fewer Crohn's disease-related hospitalizations ($P = 0.014$) and surgeries ($P = 0.01$) than episodic strategy patients. Conclusions: The scheduled infliximab groups, particularly the 10 mg/kg group, had better CDAI and Inflammatory Bowel Disease Questionnaire (IBDQ) responses than those in the episodic group. Both scheduled groups had fewer hospitalizations, higher rates of mucosal healing, and fewer developed antibodies than those in the episodic group, with no increase in side effects.

Baldassano R, Braegger CP, Escher JC, et al.

Infliximab (REMICADE) therapy in the treatment of pediatric Crohn's disease. *American Journal of Gastroenterology* 2003;98:833-8.

OBJECTIVE: The aim of this study was to assess the efficacy and safety of a single infusion of infliximab in the treatment of pediatric Crohn's disease (CD). **METHODS:** A total of 21 pediatric CD patients were enrolled at seven study centers and randomized to receive a single infusion of infliximab 1 mg/kg ($n = 6$), 5 mg/kg ($n = 7$), or 10 mg/kg ($n = 8$) over at least 2 hrs at week 0 in this multicenter, open-label, dose-blinded trial. Efficacy assessments, including the Pediatric Crohn's Disease Activity Index (PCDAI), modified CDAI, C-reactive protein concentration (CRP), and erythrocyte sedimentation rate (ESR) determinations, were made at screening and at weeks 1, 2, 4, 8, and 12. Adverse events were assessed throughout study participation. **RESULTS:** Improvements in the PCDAI, modified CDAI, ESR, and CRP were observed with all infliximab doses, beginning at week 1. On average, all treated patients experienced approximately 50% improvement in the PCDAI by week 2. By week 12, the PCDAI remained approximately 30% improved from baseline. During the study, all 21 patients (100%) achieved a clinical response, and 10 patients (48%) achieved clinical remission. There were no infusion reactions in any of the treatment arms. **CONCLUSIONS:** The results of this trial suggest that infliximab may be safe and effective as short-term therapy of medically refractory moderate to severe CD in a pediatric population.

Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002; 359(9317):1541-9.

BACKGROUND: We did a randomised controlled trial to assess the benefit of maintenance infliximab therapy in patients with active Crohn's disease who respond to a single infusion of infliximab. **METHODS:** 573 patients with a score of at least 220 on the Crohn's disease activity index (CDAI) received a 5 mg/kg intravenous infusion of infliximab at week 0. After assessment of response at week 2, patients were randomly assigned repeat infusions of placebo at weeks 2 and 6 and then every 8 weeks thereafter until week 46 (group I), repeat infusions of 5 mg/kg infliximab at the same timepoints (group II), or 5 mg/kg infliximab at weeks 2 and 6 followed by 10 mg/kg (group III). The prespecified co-primary endpoints were the proportion of patients who responded at week 2 and were in remission (CDAI <150) at week 30 and the time to loss of response up to week 54 in patients who responded. Analyses of the co-primary endpoints were by intention to treat. **FINDINGS:** 335 (58%) patients responded to a single infusion of infliximab within 2 weeks. At week 30, 23 of 110 (21%) group I patients were in remission, compared with 44 of 113 (39%) group II ($p=0.003$) and 50 of 112 (45%) group III ($p=0.0002$) patients. Thus, patients in groups II and III combined were more likely to sustain clinical remission than patients in group I (odds ratio 2.7, 95% CI 1.6-4.6). Throughout the 54-week trial, the median time to loss of response was 38 weeks (IQR 15 to >54) and more than 54 weeks (21 to >54) for groups II and III, respectively, compared with 19 weeks (10-45) for group I ($p=0.002$ and $p=0.0002$, respectively). Infliximab safety was consistent with that seen in other trials of infliximab in Crohn's disease and rheumatoid arthritis. In particular, the incidence of serious infections was similar across treatment groups. **INTERPRETATION:** Patients with Crohn's disease who respond to an initial dose of infliximab are more likely to be in remission at weeks 30 and 54, to discontinue corticosteroids, and to maintain their response for a longer period of time, if

infliximab treatment is maintained every 8 weeks.

Predictors of response

Maser EA, Vilella R, Silverberg MS, Greenberg GR. Association of Trough Serum Infliximab to Clinical Outcome After Scheduled Maintenance Treatment for Crohn's Disease. *Clinical Gastroenterology & Hepatology* 2006;4:1248-54.

Background & Aims: The effect of infliximab infused at scheduled intervals on antibody formation, preinfusion trough serum concentrations of infliximab, and their clinical significance was evaluated in patients with Crohn's disease. **Methods:** Antibodies to infliximab and trough serum infliximab were measured in 105 patients with Crohn's disease treated with 5 mg/kg infliximab for induction followed by maintenance episodic re-treatment (n = 23) or scheduled therapy at 6- to 8-week intervals (n = 82). **Results:** After a median of 14 infusions (range, 2-45), 21% of patients had detectable antibodies, 25% were antibody negative, and 54% were antibody inconclusive. Antibody formation was higher after episodic compared with scheduled treatment (39% vs 16%; P = .036) and was associated with a higher rate of infusion reactions (50% vs 21%; P = .018). Ninety patients continued maintenance scheduled therapy beyond 12 months including 12 converted episodic patients, with a median follow-up of 23 months (range, 16-68 months). The rate of clinical remission was higher for patients with a detectable trough serum infliximab compared with patients in whom serum infliximab was undetectable, including those without antibodies (82% vs 6%; P < .001). A detectable trough serum infliximab was also associated with a lower C-reactive protein (2.0 vs 11.8 mug/L; P < .001) and a higher rate of endoscopic improvement (88% vs 33%; P < .001). Concurrent immunomodulators did not alter outcomes. **Conclusions:** For Crohn's disease patients treated with scheduled maintenance infusions of infliximab, the trough serum concentration of infliximab predicts clinical outcome. Factors in addition to antibody formation, likely pharmacokinetic, modulate

serum infliximab and thus the response to infliximab therapy.

Dideberg V, Theatre E, Farnir F, et al. The TNF/ADAM 17 system: Implication of an ADAM 17 haplotype in the clinical response to infliximab in Crohn's disease. *Pharmacogenetics & Genomics* 2006;16:727-34.

Infliximab, a chimeric anti-tumour necrosis factor (TNF)- α antibody induces a clinical response in 70% of Crohn's disease patients and the response to infliximab therapy could be partially determined by genetic factors. The implication of both transmembrane and soluble forms of the TNF- α in the mechanism of action of infliximab has been demonstrated. The aim of our work was first to perform a complete study of TNF variants role in the response to infliximab in Crohn's disease. Secondly, considering the role of ADAM 17 in TNF- α shedding, the ADAM 17 locus was also studied. The response to infliximab was evaluated in 222 Caucasian Crohn's disease patients with a luminal (n=160) or fistulizing (n=62) form of the disease. Clinical and biological response evaluation was based on the Crohn's Disease Activity Index score and C-reactive protein level evolutions, respectively. The entire TNF gene was sequenced on the complete cohort. Twelve single nucleotide polymorphisms spanning the ADAM 17 locus were studied and haplotypes rebuilt. A clinical response was observed in 64% of the patients and biological response in 77.1% of patients. No association was found between the TNF gene and the response to infliximab. One haplotype in the ADAM 17 region was associated with a clinical response to infliximab in CD patients (adjusted P=0.045). In conclusion, our results exclude, with a reasonable power, an implication of the TNF gene in the response to infliximab in Crohn's disease, but reveal a potential role of the ADAM 17 gene in this response.

Orlando A, Colombo E, Kohn A, et al. Infliximab in the treatment of Crohn's disease: Predictors of response in an Italian multicentric open study. *Digestive & Liver Disease* 2005;37:577-83.

Background.: Almost 20% of patients with active Crohn's disease are refractory to

conventional therapy. Infliximab is a treatment of proven efficacy in this group of patients and it is not clear which variables predict a good response. Aims.: To evaluate the role of infliximab looking at the predictors of response in a large series of patients with Crohn's disease. Patients and methods.: Five hundred and seventy-three patients with luminal refractory Crohn's disease (Crohn's Disease Activity Index (CDAI) > 220-400) (312 patients) or with fistulising disease (190 patients) or both of them (71 patients) were treated with a dose of 5 mg/kg in 12 Italian referral centres. The primary endpoints of the study were clinical response and clinical remission for luminal refractory and fistulising disease. We evaluated at univariable and multivariable analysis the following variables: number of infusions, sex, age at diagnosis, smoking habit, site of disease, previous surgery, extraintestinal manifestations and concomitant therapies, and type of fistulas. Results.: Patients with luminal refractory disease: 322 patients (84.1%) had a clinical response and 228 (59.5%) reached clinical remission. Patients with fistulising disease: 187 patients (72%) had a reduction of 50% of the number of fistulas and in 107 (41%) a total closure of fistulas was observed. For luminal disease, single infusion (OR 0.49, 95% CI 0.28-0.86) and previous surgery (OR 0.53, 95% CI 0.30-0.93) predicted a worse response for fistulising disease. Other fistulas responded worse than perianal fistulas (OR 0.57, 95% CI 0.303-1.097). Conclusion.: In Crohn's disease infliximab is effective in luminal refractory and in fistulising disease. A single infusion and previous surgery predicted a worse response in luminal disease whereas perianal fistulas predicted a better response than other type of fistulas.

Arnott IDR, McNeill G, Satsangi J. An analysis of factors influencing short-term and sustained response to infliximab treatment for Crohn's disease. *Alimentary Pharmacology & Therapeutics* 2003; 17:1451-1457.

Background: 59-81% of patients given infliximab for Crohn's disease will respond. Although now in widespread use, little consensus exists regarding the optimal place in patient care. Recently developed

guidelines have identified need for markers that predict response. Aims: We aimed to identify markers of response to infliximab given for Crohn's disease. Methods: Markers of response (defined at 4 weeks) were prospectively assessed in 74 infliximab-treated patients with Crohn's disease. Patients were followed-up to 1 year. Results: Fifty-four of 74 (73%) patients responded. Univariate analysis identified that smokers were less likely to respond than non-smokers [P = 0.005, odds ratio (OR) 0.22]. Patients established on immunosuppression (P = 0.034, OR 7.31) and with isolated colonic disease (P = 0.042, OR 3.83) were more likely to respond. Multiple logistic regression confirmed smoking (P = 0.035, OR 0.24) and colonic disease (P = 0.035, OR 4.87) as independent markers of response. One-year relapse rates differed significantly between smokers and non-smokers (100% vs. 39.6%, P = 0.0026, relative risk 3.2) and between patients established on immunomodulators or not (58.0% vs. 92.8%, P = 0.0054, relative risk 2.6). Conclusions: Smoking has a strong adverse effect on the response rates and maintenance of response to infliximab. Patients on immunomodulators have a more favourable short- and long-term response. These results have important implications for clinical practice.

Vermeire S, Louis E, Carbonez A, et al. Demographic and clinical parameters influencing the short-term outcome of anti-tumor necrosis factor (infliximab) treatment in Crohn's disease. *American Journal of Gastroenterology* 2002; 97:2357-2363.

OBJECTIVE: Infliximab is an effective treatment for refractory or fistulizing Crohn's disease (CD). However, about 30% of patients do not respond to infliximab for unknown reasons. Identifying predictive factors of response is important for optimizing clinical management and for better understanding infliximab's mechanisms of action. The aim of this study was to assess whether demographic or clinical parameters influence short-term response to infliximab. METHODS: The first 240 CD patients of the Belgian Infliximab Expanded Access Program were studied for

response to infliximab treatment and assessed at 4 (refractory luminal CD) or 10 wk (fistulizing CD) after the first infusion. Detailed demographic and clinical information on age, sex, type of disease (fistulizing or refractory), Crohn's Disease Activity Index score, C-reactive protein (CRP), smoking habits, disease duration, localization of disease, concomitant medication, and previous surgery were obtained from all patients. Logistic regression and decision tree analysis were performed. RESULTS: There were 73.5% responders and 26.5% nonresponders to treatment. Stepwise logistic regression identified age (OR = 0.971, 95% CI = 0.947-0.995, $p = 0.018$), isolated ileitis (OR = 0.359, 95% CI = 0.177-0.728, $p = 0.004$), and previous surgery (OR = 0.429, 95% CI = 0.233-0.787, $p = 0.006$) as inversely correlated with response, whereas isolated colitis (OR = 1.905, 95% CI = 1.010-3.597, $p = 0.046$) and concomitant immunosuppressive treatment (OR = 2.670, 95% CI = 1.430-5.016, $p = 0.0022$) were positively correlated with response to infliximab. Surprisingly, smoking habits were not retained as predictors for response. Decision tree analysis provided a working algorithm based on age and immunosuppressive treatment that warrants further exploration. CONCLUSIONS: In this large cohort of infliximab-treated CD patients, young age, Crohn's colitis, and concomitant immunosuppressive treatment were identified as independent variables favoring short-term response to infliximab.

Parsi MA, Achkar JP, Richardson S, et al. Predictors of response to infliximab in patients with Crohn's disease. *Gastroenterology* 2002; 123:707-713.

Background & Aims: Identifying predictors of response to infliximab in Crohn's disease may lead to better selection of patients for this therapy. **Methods:** One hundred patients with either inflammatory or fistulous Crohn's disease and at least 3 months of follow-up after infliximab infusion were evaluated. Clinical response and duration of response were the primary outcome measures. **Results:** For inflammatory disease, 73% of nonsmokers, compared with 22% of smokers, responded to infliximab ($P < 0.001$). Among patients taking concurrent

immunosuppressives, 74% responded to infliximab compared with 39% not taking any immunosuppressives ($P = 0.007$). Prolonged response (duration >2 months) was achieved in 59% of nonsmokers compared with 6% of smokers ($P < 0.001$) and in 65% of patients on immunosuppressives compared with 18% not on immunosuppressives ($P < 0.001$). For fistulous disease, overall response rates were not different between nonsmokers and smokers, but nonsmokers had a longer duration of response ($P = 0.046$). Concurrent use of immunosuppressive medications had no effect on rate or duration of response. Multivariable logistic regression analysis confirmed the harmful effect of smoking and the beneficial effect of immunosuppressive use on response in patients with inflammatory disease. The same analysis for fistulous disease did not show an association between smoking or concurrent immunosuppressive use and response to infliximab. **Conclusions:** In patients with inflammatory disease, nonsmoking and concurrent immunosuppressive use are associated with higher rates of response and longer duration of response to infliximab. In patients with fistulous Crohn's disease, nonsmoking is associated with longer duration of response to infliximab.

Safety

Brassard P, Kezouh A, Suissa S.

Antirheumatic drugs and the risk of tuberculosis. *Clinical Infectious Diseases* 2006;43:717-22.

Background. We aimed to quantify the rate of *Mycobacterium tuberculosis* disease (TB) among a cohort of patients with rheumatoid arthritis (RA) and to assess whether the independent use of disease-modifying antirheumatic drugs (DMARDs) is associated with the risk of developing TB. **Methods.** The study was performed using the PharMetrics Patient-Centric database (PharMetrics). The cohort consisted of all subjects with ≥ 1 occurrence of a diagnosis of RA during an inpatient or outpatient visit during the period of September 1998 through December 2003. Conditional logistic regression was used in a nested case-control analysis to estimate the rate ratio

(RR) of TB with any use of biological or traditional DMARDs during the year before the index date. We also assessed the interaction between DMARDs and the current use of corticosteroids. Results. The cohort consisted of 112,300 patients with RA. A total of 386 cases of TB were identified, which resulted in an overall rate of 2.19 cases per 1000 person-years. The adjusted RR of TB for biological DMARD use is 1.5 (95% CI, 1.1-1.9). Use of traditional DMARDs was also independently associated with TB (RR, 1.2; 95% CI, 1.0-1.5). RRs of developing TB disease with the use of biological or traditional DMARD were lower among current users of corticosteroids than among noncurrent users of corticosteroids. Conclusion. We found that the use of biological and traditional DMARDs is associated with an increased risk of developing TB in patients with RA, mainly among noncurrent users of corticosteroids.

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* 2006; 54:2368-76.

Objective. To determine whether the rate of serious infection is higher in anti-tumor necrosis factor (anti-TNF)-treated rheumatoid arthritis (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 anti-TNF-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 anti-TNF-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 anti-TNF-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 anti-TNF-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 anti-TNF drugs. Nineteen serious bacterial intracellular infections occurred, exclusively in patients in the anti-TNF-treated cohort. Conclusion. In patients with active RA, anti-TNF 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.

Sands BE, Blank MA, Diamond RH, Barrett JP, Van Deventer SJ. Maintenance infliximab does not result in increased abscess development in fistulizing Crohn's disease: Results from the ACCENT II study. *Alimentary Pharmacology & Therapeutics* 2006; 23:1127-1136.

Background: Rapid fistula healing may predispose Crohn's disease patients to abscess development. Aim: Data from ACCENT II were analysed to determine whether fistula-related abscess development is affected by infliximab exposure. Methods: Following infliximab 5 mg/kg infusions at weeks 0, 2 and 6, patients were evaluated for fistula response for two consecutive visits at least 4 weeks apart. Patients (N = 282) were randomized at week 14 to either placebo or infliximab 5 mg/kg every 8 weeks through week 46. If response was lost at or after week 22, patients could crossover to a 5 mg/kg higher infliximab dose. Fistula-related abscesses were diagnosed by physical examination or by imaging procedures according to usual practice. Results: Infliximab exposure was approximately twofold higher for the infliximab maintenance group. Twenty-one (15%) patients in the infliximab maintenance group had at least one newly developed fistula-related abscess compared with 27 (19%) in the placebo maintenance group (P = 0.526). The proportion of patients with a new fistula-related abscess was similar regardless of whether or not patients

crossed over to a 5 mg/kg higher infliximab dose. The number of fistula-related abscesses diagnosed over time did not differ between groups. Conclusion: Abscess development in patients with fistulizing Crohn's disease is not dependent on cumulative infliximab exposure.

Melichar B, Bures J, Dedic K. Anorectal carcinoma after infliximab therapy in Crohn's disease: Report of a case. *Diseases of the Colon & Rectum* 2006;49:1228-33.

Infliximab, monoclonal antibody against tumor necrosis factor α , is an effective agent in the therapy of Crohn's disease. Although therapy with infliximab is generally well tolerated, there is an obvious concern about the effect of this treatment on the incidence of cancer. We report a case of mucinous anorectal adenocarcinoma observed in a 39-year-old patient with long-standing Crohn's disease after therapy with two courses of infliximab. The carcinoma was discovered fortuitously after abdominoperineal resection. Despite clear margins, the tumor recurred in a few months and progressed during combination chemotherapy. Although there is currently no definitive proof of a causal link between infliximab therapy and cancer, the present observation and other reports in the literature should lead to a careful evaluation of the possibility of increased cancer risk in patients treated with this new agent.

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* 2005;64:1421-6.

Background: Existing studies of solid cancers in rheumatoid arthritis (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 tumour necrosis factor (TNF) treatment by obtaining cancer data from cohorts treated in routine care rather than trials. Methods: A population based study of three RA cohorts (one

prevalent, admitted to hospital 1990-2003 (n = 53 067), one incident, diagnosed 1995-2003 (n = 3703), and one treated with TNF antagonists 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. TNF antagonist 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 TNF antagonists 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.

Dederichs F, Pinciu F, Gerhard H, et al. Listeria meningitis in a patient with Crohn's disease - A seldom, but clinically relevant adverse event of therapy with infliximab. *Zeitschrift fur Gastroenterologie* 2006;44:657-60.

A 42-year-old man with steroid-dependent Crohn's disease developed fever, vomiting and headache after the second administration of infliximab. Extensive microbiological and biochemical work-up revealed an atypical meningitis caused by *Listeria monocytogenes*. After antibiotic therapy of 21 days duration, the patient could be discharged from hospital totally recovered without any further complications. As previously demonstrated, TNF- α plays an important role in resistance to *Listeria monocytogenes*. *Listeria* infections have been reported in 26 patients receiving TNF- α inhibitors. An additional therapy with other immunosuppressants increases the risk for *Listeria* infections. *Listeria meningitis* is a seldom adverse event of therapy with TNF- α inhibitors but is associated with a high lethality. Therefore patients should be informed about the possible adverse event

of a *Listeria* infection during anti-TNF- α therapy before receiving immunosuppressive treatment. Furthermore, therapy with TNF- α inhibitors should only be executed within a close doctor-patient relationship and in cooperation with specialised centres.

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* 2005;64:1414-20).

Background: Patients with rheumatoid arthritis (RA) are at increased risk of malignant lymphomas, and maybe also of leukaemia and multiple myeloma. The effect of tumour necrosis factor (TNF) antagonists on lymphoma risk and characteristics is unclear. Objective: To assess expected rates and relative risks of haematopoietic malignancies, especially those associated with TNF antagonists, 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 TNF antagonist 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 TNF antagonists 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 TNF antagonists 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 TNF antagonists was no higher than in the other RA cohorts. Lymphomas associated with TNF antagonists 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 TNF antagonists did not have higher

lymphoma risks than other patients with RA. Prolonged observation is needed to determine the long term effects of TNF antagonists on lymphoma risk.

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* 2005;22:453-61.

Background: The potential clinical implications of autoimmunity during treatment with infliximab are unclear. Aim: To determine the frequency and correlation of autoantibody formation in patients with Crohn's disease treated with infliximab in a routine clinical setting. Methods: Sixty-three patients with refractory/inflammatory (31) and/or fistulising Crohn's disease (32), received an infliximab infusion at a dose 5 mg/kg in weeks 0, 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 five 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, nine 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 two 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 Crohn's disease receiving induction treatment with infliximab, but the clinical significance of this remains to be determined.

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
2005;72:330-4.

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 rheumatoid arthritis or ankylosing spondylitis with data collection on standardized 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 five (6%) patients (three women and two men), all of whom had acute or underlying risk factors. Higher values were found in these five 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. Our data also emphasize the need for a careful search for risk factors before each infliximab infusion.

Elkayam O, Burke M, Vardinon N, et al.
Autoantibodies profile of rheumatoid
arthritis patients during treatment
with infliximab. Autoimmunity
2005;38:155-60.

Purpose: Therapy with TNF α blocking agents has been associated with increased rate of anti-nuclear antibodies (ANA) and rare cases of lupus like syndromes. Our aim was to prospectively analyze a wide array of autoantibodies in rheumatoid arthritis (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 methotrexate. 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 cytoplasmic (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 our cohort, the appearance of some autoantibodies seemed to predict late cessation of treatment.

Vissers WHPM, De Jong EMGJ, Flendrie M, Creemers M. Infliximab (Remicade) induced skin reaction in a patient with rheumatoid arthritis. Nederlands Tijdschrift voor Dermatologie & Venereologie 2005;15:213-4.

An 87-year-old patient with rheumatoid arthritis (RA) was admitted to our inpatient department because of a severely itching

skin rash after starting treatment with the TNF α blocking agent infliximab. Skin rashes on TNF α blocking agents 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 TNF α blocking agents with RA patients in a control group. The frequency and nature of the skin disorders was recorded. Results from this study will be presented at the annual scientific meeting on the 10th of June 2005.

Jacobstein DA, Markowitz JE, Kirschner BS, et al. Premedication and infusion reactions with infliximab: Results from a pediatric inflammatory bowel disease consortium. *Inflammatory Bowel Diseases* 2005;11:442-6.

Background: Infusion reactions (IRs) are the most common adverse events associated with the use of infliximab for inflammatory bowel disease (IBD). Antipyretics, antihistamines, and corticosteroids have been used to prevent the development of IRs, but their efficacy is not known. We studied the proportion of pediatric patients receiving infliximab for IBD that developed IRs and the potential effects of premedication on IR. Methods: Uniformly collected data from a cohort of pediatric patients with IBD enrolled between January 2000 and May 2003 at 6 pediatric centers were analyzed. Data were retrospectively reviewed and analyzed. Results: A total of 1652 infusions given to 243 patients in 6 centers was analyzed. 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 pediatric 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.

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

Background: Several placebo controlled studies have demonstrated the efficacy of infliximab in inflammatory bowel disease (IBD) but the potential toxicity of this new biological compound has been less studied. 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 Crohn's disease (CD), and infliximab was used off label for ulcerative colitis (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 two 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 two were fatal), opportunistic infections occurred in two patients (one with UC, fatal), and two 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.

Colombel JF, 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* 2004; 126:19-31.

Background & Aims: The aim of this study was to evaluate the short- and long-term safety of infliximab in patients with Crohn's disease in clinical practice. **Methods:** 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.

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* 2004;70:3-9.

Background: Infliximab, a chimeric anti-tumour necrosis factor monoclonal antibody with potent anti-inflammatory effects, represents an effective treatment option in patients with severe inflammatory bowel disease (IBD). Serious side-effects of such an immunomodulating therapy are speculated and therefore we reviewed our 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 Crohn's disease (n = 92), ulcerative colitis (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 tuberculosis 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.

Godinho F, Godfrin B, El Mahou S, et al.
Safety of leflunomide plus infliximab combination therapy in rheumatoid arthritis. *Clinical & Experimental Rheumatology* 2004;22:328-30.

Objective. To analyse the safety of leflunomide plus infliximab combination therapy, in adult rheumatoid arthritis (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 continued 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.

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 2004;19:749-54.

Background: By temporarily suppressing the immune response, the anti-tumour necrosis factor agent, infliximab, may increase the risk of peri-operative complications. Aim: To test this hypothesis for intestinal resection in a cohort of 313 Crohn's disease 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.

Hommes DW, Parlevliet W, Sterringa GJ, et al. Infliximab therapy in patients with Crohn's disease; experience with 132 patients. *Nederlands Tijdschrift voor Geneeskunde* 2002;146:1187-91.

Objective. The aim of this study was to report the experience with infliximab treatment for a large cohort of Crohn's disease (CD) patients in the Netherlands. Design. Descriptive. Method. All 134 CD patients receiving infliximab infusions in the Amsterdam Medical Centre, the Netherlands, after the drug's registration in the Netherlands in 1999 were followed prospectively (study period: 1 November 1999-31 January 2002). Reliable follow-up data were absent in two 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 134 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 Crohn's disease and 89% in fistulous disease. Adverse effects were recorded in 17% (n = 22) of the patients, including three with serious allergic reactions. No tuberculosis 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 Crohn's disease.

Kamm MA. Safety issues relating to biological therapies, with special reference to infliximab therapy. *Research & Clinical Forums* 2002;24:79-86.

The only licensed biological therapy for inflammatory bowel disease is infliximab, a potent antitumour necrosis factor (TNF)- α antibody. This drug is highly effective in treating acute intestinal disease, fistulating disease (especially anorectal), and in maintaining remission in the short-to-medium term. Given the experience of use of infliximab for approximately 2 years in over 100,000 patients, it is now timely to review the medium-term benefits, and side effects, of treatment. 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 diminution 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 tuberculosis has been estimated as approximately 3 per 10,000, and has led to some deaths. Crohn's disease (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. Anti-TNF- α therapy is 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.

Maksymowych WP, Jhangri GS, Lambert RG, et al. Infliximab in ankylosing spondylitis: A prospective observational inception cohort analysis of efficacy and safety. *Journal of Rheumatology* 2002;29:959-65.

Objective. Infliximab, a neutralizing antibody to tumor necrosis factor- α , appears to be effective therapy in ankylosing spondylitis (AS), although treatment is costly and serious infections are an increasing concern. We investigated the efficacy and tolerability of infliximab in a prospective observational inception cohort of patients with nonsteroidal antiinflammatory drug-refractory AS seen in both university and community based practice. We also used a lower dose, 3 mg/kg, than has been evaluated to date in AS. Methods. We included all consecutive patients with AS starting infliximab therapy 3 mg/kg IV at 0, 2, and 6 weeks and q 2 months between April 2000 and October 2001. Data were systematically collected at baseline, 14 weeks, and 1 year, or at withdrawal, and included demographic characteristics, Bath AS indexes (BASDAI, BASFI, BASGI, BASMI), adverse events, and reasons for withdrawal. Laboratory measures included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum matrix metalloproteinases (MMP) 1 and 3, and serum human cartilage glycoprotein-39 (YLK-40). The first 6 consecutive patients were also studied by several magnetic resonance sequences, including dynamic MRI with gadolinium augmentation of affected joints. Maximal rate of augmentation was determined at baseline and 84 days. Analysis was by intention-to-treat. Results. Twenty-one patients (m:f = 17:4), mean age 42.5 years (range 24-66), mean disease duration 13.8 years (range 3-26), were studied: 13 had active peripheral synovitis at baseline. Mean followup was 47.5 weeks (range 10-77).

Four patients withdrew, 2 for serious adverse events (septic osteomyelitis and severe hypersensitivity after 3 and 2 infusions, respectively), one for lack of efficacy, and one lost to followup. Three patients required an increased dose to 5 mg/kg after 14 weeks. Efficacy data were available on 17 patients at 14 weeks; mean BASDAI improved significantly from baseline (6.2) to 14 weeks (2.8) ($p < 0.001$), with 10 patients (58.8%) showing at least 50% improvement (range 0-99.6%). Significant reduction in mean BASFI (43.4%; $p < 0.001$), BASGI (44%; $p = 0.001$), ESR (55%; $p < 0.001$), and CRP (63.5%; $p = 0.01$) was evident. Complete remission of peripheral joint disease was seen in 5 of 11 (45.4%) patients evaluated at 14 weeks and maximal rate of MRI defined gadolinium augmentation was significantly decreased ($p = 0.04$). Reductions in serum YKL-40 and MMP-1 and 3 were nonsignificant, but significant correlations were observed between changes in BASDAI, ESR, CRP, and changes in serum levels of MMP-3 and YKL-40 ($p < 0.005$ to $p < 0.05$). Followup data on 8 patients completing 1 year of therapy revealed continued efficacy at a dose of 3 mg/kg every 8 weeks. Conclusion. Infliximab appears to be effective and well tolerated for both axial and peripheral joint disease in AS even at lower doses than those examined to date. Suppression of markers of cartilage degradation/turnover commensurate with reductions in clinical and laboratory measures of disease activity suggests that these markers should be further validated as surrogates for structural damage in AS. Controlled trials are warranted to further assess the potential of this agent in ameliorating structural damage.

Health economics, resources, risk/benefit

Siegel CA, Hur C, Korzenik JR, Gazelle GS, Sands BE. Risks and Benefits of Infliximab for the Treatment of Crohn's Disease. *Clinical Gastroenterology & Hepatology* 2006; 4:1017-1024.

Background & Aims: Infliximab is effective for the treatment of active Crohn's disease. However, rare but serious complications related to infliximab therapy including

lymphoma, sepsis, and death have been reported. The purpose of this study was to analyze the risks and benefits of infliximab for the treatment of Crohn's disease with the goal of providing data to aid both physicians and patients in the process of making a decision about treatment. Methods: A decision analytic model was constructed to determine the risks and benefits of infliximab when compared with standard therapy. The analysis simulated 2 cohorts of 100,000 patients each, with one arm receiving infliximab while the other remained on standard therapy. Results: Model results showed that in 100,000 patients at 1 year, infliximab will lead to 12,216 more patients in remission, 4255 fewer surgeries, and 33 fewer deaths from flares of disease. This is at the cost of 201 more lymphomas and 249 more deaths related to complications from infliximab. Overall, the infliximab strategy resulted in more quality-adjusted life years (QALYs/patient) than the standard therapy strategy (.77 QALYs/patient vs .75 QALYs/patient). Conclusions: Despite an increased risk of lymphoma and death associated with use of infliximab, the substantial clinical improvement and fewer surgeries as a result of infliximab result in an increase in QALYs. In properly selected patients, the benefits of infliximab could outweigh its risks. These data should help guide decision making and the informed consent process when considering the use of infliximab for the treatment of Crohn's disease.

Jewell DP, Satsangi J, Lobo A, et al. Infliximab use in Crohn's disease: Impact on health care resources in the UK. *European Journal of Gastroenterology & Hepatology* 2005; 17:1047-1052.

Objective: To quantify the impact of infliximab therapy on health care resource utilization in the UK. Methods: A retrospective audit was undertaken at seven centres in the UK, which reviewed patient notes for a period of 6 months before and 6 months after an initial infliximab infusion. Details of hospital admissions, out-patient visits, operations, diagnostic procedures, drug usage, and overall efficacy were collected. Results were compared for the two 6 month study periods. Results: A total of 205 patients (62% female, median age 33

years) with moderate/severe Crohn's disease were audited. The majority of patients had chronic active disease (62%) and most received one infusion initially (72%). Clinicians rated 74% of responses as good to excellent and patients 72%. Most patients had concomitant immunosuppression (pre: 75%, post: 75%). Approximately half of the patients (45%) stopped taking steroids, with a further 34% having a dosage reduction. A fall of 1093 inpatient days was seen (1435 vs. 342) in the 6 months following infliximab administration. There were seven fewer operations, 33 fewer examinations under anaesthetic, and 99 fewer diagnostic procedures. Outpatient visits were similar pre- versus post- (555 vs. 534). The total reduction in direct costs amounted to an estimated 591 006. Three hundred and fifty-three infliximab infusions were administered at an estimated cost of 562719. Thus, there was a net reduction of 28287 or 13798 per patient. Conclusions: Infliximab appears to be a potentially cost effective treatment for selected patients based on the reduced number of inpatient stays, examinations under anaesthetic, and diagnostic procedures over a 6 month period.

Lichtenstein GR, Yan S, Bala M, Blank M, Sands BE. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn's disease. *Gastroenterology* 2005; 128:862-869.

Background & Aims: Infliximab is effective in closing fistulas in patients with Crohn's disease. We examined the effect of infliximab maintenance treatment on hospitalizations, surgeries, and procedures in patients with fistulizing Crohn's disease enrolled in the ACCENT II study. Methods: After 5 mg/kg infliximab at weeks 0, 2, and 6, a total of 282 patients were separately randomized at week 14 as responders (at least a 50% reduction from baseline in the number of draining fistulas at both weeks 10 and 14) or nonresponders to receive placebo or 5 mg/kg infliximab maintenance every 8 weeks. At week 22 and later, patients who lost response could be treated with a maintenance dose 5 mg/kg higher. Data on Crohn's disease-related hospitalizations, surgeries, and procedures

were compared between the treatment groups for responders and all randomized patients. Results: A total of 282 patients were randomized at week 14, of whom 195 were randomized as responders. Among patients randomized as responders, those who received infliximab maintenance had significantly fewer mean hospitalization days (0.5 vs. 2.5 days; $P < .05$), mean numbers (per 100 patients) of hospitalizations (11 vs. 31; $P < .05$), all surgeries and procedures (65 vs. 126; $P < .05$), inpatient surgeries and procedures (7 vs. 41; $P < .01$), and major surgeries (2 vs. 11; $P < .05$), compared with those who received placebo maintenance. Conclusions: In patients with fistulizing Crohn's disease, infliximab 5 mg/kg every 8 weeks significantly reduced hospitalizations, surgeries, and procedures compared with placebo.

Orlando A, Colombo E, Kohn A, et al. Infliximab in the treatment of steroid resistant/dependant and fistulating Crohn's disease: An analysis of predictors of response in a italian multicentric open study in 573 patients. *European Review for Medical & Pharmacological Sciences* 2004; 8

Background: The treatment of moderate-severe Crohn's disease is difficult and approximately 20% of patients do not respond to conventional therapy, including corticosteroids and immunosuppressive drugs. Infliximab is a treatment of proven efficacy in this group of patients. It is not clear which variables predict a good response. Aims: To evaluate in a large series of patients (pts) with acute steroid resistant Crohn's Disease or fistulating disease the role of Infliximab looking at the predictors of response. Patients and Methods: 573 pts (265 men, 308 women) with steroid dependent/resistant moderate severe Crohn's disease (CDAI > 220-400) (312 pts) or with fistulating disease (190 pts) or both of them (71 pts) (perianal 72%, enterocutaneous 11%, others 17%) in 12 Italian referral centers were treated with a dose of 5 mg per kg of body weight. In dependant/resistant steroid disease one single or 3 infusions were given whereas in fistulating disease 3 infusions (at 0,2,6 weeks) were given. Primary endpoints were: (a) clinical response, defined as a reduction

of 70 or more points in the score on the Crohn's disease activity index at 12 weeks after first infusion and clinical remission, defined as CDAI < 150 in pts with steroid/dependant patients; (b) reduction of at least 50% of the number of fistulas or complete closure of fistulas in pts with fistulating disease. The following variables were evaluated in a univariable analysis: sex, age at diagnosis, smoking habit, site of disease, previous surgery, extraintestinal manifestations and concomitant therapies, type of fistulas. Side effects were evaluated. Results: (a) steroid dependant/resistant disease: 94 pts (24,5%) had a clinical response and 228 pts (59,5%) reached clinical remission. (b) fistulating disease: 80 pts (30,6%) had a reduction of 50% of the number of fistulas and in 107 pts (41%) a total closure of fistulas was observed. For luminal disease previous surgery predicted a worse response (OR 0.54, CI 0.296-0.975); for fistulating disease other fistulas responded less than perianal fistulas (0.57, CI 0.303-1,097). No serious side effects were observed. Conclusion: Infliximab is effective in steroid dependant/resistant patients and in fistulating disease. Previous surgery and other fistulas predicted a worse response in luminal and fistulating disease respectively.

Jaisson-Flot I, Flourie B, Descos L, Colin C. Management for severe Crohn's disease: A lifetime cost-utility analysis. *International Journal of Technology Assessment in Health Care* 2004; 20:274-279.

Objectives: Infliximab is a costly therapy for active Crohn's disease resistant to corticosteroids and immunosuppressive medication. The purpose of this study was to examine whether a treatment including infliximab (episodic re-infusions for relapse or maintenance therapy every 8 weeks) was relevant compared with conventional management (surgery and medical treatment without infliximab) for nonfistulizing resistant Crohn's disease. Methods: We performed a life-time cost-utility analysis with an analytic Markov decision model from the perspective of the third-party payer system. Utility measurement using Standard Gamble was used to adjust the survival time for each health state of the disease. Direct costs

were estimated from standard management based on expert opinion. A sensitivity analysis was conducted to gauge the effects of uncertainty in the values assigned to variables. Results: The incremental effectiveness with infliximab therapy is .761 Quality-Adjusted Life Years (QALYs) for an added cost ranging from 48,478.79 euros to 596,990.35 euros, depending on treatment procedure. The incremental cost utility ratio expressed in euros per QALYs saved varied from 63,700.82 euros (episodic re-infusions) to over 762,245.09 euros (maintenance therapy). Conclusions: Infliximab therapy could be cost-effective in the case of relapse treatment only, whereas the marginal cost-utility ratio exceeds conventional benchmarks for maintenance therapy. This analysis will be supplemented by conducting further randomized controlled trials and prospective observational study, focused on the costs of illness (direct and indirect), patient preferences, the disease's clinical course, and infliximab safety.

Lichtenstein GR, Yan S, Bala M, Hanauer S. Remission in patients with Crohn's disease is associated with improvement in employment and quality of life and a decrease in hospitalizations and surgeries. *American Journal of Gastroenterology* 2004; 99:91-96.

OBJECTIVES: Hospitalization, surgery, work loss, and impaired quality of life contribute to the cost and burden of care for patients with Crohn's disease. We examined the impact of remission on patients' employment, quality of life, and hospitalization and surgery in a clinical trial to validate clinical remission, as defined by the Crohn's disease activity index (CDAI), as the key treatment goal in managing Crohn's disease. METHODS: ACCENT I evaluated the efficacy and safety of long-term dosing of infliximab compared to a single dose of infliximab in 573 patients with moderately-to-severely active Crohn's disease. At wk 54, employment status was compared between patients in CDAI remission and those not in CDAI remission, for those not employed at baseline. Physical component summary (PCS) and mental component summary (MCS) scores of the SF-36 questionnaire were also compared between these two groups. The numbers of Crohn's-related

hospitalizations and surgeries were compared among four groups of patients who spent 0-25%, 25-50%, 50-75%, and 75-100% of time, respectively, in CDAI remission during the study. RESULTS: At baseline, patients had a severely impaired quality of life and a high unemployment rate (38.4%). Among the group of patients who were unemployed at baseline, 31% of those patients who achieved CDAI remission (CDAI < 150) at wk 54 were employed, compared to 16% who were not in CDAI remission at wk 54 ($p < 0.05$). PCS and MCS scores of patients in CDAI remission at wk 54 were significantly higher ($p < 0.0001$), indicating better mental and physical functioning, than those of patients not in CDAI remission at wk 54, and were similar to those of the general U.S. population. Hospitalization and surgery rates decreased as the percentage of time patients were in CDAI remission increased ($p < 0.01$, and $p < 0.05$, respectively). CONCLUSIONS: CDAI remission is associated with reduced hospitalizations and surgeries, increased employment, and normalized quality of life. Sustained CDAI remission should be the key therapeutic goal in managing Crohn's disease.

Feagan BG, Yan S, Bala M, Bao W, Lichtenstein GR. The Effects of Infliximab Maintenance Therapy on Health-Related Quality of Life. *American Journal of Gastroenterology* 2003; 98:2232-2238.

OBJECTIVES: The ACCENT I study evaluated the long term effects of infliximab as maintenance therapy for patients with Crohn's disease. Health-related quality of life (HRQL) was also assessed in the trial. METHODS: In ACCENT I, a total of 573 patients received a single infusion of 5 mg/kg infliximab at baseline. After assessment of response at wk 2, patients were randomly assigned repeat infusions of placebo at wk 2 and 6 and then every 8 wk thereafter until wk 46 (single dose), repeat infusions of 5 mg/kg of infliximab at the same time points (5 mg/kg maintenance), or 5 mg/kg of infliximab at wk 2 and 6 followed by 10 mg/kg (10 mg/kg maintenance). HRQL analyses presented include the 335 patients classified as wk-2 responders. The treatment regimens were compared with

regard to their change from baseline in the IBDQ and Short Form-36 (SF-36) scores. RESULTS: Baseline scores indicated substantial impairment in HRQL. Throughout the study, all IBDQ and SF-36 scores were improved at all time points compared to baseline. After wk 10 and through wk 54, these improvements were greater in the two infliximab maintenance groups than in the single-dose group. The mean change from baseline to wk 54 in total IBDQ was greater in the 5-mg/kg maintenance group (22.1, $p < 0.05$) and 10-mg/kg maintenance group (30.2, $p < 0.001$) than in the single-dose group (8.9). Similarly, the mean change from baseline to wk 54 in the PCS of the SF-36 was greater in the 5-mg/kg maintenance group (6.1, $p < 0.05$) and 10-mg/kg maintenance group (7.2, $p < 0.01$) than in the single-dose group (2.5).

CONCLUSIONS: Infliximab therapy provides substantially improved HRQL as measured by both the disease-specific IBDQ and the generic SF-36. A maintenance regimen of either 5 mg/kg or 10 mg/kg of infliximab is more effective than a single 5-mg/kg infliximab infusion in sustaining this benefit.

Smits S, Heijman JA, Rutten W, Van Dullemen HM, Brouwers J, Postma MJ. Hospital admission increases costs. Costs induced by infliximab for Crohn disease. [Dutch]. *Pharmaceutisch Weekblad* 2003; 138:1200-1205.

This paper presents a cost analysis of the utilisation of infliximab for the treatment of Crohn's disease. The indication for infliximab for Dutch Crohn patients is an active disease with insufficient improvement on adequate therapy with corticosteroids and/or immunosuppressive therapy. We compared direct health-care costs (hospital and community pharmacy) before and after first infliximab treatment for 21 Crohn patients in the University Hospital Groningen who started infliximab during 1 January 2000 to 15 March 2001. Our study design was observational and patients served as their own controls with similar periods before and after infliximab per patient considered (minimally 3 months before and 3 months after infliximab). Drug costs for infliximab (including administration) were estimated at Euro sign 5800,- per patient-year. Excluding infliximab costs, costs per patient-year were

Euro sign 6400,- and Euro sign 8600,-before and after first infliximab treatment, respectively. In both periods, the majority of the other costs was related to hospitalization. Also, drug costs in the community pharmacy were estimated to contribute relevant shares. Other researchers have found decreases in medical costs after the start of infliximab treatment. We found the opposite development. More experience and routine with infliximab treatment may lower costs in the future.

Rubenstein JH, Chong RY, Cohen RD.

Infliximab decreases resource use among patients with Crohn's disease. *Journal of Clinical Gastroenterology* 2002; 35:151-156.

Goals: Surgery accounts for one half, and hospitalizations for one third, of overall costs for patients with Crohn's disease (CD). Infliximab induces remission and heals fistulas in CD but is more costly than traditional therapies. Its impact upon resource use in CD is unknown. Study: The medical records were reviewed for all CD patients managed at our institution for at least 1 full year both before and after initial infliximab infusion. The incidences of hospitalizations, hospitalized days, surgeries, endoscopies, radiologic examinations, outpatient and emergency room (ER) visits were studied (weighted according to time period). Results: There were 79 patients (59% female, mean age 38.6 years). A decrease was seen in the annual incidence of all surgeries (38%, $p < 0.01$), gastrointestinal (GI) surgeries (18%, $p < 0.05$), endoscopies (43%, $p < 0.01$), ER visits (66%, $p < 0.05$), all outpatient visits (16%, $p < 0.05$), outpatient GI visits (20%, $p < 0.01$), all radiologic examinations (12%, $p < 0.01$), and non-plain films (13%, $p < 0.01$). Fistula patients ($n = 37$) had decreases in hospitalizations (59%, $p < 0.05$); GI surgeries (59%, $p < 0.01$); all surgeries (66%, $p < 0.01$); all, GI, and surgical outpatient visits (27%, 26%, and 70%, respectively, $p < 0.05$ for all); ER visits (64%, $p < 0.05$); all radiologic examinations (40%, $p < 0.05$); and non-plain films (61%, $p < 0.05$). Patients with luminal disease ($n = 42$) had decreases in endoscopies (52%, $p < 0.05$), and ER visits (69%, $p < 0.05$). Patients of both genders and all ages

experienced decreases in resource use. Conclusion: Patients with CD decreased their use of some services, with a decreased number of hospitalizations and a decrease in the use of surgical services seen primarily in the patients infused for fistulas. This decrease in use of healthcare resources raises the potential of overall cost savings in CD patients receiving this drug.

Lichtenstein GR, Bala M, Han C, DeWoody K, Schaibe T. Infliximab improves quality of life in patients with Crohn's disease. *Inflammatory Bowel Diseases* 2002; 8:237-243.

Objective: The aim of this study was to assess the effect of infliximab on quality of life in patients with active Crohn's disease (CD) inadequately responsive to concomitant therapies. Methods: We examined responses to the Inflammatory Bowel Disease Questionnaire (IBDQ) from patients enrolled in a previously reported, randomized, placebo-controlled study. Patients with active CD received a single intravenous infusion of either placebo or infliximab 5, 10, or 20 mg/kg. Most patients received stable doses of mesalamine, corticosteroids, azathioprine, or 6-mercaptopurine throughout the study. Changes from baseline in overall IBDQ score and individual dimensions at 4 weeks postinfusion were compared. Results: Patients treated with infliximab had a significantly larger improvement in overall IBDQ score than those treated with placebo at 4 weeks ($p < 0.001$). Infliximab-treated patients also had larger improvements in all IBDQ dimensions: bowel ($p = 0.007$), social ($p = 0.002$), emotional ($p < 0.001$), and systemic ($p < 0.001$). A significantly larger proportion of infliximab-treated patients reported having normal or near-normal frequency of bowel movements in the past week ($p < 0.001$), full or a lot of energy ($p = 0.019$), and no or hardly any difficulty doing leisure or sports activities ($p = 0.011$), and being extremely or very satisfied with their personal life ($p = 0.046$). They also significantly differed in responses regarding fatigue, frustration, ability to work, general well-being, depression, anxiety, and anger resulting from bowel problems. Conclusions: These results indicate that infliximab significantly improved quality of life in patients with active CD, increasing their

ability to work and participate in leisure activities, and decreasing feelings of fatigue, depression, and anger.

Bokemeyer B. Infliximab in an outpatient gastroenterological practice: Tolerance, prognostic parameters and cost-effectiveness. [German]. *Verdauungskrankheiten* 2002; 20:107-113.

Infliximab is effective to control refractory Crohn's disease in many patients, thus greatly improving quality of life. Because of the possibility of an outpatient treatment with Infliximab in a private practice of a gastroenterologist we have to consider the relatively high costs of this therapeutic option in regard of cost effectiveness and prognostic parameters. We report about our experience with 38 Infliximab infusions in refractory Crohn's Disease between 10/1999 and 03/2001. We had no acute infusions-reaction and delayed hypersensitivity was rare. A beneficial prognostic parameter for an therapeutic effect of Infliximab seems to be an elevated CRP-level before the Infliximab therapy. These patients with an elevated CRP-level before Infliximab had a statistically significant higher CDAI decrease after Infliximab. The medication costs of a M.C.-patient/quarter were calculated to an average amount of DM 1238,-, the medication costs/quarter of a colitis ulcerosa patient were calculated to an amount of DM 742,-. Infliximab seems to be cost-effective in an outpatient gastroenterological practice by compensatory savings of other medication costs. In regard of some requirements the Infliximab therapy is practicable in an outpatient gastroenterological practice.

Van Balkom BPJ, Schoon EJ, Stockbrugger RW, et al. Effects of anti-tumour necrosis factor- α therapy on the quality of life in Crohn's disease. *Alimentary Pharmacology & Therapeutics* 2002; 16:1101-1107.

Background: Infusion of anti-tumour necrosis factor- α appears to be highly effective in patients with Crohn's disease. Aim: To assess the effect of infliximab on the quality of life in patients with active or fistulizing disease, as measured by the inflammatory bowel disease questionnaire, and to examine the impact on its four

dimensions. Methods: An observational study was conducted in 65 patients. An infusion of 5 mg/kg infliximab was given at week 0 in patients with active disease and at week 0, 2 and 6 in fistulizing disease. Changes from baseline in the total and dimensional inflammatory bowel disease questionnaire scores were calculated and compared between the patient groups. Potential predictors of change in the quality of life were identified. Results: In the active disease group, at week 4, the mean total and dimensional inflammatory bowel disease questionnaire scores improved compared to baseline ($P < 0.001$). In the fistulizing group, at week 6, all scores changed from baseline ($P < 0.05$). Improvement in the total inflammatory bowel disease questionnaire score correlated well with the improvement of the Crohn's disease activity index. Systemic and social scores improved more than bowel and emotional scores. Inflammatory Crohn's disease and a young age at diagnosis were predictors for a better response to infliximab therapy. Conclusions: Infliximab therapy improves all dimensions of the quality of life in patients with Crohn's disease.

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