# TNFa-inhibitors in inflammatory bowel diseasea

This is an excerpt from the full technical report, which is written in Norwegian.

The excerpt provides the report's main messages in English.

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Norwegian Knowledge Centre for the Health Services summarizes and disseminates evidence concerning the effect of treatments, methods, and interventions in health services, in addition to monitoring health service quality. Our goal is to support good decision making in order to provide patients in Norway with the best possible care. The Centre is organized under The Norwegian Directorate for Health, but is scientifically and professionally independent. The Centre has no authority to develop health policy or responsibility to implement policies.

We would like to thank all contributers for their expertise in this project. Norwegian Knowledge Centre for the Health Services assumes final responsibility for the content of this report.

Norwegian Knowledge Centre for the Health Services
Oslo, December 2008

# Key messages

**TNFα-inhibitors in inflammatory bowel disease**

**Background**: Patients with the inflammatory bowel diseases ulcerative colitis and Crohn's disease need lifelong treatment and care. Effect of traditional treatments is varied and may cause serious adverse events. Biological drugs aimed at blocking specific molecular steps in the inflammatory process have been developed. Tumor necrosis factor (TNF)α is a proinflammatory cytokine with a role in the inflammatory process associated with inflammatory bowel disease. Hence, a drug blocking this cytokine might be useful for patients with ulcerative colitis and Crohn's disease. This report includes knowledge of the TNFα-inhibitors infliximab (Remicade®), adalimumab (Humira®), etanercept (Enbrel®) and certolizumab pegol (Cimzia®).

**Method**: We systematically reviewed and critically appraised available documentation on effect and safety of TNFα-inhibitors. In addition, we have reviewed health economic studies. We identified documentation by a systematic search in Cochrane Library, Medline, Embase, PubMed and NHS Economics Evaluation Database. Our evaluation on efficacy and safety was based on systematic reviews. However, to make sure that all available data was included, we searched for randomized controlled trials published afer the literature seach in the systematic reviews was performed.,

**Results**: In patients with ulcerative colitis, infliximab was more effective than placebo in achieving improvement of the disease. Data on response and remission are available up to 54 weeks. Infliximab gives a higer proportion of patients with endoscopic remission compared to placebo. None of the other TNFα-inhibitors were tested in patients with ulcerative colitis.

In patients with Crohn's disease, infliximab, adalimumab and certolizumab were more effective than placebo in achieving response after induction treatment (1-3 administrations of drug or placebo). Based on patients responding to induction treatment, it has been shown that maintenance treatment with infliximab, adalimumab and certolizumab is more effective than placebo in maintaining the initial response. Infliximab have been showed to be more effective than placebo in achieving fistula closure. Data on etanercept in treatment of Crohn's disease is limited. There is no basis to claim that etanercept has effect in treatment of Crohn's disease.

We identified four economic evalutations in a systematic literature search. All studies were from contries outside Norway and delt with infliximabtreatment of patients with Crohn's disease.

**Conclusion**: Infliximab is effective in treatment of ulcerative colitis and Crohn's disease. Adalimumab and certolizumab have documented effect in treatment of Crohn's disease, while studies on patients with ulcerative colitis are lacking. There is too limited data available to conclude regarding safety of long-term treatment with TNFα-inhibitors for both ulcerative colitis and Crohn's disease.

Based on results from countries outside Norway, infliximab does not seem to be cost-effective as continuous treatment for patients with Crohn's disease. There might be an exception in the case of patients exhibiting good and long-lasting response. No relevant economic studies were found for ulcerative colitis or for the other TNFα-inhibitors.

# Executive summary

**TNFα-inhibitors in inflammatory bowel disease**

## BACKGROUND

The inflammatory bowel diseases, ulcerative colitis and Crohn's disease, need long-term treatment and care. The burden of these illnesses and the economic expenses are considerable.

The hallmark of ulcerative colitis is episodes of inflammation of the mucous membrane in the colon. In most cases the rectum is affected, while the degree of inflammation in the rest of the colon varies. In Crohn's disease the inflammation passes through all layers of the intestine wall. Any part of the intestine system may be affected, but in most cases the last part of the small intestine and adjacent part of the colon is affected. As the inflammation passes through the intestine wall, fissures and fistulae may occur. Fistulae are abnormal passageways between different segments of the intestine, between the intestine and other organs or from the intestine to the skin.

The cause of ulcerative colitis and Crohn's disease in not known, but inflammation of the intestine mucousa is sentral in the patogenesis.

Medical treatement of ulcerative colitis and Crohn's disease has traditionally included sulfasalazin, 5-aminosalicylates, corticosteroids and immunosuppressive drugs like azathioprine, 6- mercaptopurine or methotrexate. Some patients do not get the desired effect of these drugs, while other experience serious adverse events. Hence, new treatments alternatives have are longed-for.

Biological treatments aimed at blocking specific molecular steps in the inflammatory process have been developed. Tumour necrosis factor (TNF)α is a proinflammatory cytokine with a role in the inflammatory process associated with inflammatory bowel disease. Hence a drug blocking this cytokine might be useful for patients with ulcerative colitis and Crohn's disease. This report includes information of the TNFα-inhibitors infliximab (Remicade®), adalimumab (Humira®), etanercept (Enbrel®) and certolizumab pegol (Cimzia®). The first three are available in Norway, but etanercept is not approved for treatment of inflammatory bowel disease. Certolizumab is not approved for any indication.

## AIM

The aim of this report was to systematically collect, critically appraise and sum up data regarding the use of TNFα-inhibitors in treatment of inflammatory bowel disease. Effect and safetydata will form part of the basis for Norwegain guidelines for the use of TNFα-inhibitors. In addition, we examined anlysis of cost- benefit regarding the use of TNFα-inhibitors in inflammatory bowel disease.

## METHOD

Employees at the Norwegian Knowledge Centre for the health services and selected gastroenterologists undertook this report.

The literature was identified by a systematic search in Cochrane Library, Medline, Embase, PubMed and NHS Economic Evaluations Database in December 2006 and February 2007. To make sure that we did not miss any

relevant publications, the drug companies holding marketing authorizations for the TNFα-inhibitors in Norway were asked to supplement with further relevant publications according to the specified inclusion criteria. The specialists were also encouraged to supplement relevant publications.

We included systematic reviews and randomized controlled trials published after the searches in the systematic reviews. Use of systematic reviews stop us from doing work already performed by others, while supplementing with new randomized controlled trials make sure that also the most recent knowledge is included.

## RESULTS

For evaluation of efficacy and safety, a total of 15 publications are included in this report, 5 systematic reviews and 8 randomized controlled trials (10 publications). Two systematic reviews relates to ulcerative colitis, while the remaining publications relates to Crohn's disease. We also included 4 health economic publications.

The systamtic review regarding ulcerative colitis had only identified studies which used infliximab as TNFα-inhibitor. The systematic reviews included 7 randomized controlled trials, dealing with patients with moderate to severe ulcerative colitis, even if not all outcomes were included in all trials. Short-term response, up to week 8, was achieved in 65 % of patients treated with infliximab and 33 % of patients treated with placebo. Long-term response was achieved in 50 % of patients treated with infliximab and approximately 25 % of patients treated with placebo. The proportion of patients achieving remission was also larger in patients given infliximab compared to those given placebo. Results further indicate that infliximab give a larger proportion of patients with endoscopic remission than placebo. Two of the studies included in the systematic reviews compared infliximab to steriodtreatement. The studies were small; making it hard to distinguish whether or not there is a difference in response and remissionrates between treatments.

For Crohn's disease we included studies with all four TNFα-inhibitors, infliximab, adalimumab, etanercept and certolizumab. We identified systematic reviews only for infliximab and etanercept. New randomized controlled studies were identified for infliximab, adalimumab and certolizumab. When infliximab was given as open-label treatement to patients with moderate to severe Crohn's disease nearly 60 % of patients has a response after two weeks. Response was defined as reduction of 70 or more on the Crohn's disease activity index (CDAI). Upon maintenance treatment with infliximab or placebo, those patients receiving infliximab 5 mg/kg or 10 mg/kg had significantly longer time to loss of initial response. There difference between maintenance treatment with infliximab or placebo was also present for remission (CDAI <150). At week 30 approximately 40 % of patients given infliximab were in remission compared to approximately 20 % of patients given placebo.

Treatment with adalimumab at week 0 and 2 gave response at week 4 in nearly 60 % of patients with moderate to severe Crohn's disease. Response was defined as reduction of 70 or more on CDAI. Resoponse was consistent across trials wether adalimumab was given as open-label or blinded treatment (placebo gave 37 % responders). Upon blinded maintenance treatement after week 4 with adalimuamb every week, every other week or placebo, 40 %, 47 % and 17 % of patients repectively were in remission (CDAI<150) at week 26.

Data from studies on certolizumab in the treatment of moderate to severe Crohn's disease have shown that the probability of achieving response is greater with certolizumab than with placebo, both on short-term and long-term. For patients with CRP >10 mg/L at the beginning of the study, 37 % of certolizumabtreated and 26 % of placebotreated patients had a reduction of >100 on CDAI at week 6. Data also indicate that maintenance treatment with certolizumab is better than placebo in maintaining an initial response. For randomized responders further treatement with certolizumab or placebo gave 48 % and 29 % respectively in remission at week 26.

Data on etanercept in treatment of Crohn's disease is limited to 43 patients. There is no basis to claim that etanercept has effect in treatment of Crohn's disease.

In addition, the studies showed that treatment with infliximab, adalimumab and certolizumab gave a significantly improved quality of life in patients with moderate to severe Crohn's disease. Quality of life was determined as change in score in the Inflammatory Bowel Disease Questionnaire (IBDQ).

Neither of the included studies report significant differences in adverse events between TNFα-inhibitors and placebo independently of whether the patient population had ulcerative colitis or Crohn's disease. However, the study durations are too short to conclude on long-term safety.

We did not identify any studies that compared different TNFα-inhibitors. We did identify one study which examined the effect of adalimumab on patients previously treated with infliximab. They had either lost response to infliximab or not being able to tolerate the treatment. After two injections at week 0 and 2, 52 % of the patients treated with adalimumab and 34 % treated with placebo had response defined as decrease in CDAI >70 at week 4.

TNFα-inhibitors are more expensive than other drugs used in the treatment of inflammatory bowel disease. We wanted to examine whether the costs were reasonable in relation to an expected heatlh improvement of these new drugs. In a systematic search for literature, we identified four economic evaluations of infliximab in the treatment of Crohn's disease. Based on these four studies performed outside Norway it appears that infliximab, in general is not cost-effective as continuous treatment of patients with fistulating or active, refractory Crohn's disease. There might be an exception with respect to patients with a good and long-lasting response. Due to the lack of data regarding quality of life in patients with Crohn's disease and limited transferability to a Norwegian setting, the results shold be interpreted with caution. We did not identify any economic evaluations relating to the other TNFα-inhibitors or to ulcerative colitis.

## CONCLUSION

Infliximab is effective in treatment of ulcerative colitis and Crohn's disease. Adalimumab and certolizumab have documented effect in treatment of Crohn's disease, while studies on patients with ulcerative colitis are lacking. There is too limited data available to conclude regarding safety of long-term treatment with TNFα-inhibitors for both ulcerative colitis and Crohn's disease.

Based on results from countries outside Norway, infliximab does not seem to be cost-effective as continuous treatment for patients with Crohn's disease. There might be an exception in the case of patients exhibiting good and long-lasting response. No relevant economic studies were found for ulcerative colitis or for the other TNFα-inhibitors.

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