Systematic review: steroid withdrawal in anti-TNF-treated patients with inflammatory bowel disease

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CRD summary
In patients with inflammatory bowel disease treated with anti-tumour necrosis factor therapy (infliximab), 24% to 38% of adult patients and 67% to 75% of paediatric patients on steroids at baseline were off steroids without surgery at follow-up. Limitations of the review process and evidence and uncertainties about study quality mean that the authors’ conclusions should be treated with caution.

Authors’ objectives
To evaluate steroid withdrawal in anti-tumour necrosis factor-treated patients with inflammatory bowel disease.

Searching
MEDLINE was searched to August 2009 for publications in English; search terms were reported. Relevant reviews published after 2006 were handsearched. Only full papers were included.

Study selection
Studies that compared anti-tumour necrosis factor therapy that used infliximab or adalimumab were eligible for inclusion. Controls needed to receive either placebo or conventional medication. Studies of patients who acted as their own control before and after anti-tumour necrosis factor therapy were eligible. Paediatric and adult patients with non-fulminant active ulcerative colitis or active luminal Crohn’s Disease were eligible for inclusion. Infliximab treatment could be either as induction therapy (one to three infusions within 10 weeks) or as maintenance therapy (induction therapy followed by scheduled infusions). Studies had to assess numbers of patients able to withdraw corticosteroids (the primary outcome) and have follow-up of at least 26 weeks. Non-randomised and non-controlled trials were included. Studies were excluded if there was no clear distinction between ulcerative colitis and Crohn’s Disease patients, if anti-tumour necrosis factor treatment schedule was not known and if there was episodic infliximab treatment. Studies were excluded if they contained overlapping patient sets.

Reported induction therapy dose for infliximab was usually 5mg/kg and was sometimes followed by 10mg/kg infliximab. Maintenance therapy was 5mg/kg or 10mg/kg infliximab every eight to 12 weeks. Adalimumab maintenance regimes were compared to placebo. Concomitant immunosuppressants were given in most studies. There were two paediatric studies (median age range 12 to 14.5 years for different patient groups). The age range for different patient groups in the other studies was a median of 26 to a mean of 42.4 years. Where reported, the proportion of males ranged from 31% to 65% in different patient groups. Disease duration ranged from a mean of 1.6 years in one paediatric group to a mean of 8.4 years. The proportion of Crohn’s Disease patients with disease located in the ileum ranged from 11% to 75%, in the colon from 13% to 92% and in both areas from zero to 59%. Studies that provided relevant data patients had either active or moderate to severe disease.

Two reviewers performed the selection. Disagreements were resolved by consensus.

Assessment of study quality
Methodological quality was assessed by one reviewer. Criteria assessed to gauge the risk of bias included sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting.

Data extraction
One reviewer performed data extraction. Data were extracted only for patients who received anti-tumour necrosis factor treatment. Percentages were calculated for patients in the treatment and control groups who took steroids at baseline and discontinued steroids, discontinued steroids with surgery and who were unable to discontinue steroids or needed re-initiation at follow-up. Percentages were calculated for patients in the treatment and control groups who did not take steroids at baseline and remained steroid free, remained steroid free with surgery and who needed initiation
with steroids at follow-up. Authors were contacted for missing data.

**Methods of synthesis**
A narrative synthesis was provided as the studies were of heterogeneous designs.

**Results of the review**
Seven studies were identified (n=2,155 patients, range 22 to 854). One article included two studies. Most were randomised controlled trials, but no further details were provided. Follow-up was for 30 to 54 weeks.

**Corticosteroids in Crohn’s Disease:** Three studies were of infliximab and one was of adalimumab treatment. One adult study found for the intervention group that took maintenance infliximab that 30% of patients on steroids at baseline were off steroids without surgery at follow-up and 81% patients not on steroids at baseline remained steroid-free without surgery at follow-up. One paediatric study found that for the intervention group that took maintenance infliximab, 67% of patients on steroids at baseline were off steroids without surgery at follow-up and 99% patients not on steroids at baseline remained steroid-free without surgery at follow-up. No relevant data were available for two studies in adult patients.

**Corticosteroids in ulcerative colitis:** One of the three studies of infliximab treatment found that the intervention group that took maintenance infliximab that 24% of patients on steroids at baseline were off steroids without surgery at follow-up and 72% patients not on steroids at baseline remained steroid-free without surgery at follow-up. One study of adults found that the intervention group that took maintenance infliximab, 38% of patients on steroids at baseline were off steroids without surgery at follow-up and 91% patients not on steroids at baseline remained steroid-free without surgery at follow-up.

A small paediatric study found that four of eight patients (50%) on steroids at baseline in the intervention group and who took induction infliximab were off steroids without surgery at follow-up. Two patients not on steroids at baseline needed total colectomy. The same small paediatric study found that all eight patients who took maintenance infliximab were treated with steroids at baseline and all were off steroids at follow-up.

**Authors' conclusions**
There was no consensus on the definition of steroid-sparing, but approximately two-thirds of inflammatory bowel disease patients were unable to withdraw corticosteroid treatment during anti-tumour necrosis factor therapy.

**CRD commentary**
The review addressed a well-defined question in terms of study design, participants, interventions and relevant outcomes. Only one relevant database was searched and studies needed to be published and in English, so some relevant studies may have been missed. Publication bias was not assessed. Study quality was assessed, but no relevant information was provided and the study design of the included studies was unclear and so it was impossible to assess study quality. Some efforts were made to avoid error and bias in study selection, but validity assessment and data extraction were each performed by only one reviewer, which risked errors and bias. Some relevant study details were reported. Outcome results were extracted only for intervention groups and not for controls. No comparisons were made between results for different interventions and placebo groups. Outcomes were extracted for only patients who took anti-tumour necrosis factor therapy. No relevant data were available for two of the seven included studies and one of these was the only study of adalimumab treatment. A narrative synthesis was provided due to the reported heterogeneity in study design.

One author had been a speaker, consultant and advisory board member for Abbott Laboratories, Shire, Schering-Plough and Centocor and had received funding from Abbott Laboratories and Schering-Plough.

The authors commented that two of the included studies were of responders to infliximab and the results should be considered with caution. In view of the limitations of the review process and evidence, and uncertainties about the quality of included studies, the authors' conclusions should be treated with caution.
Implications of the review for practice and research

**Practice:** The authors stated that it may be necessary to introduce biologicals earlier in the course of disease to avoid combination therapy with immunosuppressants and thus avoid the risk of severe infection.

**Research:** The authors identified a need for further research and recommended that future studies assess the whole population receiving infliximab for luminal Crohn's Disease or ulcerative colitis. Complete withdrawal and initiation of steroid treatment should be taken into account.

**Funding**
None stated.

**Bibliographic details**

**PubMedID**
20497138

**DOI**
10.1111/j.1365-2036.2010.04373.x

**Original Paper URL**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Anti-Inflammatory Agents /therapeutic use; Antibodies, Monoclonal /therapeutic use; Child; Chronic Disease; Drug Therapy, Combination; Humans; Immunosuppressive Agents /therapeutic use; Inflammatory Bowel Diseases /drug therapy; Infliximab; Steroids /therapeutic use; Tumor Necrosis Factor-alpha /therapeutic use; Withholding Treatment

**AccessionNumber**
12010005318

**Date bibliographic record published**
10/11/2010

**Date abstract record published**
06/07/2011

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.