NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of extracorporeal photopheresis for Crohn's disease

Crohn's disease is a chronic inflammatory disease that affects the gastrointestinal tract. It is sometimes associated with other complications such as skin rashes and arthritis. In extracorporeal photopheresis blood is removed from the patient, then the white blood cells are separated from the whole blood, treated with ultraviolet light and re-infused into the patient.

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in July 2008

Procedure name

- Extracorporeal photopheresis for Crohn's disease
- Extracorporeal photochemotherapy for Crohn's disease

Specialty societies

- Royal College of Physicians and Surgeons of Glasgow
- Scottish Blood Transfusion Service
- British Society of Haematology.

Description

Indications and current treatment

Crohn's disease is a chronic inflammatory disorder of the gastrointestinal tract that may affect any part from the mouth to the anus, but most commonly affects the lower part of the small intestine (ileum) and the large intestine (colon). Affected parts of the intestine become inflamed and may develop fistulae to other parts of the bowel or skin, or strictures causing narrowing of the bowel. The symptoms and signs of Crohn's disease vary according to the site affected and the extent and severity of the disease. Typically they include diarrhoea, abdominal pain, weight loss, rectal bleeding, fever and tiredness. Complications may include rectal abscesses, joint disease and skin ulcers.

Some patients have long periods of remission when they are free of symptoms. However, the disease usually recurs several times over a patient's lifetime.

Treatment depends on the severity and extent of the disease and is aimed at reducing the frequency and severity of recurrences. Drug therapy, which may include corticosteroids and immunosuppressive agents (mainly azathioprine or 6-mercaptopurine), in many cases can control the inflammation, keep symptoms under control and reduce the probability of relapse. For more severe cases, treatment with infliximab, which is a monoclonal antibody against tumour necrosis factor alpha (TNF-α), can be considered. Surgical removal of the affected areas is sometimes necessary, but this is not curative as the disease can recur elsewhere.

The Crohn's Disease Activity Index (CDAI) is a composite index frequently used in research studies to assess the severity of the disease, although it is not widely used in everyday clinical practice. The CDAI score ranges from 0 to over 600, and is assessed using a clinical diary of symptoms kept by the patient for 1–7 days and other measurements such as the patient's weight and haematocrit. A score of 150 or lower represents inactive disease, whereas scores over 450 represent severe, active disease.

What the procedure involves

Extracorporeal photopheresis (ECP) therapy involves drawing blood from the patient via a peripheral line. The leukocyte-containing buffy coat cells (which contain about 5–10% of peripheral blood mononuclear cells) are separated from the red blood cells (RBCs). The RBCs and the remaining plasma are then returned to the patient via the same indwelling catheter.

A photosensitive drug (8-methoxypsoralen) and an anticoagulant are added to the remaining buffy coat cells which are passed through a sterile chamber. The cells are then irradiated with ultraviolet light, which activates the drug. The photosensitive drug binds to DNA in the buffy coat cells when activated by light-arresting cell proliferation, causing cell death.

Finally, the buffy coat cells are returned to the patient. The re-infused dying cells produce a generalised immune response against pathogenic T-cell clones that are involved in the pathogenesis of inflammation in Crohn's disease.

ECP is usually performed over 2 consecutive days at intervals of 2–4 weeks for about 20 treatment sessions. One ECP session takes about 3–4 hours.

Efficacy

Limited evidence has been published on the use of ECP in patients with Crohn's disease.

In a case series of 28 patients with moderate to severe Crohn's disease (some refractory or intolerant to immunosuppressants or anti-TNF agents) treated by extracorporeal photopheresis, 50% (14/28) of patients reported a clinical response and 25% (7/28) were in remission at 12-week follow-up[x]. In the same study the mean Inflammatory Bowel Disease Questionnaire score improved from 122 points at baseline to 154 points at 12-week follow-up ($p < 0.001$).

In a case series of 10 patients, a response (defined as a 50% reduction in steroid use) was observed in eight patients, with remission in four, as defined by a CDAI score of less than 150 points at a median follow-up of 20 weeks. Three of the four patients remained in remission at the end of follow-up (mean 16.5 weeks, range 4–20 weeks)[1].

In a first case report of two patients, a subjective improvement during the early stages of ECP therapy was reported in both patients, although this improvement was not maintained at the end of the treatment or at 6-month follow-up[2]. In a second case report of two patients, after at least 24 weeks of ECP, the patient with moderate disease (CDAI score of 323) achieved a clinical response, with a CDAI score of 105 at 6 weeks. The other patient with a CDAI score of 461 at baseline had a CDAI score of 369 at the end of treatment, and an improvement in the pain intensity and frequency of loose or watery stools [3].

Safety

In a case series of 28 patients treated by extracorporeal photopheresis 7% (2/28) of patients discontinued treatment because of adverse events, one with nausea and malaise, and one with increased C-reactive protein concentration and fever[x]. Headaches and nasopharyngitis occurred in 29% (8/28) of patients, and nausea in 18% (5/28) of patients.

Across the three other studies totalling 14 patients, seven adverse events were reported following the procedure. These included two instances of asymptomatic hypotension[2,1], one of mild headache[1] and one of small haematoma at the infusion site[1]. One patient developed monoclonal gammopathy[1]. Worsening of anaemia following the procedure was noted in three patients[2,3].

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to ECP for Crohn's disease. Searches were conducted via the following databases, covering the period from their commencement to 13 May 2008, and updated to 27th Oct 2008 : MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches. (See appendix C for details of search strategy.)

The following selection criteria (Table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good-quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients with Crohn's disease
Intervention/test	Extracorporeal photopheresis
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on two case series[1], and two case reports[2,3], totalling 42 patients.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Existing reviews on this procedure

There were no published reviews identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B details the recommendations made in each piece of guidance listed below.

Interventional procedures

- Leukapheresis for inflammatory bowel disease. NICE interventional procedures guidance 126 (2005). Available from http://www.nice.org.uk/guidance/IPG126

Technology appraisals

- The clinical effectiveness and cost effectiveness of infliximab for Crohn's disease. NICE technology appraisal 40 (2002). Available from http://www.nice.org.uk/guidance/TA40
- Crohn's disease – infliximab (review) and adalimumab (in progress). Available from http://www.nice.org.uk/page.aspx?o=350201

Clinical guidelines

- None

Public health guidance

- None

Table 2 Summary of key efficacy and safety findings on extracorporeal photopheresis for Crohn's disease

Abbreviations used: CDAI, Crohn's Disease Activity Index; ECP, extracorporeal photopheresis; IBDQ, Inflammatory Bowel Disease Questionnaire; TNF, tumour necrosis factor

Study details	Key efficacy findings	Key safety findings	Comments
Abreu M T (XXXX) **Case series** International Study period: Feb 2005 to Mar 2006 **n = 28** Study population: age: mean 38 years (range 18–65 years), Sex = 75% female. Mean CDAI = 314. Mean IBQD = 122. 43% (12/28) of patients were on anti-TNF therapy, immunosuppressant therapy or both Indications: patients with moderate to severe Crohn's disease refractive to treatment. Confirmed diagnosis of Crohn's disease by radiologic or endoscopic study, with minimum 6-month duration. Technique: patients were treated using the UVAR photopherisis system. ECP twice a week on consecutive days each week for 4 weeks, then twice a week every other week until week 12. Patients who responded (decrease in CDAI of 100 points or more) at week 12 received additional ECP treatments for two days every other week until week 24. **Follow-up: median 12 weeks (9 patients in extended trial to 24 weeks)** Conflict of interest: none stated	**Response and remission** Mean change in CDAI score was 116 points at 12-week follow-up ($p < 0.001$). Clinical response at 12-week follow-up Partial clinical response 64% (18/28) Clinical response 50% (14/28) Remission 25% (7/28) Subgroup analysis reported that 53% (9/17) of patients who were refractory or intolerant to anti-TNF agents had some response, while 36% (4/11) of patients naive to anti-TNF therapy responded. (measure of significance not reported) Of the 14 patients with clinical response at 12 weeks who continued with therapy 75% (9/12) remained in clinical response at 24-week follow-up The mean IBQD score increased from 122 points at baseline to 154 points at week 12 ($p < 0.001$). 60% (3/5) of patients with draining fistulas at baseline had complete closure of their fistula at week 12. Conversely one patient who had a closed perineal fistula at baseline had reopening of that fistula at 12-week follow-up.	**Complications** One patient (4% (1/28)) discontinued the study due to two serious adverse events (nausea and malaise). And one patient (4% (1/28)) discontinued the study because of non-serious adverse events (increased C-reactive protein concentration and fever). Complication — Rate Headache and nasopharyngitis — 29% (8/28) Nausea — 18% (5/28) Pyrexia — 18% (5/28) Emesis — 18% (5/28)	Steroid dose was maintained at the same level during the initial 12 weeks of the study, but could be tapered in the patient in extended trial to 24 weeks. All treatments were delivered by experienced clinicians. 12 participating centres Partial clinical response was defined as a decrease in CDAI of > 70 points. Clinical response was defined as a decrease in CDAI of ≥ 100 points and/or CDAI score of < 150. Remission was defined as CDAI < 150 points. Non-response was defined as all other patients and those withdrawn because of an adverse event before 12 weeks. 6 patients did not conclude the first 12 weeks of therapy because of worsening of Crohn's symptom (n = 4) or adverse events (n = 2).

Abbreviations used: CDAI, Crohn's Disease Activity Index; ECP, extracorporeal photopheresis; IBDQ, Inflammatory Bowel Disease Questionnaire; TNF, tumour necrosis factor

Study details	Key efficacy findings	Key safety findings	Comments
Reinisch W (2001)[1] **Case series** USA Study period: March 1996 to October 1997 Study population: mean age 35 years (range 25–56 years); mean disease duration 9 years (3–24 years); disease site: Ileum (1), colon (2), Ileum and colon (7) **n = 10** patients received ECP (out of a total of 24 who were eligible), 9 of whom completed the intended treatment regimen and were followed up Age: 18–65 years Indications: confirmed diagnosis of Crohn's disease and steroid-dependent course. Patients were excluded if Crohn's disease was restricted to the rectum, if they had undergone intestinal resection within the past 12 months, or if they had severe disease complications requiring surgery Technique: the study consisted of three phases (see comments column). Phase 2 (ECP phase) involved photochemotherapy. Mean treatment time was 3.5 hours. Patients were treated on 2 consecutive days at 14-day intervals during 24 weeks, for a total of 24 photopheresis procedures **Follow-up: phase 3 had a follow-up of 16.5 weeks (range 4–20 weeks)** Conflict of Interest: none stated	**Response and remission** Response was observed in 8/10 (80%) and remission in 4/8 (50%) of patients after a median of 10 weeks (range 8–19) and 20 weeks (range 19–23), respectively One patient who terminated the ECP phase in week 12 had attained response in week 9 After termination of phase 3, three of the four patients who achieved remission remained in remission. The median duration of response (n = 4) during the follow-up phase was 16.5 weeks (range 4–20 weeks) **Prednisolone use** The authors noted that during phase 1, prednisolone dose could not be reduced among patients, therefore indicating criteria for inclusion in the ECP phase **Clinical and inflammatory measures** The mean CDAI scores decreased from phase 1 (155) to phase 2 (126; p = 0.004) IBDQ scores increased from baseline (mean 186) to the end of the ECP phase (204; n = 9, p = 0.008). Mean concentration of C-reactive protein was 28 mg/litre at baseline, decreasing to 15 mg/litre at the end of the ECP phase (p = 0.017) **Regulation of adrenocorticotropic hormone** The mean concentration at baseline was 7.4 nanograms/litre with values below the normal range in four patients. Plasma levels increased to 22 at the end of phase 2, and were within the normal range for all patients.	Complications occurred in 4 of 10 patients (228 treatment sessions) One patient developed an episode of asymptomatic hypovolaemic hypotension One patient developed a small haematoma at the venipuncture site One patient had mild headache One patient developed monoclonal gammopathy of underdetermined significance. The authors believe this complication is unrelated to ECP	The study was performed in three phases over a period of 24 weeks Phase 1 = steroid-tapering phase Phase 2 = ECP Phase 3 = follow-up Each phase had a minimum duration of 24 weeks The authors note that the high dropout rate during the steroid-tapering phase may have been due to non-compliance, attributable to clinical worsening during permanent steroid reductions The primary endpoint was remission, defined by maintenance of the CDAI score below 150 points after discontinuation of prednisolone. Response was defined as a 50% reduction in steroid use Relapse was defined as a CDAI score of 200 or more C-reactive protein is an imprecise disease activity indicator but was included a priori as a secondary outcome measure. Other secondary outcomes included cumulative prednisolone intake, plasma adrenocorticotropic hormone, mean CDAI score and IBDQ score Higher scores on the IBDQ indicate a better quality of life

Abbreviations used: CDAI, Crohn's Disease Activity Index; ECP, extracorporeal photopheresis; IBDQ, Inflammatory Bowel Disease Questionnaire; TNF, tumour necrosis factor

Study details	Key efficacy findings	Key safety findings	Comments
Bisaccia E (2007)[3] **Case report** USA Study period: not stated **n = 2** Patient 1: 35-year-old white woman diagnosed with Crohn's disease more than 17 years ago. Affected portions of the gastrointestinal tract were the jejunum and the ileum Patient 2: 43-year-old white woman diagnosed with Crohn's disease more than 11 years ago. Affected portions of the gastrointestinal tract were the gastro-duodenum, ileum and jejunum. Surgery had been performed in the past. Indications: moderate or severe Crohn's disease in patients who failed prior treatment with immunosuppressants and anti-TNF agents Technique: patients were treated with ECP on 2 consecutive days each week during the first 4 weeks, and on 2 consecutive days every 2 weeks for the next 8 weeks. A clinical response was required at week 12 for entrance into an extension phase consisting of an additional 12 weeks of ECP at a frequency of 2 consecutive days every 2 weeks, for a total of 30 treatments **Follow-up: 24 weeks** Conflict of Interest: none stated	**Patient 1** At ECP baseline the CDAI score was 461 points and the mean number of loose or watery stools was 13 per day. After 12 weeks of ECP, the CDAI score was 369 points, and the ECP was discontinued because of a lack of clinical response During ECP arthralgia substantially improved and erythema nodosum resolved completely After ECP discontinuation there was a flare-up in symptoms and surgery was suggested. At the patient's request, ECP was resumed at week 20 and continued to week 30. AT ECP endpoint (after final treatment), the CDAI score was 393 points and the mean number of loose or watery stools was 12 per day **Patient 2** Over the course of 24 weeks of continuous ECP, the CDAI score decreased substantially from 323 to 105 points (achieving a clinical response)	**Patient 1** Mild nosebleed and worsening anaemia **Patient 2** No adverse events were reported	Clinical response was defined as a decrease in CDAI score from baseline of at least 100 points and/or an endpoint CDAI score of less than 150 points CDAI score evaluations were performed prior to each 2-day treatment of ECP The authors note that both patients were enrolled in a multicentre open-labelled study (see issues for consideration by IPAC section) In both patients ECP was delivered while continuing with other medications (not including anti-TNF drugs)

Abbreviations used: CDAI, Crohn's Disease Activity Index; ECP, extracorporeal photopheresis; IBDQ, Inflammatory Bowel Disease Questionnaire; TNF, tumour necrosis factor

Study details	Key efficacy findings	Key safety findings	Comments
Guariso G (2003)[2] **Case report** Italy Study period: not stated **n = 2** Patient 1: 20-year-old man with a CDAI score of 281. Disease in terminal ileum and colon. Receives enteral nutritional support. Duration of disease before treatment 9 years Patient 2: 19-year-old female with a CDAI score of 330. Disease in terminal ileum and colon. Duration of disease before treatment 7 years Indications: Crohn's disease diagnosed at less than 12 years old in both cases. CDAI scores higher than 200, despite prednisolone therapy for at least 6 months. Infliximab therapy was discontinued at least 2 months before patients enrolled in the ECP study Technique: patients were treated with ECP on 2 consecutive days at 1-week intervals for the first month, at 2-week intervals during the second and third months, and every 4 weeks for the following 3 months. A total of 22 treatments were administered to each patient **Follow-up: 6 months** Conflict of Interest: none stated	**Patient 1** The patient showed a slight general improvement after the first month, with fewer bowel moments and fever regression Anaemia deteriorated. Enteral nutrition was re-introduced because of low body weight At 3 months no significant changes in clinical status were observed. At the end of all ECP sessions, the patient still had mild fever and mild anaemia, hypoproteinaemia and a CDAI score of 341 Weight gain was recorded at 3.5 kg. No changes were made to concomitant medical therapy except for the tapering off of mesalazine to 1600 mg/day During the subsequent 6 months, the patient's clinical condition remained unchanged, with persistent anaemia and raised inflammatory markers **Patient 2** This patient showed an initial general improvement in symptoms following the procedure, but experienced a severe relapse in the third month, requiring hospitalisation because of cramp-like abdominal pain, postprandial vomiting and weight loss. Steroids were added to the medication and ECP cycles were continued Colonoscopy performed at the end of ECP therapy revealed no reduction in inflammation and the onset of anal stenosis, requiring dilation Four months later, the patient still required steroid therapy and the CDAI score was 305	Patient 1 developed an asymptomatic episode of mild hypotension during the procedure The authors note that the only significant side effect seen in both patients was worsening of anaemia (not stated whether this was because of ECP or underlying disease), although neither patient required a blood transfusion	The authors note '… a short-lived moderate subjective amelioration of clinical condition in the early stages of ECP therapy was reported by both our patients'.

Validity and generalisability of the studies

- The published evidence base for this procedure is limited to three case series reporting on a total of 14 patients. The studies were not controlled.
- Details of concomitant treatment with other medication is not well described. The study period of the first case series (1996–7) means that treatment with anti-TNF agents was not an option[1].
- Two patients in one case report[3] had severe Crohn's disease that had previously failed to respond to standard treatments.
- The authors of one study suggested that a better response was achieved in patients who had a shorter duration of steroid use[1].
- In one study recurrence rate was assessed after a phase of steroid weaning[1].

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

Dr A Cahill (Royal College of Physicians and Surgeons of Glasgow), Dr K Douglas (Scottish Blood Transfusion Service), Dr R Green (Scottish Blood Transfusion Service).

- One Adviser considered this procedure to be novel and of uncertain safety and efficacy. One classified it as established, and the third did not give an opinion.
- The key efficacy outcomes for this procedure were thought to include lymphocyte cell death, reduction of bowel frequency and abdominal cramps, improved quality of life, reduction in inflammatory markers and faecal calprotectin (a protein associated with levels of intestinal inflammation), and reduced steroid use.
- Anecdotal and published adverse events following this procedure include vasovagal episodes such as hypotension and fits, light sensitivity or allergy to photoactivating agent, anaemia and central venous line infection.
- Additional theoretical adverse events include haemorrhage due to heparin use, malignancy from light exposure and immunosuppression.
- The Specialist Advisers note that only a few small series have been published to date, and that larger studies and randomised controlled trials are needed to establish the role of this procedure in therapy.
- One Specialist Adviser noted that the procedure is not directly available from any gastroenterology unit in the UK but only from six specialist units headed by a haematologist or dermatologist.
- The procedure should only be offered in units following the British Committee for Standards in Haematology guidelines.
- There is an ongoing trial in the USA (no further details provided).
- If the procedure were found to be safe and efficacious, two Specialist Advisers thought that it would be offered at a minority of district general hospitals, and one that it would be limited to less than 10 specialist

centres. All three Advisers thought that the impact on the NHS would be moderate.

Issues for consideration by IPAC

- Photopheresis has been used in the management of several T-cell-mediated diseases, such as graft-versus-host disease and autoimmune disease.
- The exact mechanism by which ECP leads to responses in Crohn's disease is not well understood.
- There are a number of ongoing trials on ECP and Crohn's disease (one case series, n = 28; one US case series, n = 4; one US case series with steroid withdrawal, n = 10). To date, however, no results have been published from these trials, and likely publication dates are not known.

References

1. Reinisch W, Nahavandi H, Santella R et al. (2001) Extracorporeal photochemotherapy in patients with steroid-dependent Crohn's disease: a prospective pilot study. Alimentary Pharmacology and Therapeutics 15:1313–22.

2. Guariso G, D'Inca R, Sturniolo GC et al. (2003) Photopheresis treatment in severe Crohn disease. Journal of Paediatric Gastroenterology and Nutrition 37:517–20.

3. Bisaccia E, Palangio M and Gonzalez J (2007) Extracorporeal photochemotherapy for the treatment of refractory Crohn's disease. Transfusion and Apheresis Science 37:171–4.

4. Abreu MT, von Tirpitz C, Hardi R et al. (XXXX) Extracorporeal photopheresis for the treatment of refractory Crohn's disease: results of an open-label pilot study. Inflammatory Bowel Diseases XX: XX-XX

Appendix A: Additional papers on extracorporeal photopheresis for Crohn's disease

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Abreu M, Von Tirpitz C, Mannon PJ (2007) Extracorporeal photoimmune therapy (ECP) for refractory moderately active Crohn's disease (CD): a multi-centre, open label study. Digestive Disease Week, May: Abstract 1033.	n = 28 patients Follow-up: 24 weeks	13/28 (46%) patients had a response by week 6; 7/28 patients went into remission All 14 patients who achieved a clinical response by week 12 continued on a 12-week extension phase and 71% maintained their response through to week 24 Safety: two serious adverse events were reported: general health deterioration and anemia	Conference abstract
Parenti D, Abreu M, von Tirpitz C et al. (2008) Extracorporeal photoimmune therapy (ECP) for refractory moderately active Crohn's disease (CD): a multicenter, open-label study. Journal of Clinical Apheresis 23: Abstract 3.	n = 28	As above	Conference abstract – appears to be the same patient population as above

Appendix B: Related published NICE guidance for extracorporeal photopheresis for Crohn's disease

Guidance programme	Recommendation
Interventional procedures	**Leukapheresis for inflammatory bowel disease. NICE interventional procedures guidance 126 (2005)** 1.1 Current evidence suggests that there are no major safety concerns for the use of leukapheresis for inflammatory bowel disease. 1.2 Leukapheresis may be beneficial in carefully selected patients with ulcerative colitis, but the evidence on efficacy is not yet adequate to support its use in these patients without special arrangements for consent, and for audit and research as set out in 1.4 (below). 1.3 There is inadequate evidence to draw any conclusions about the efficacy of leukapheresis in patients with Crohn's disease and it should only be used in accordance with special arrangements for consent, and for audit and research as set out in 1.4 (below). 1.4 Clinicians wishing to undertake leukapheresis for inflammatory bowel disease should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's efficacy and provide them with clear written information. Use of the Institute's 'Information for the public' is recommended. • Audit and review clinical outcomes of all patients having leukapheresis. 1.5 Publication of current and future research studies will be useful. The Institute may review the procedure upon publication of further evidence.
Technology appraisals	**The clinical effectiveness and cost effectiveness of infliximab for Crohn's disease. NICE technology appraisal 40 (2002).** 1.1 Infliximab is recommended for the treatment of patients with severe Crohn's disease who fulfil all three of the following criteria: • Patients who have severe active Crohn's disease. These patients will already be in very poor general health with weight loss and sometimes fever, severe abdominal pain and usually frequent (3–4 or more) diarrhoeal stools daily. They may or may not be developing new fistulae or have extra-intestinal manifestations of the disease. This clinical definition normally corresponds to a Crohn's Disease Activity Index (CDAI) score of 300 or more and a Harvey-Bradshaw Index of 8/9 or above (see Appendix D) • Patients whose condition has proved to be refractory to treatment with immunomodulating drugs (e.g.

	azathioprine or 6- mercaptopurine, methotrexate) and corticosteroids, or who have been intolerant of, or experienced toxicity from, these treatments. • Patients for whom surgery is inappropriate (e.g. because of diffuse disease and/or a risk of short bowel syndrome). 1.2 Treatment can be repeated for those patients who match the above criteria and have responded to the initial treatment course, but then relapsed. A decision about whether or not to re-administer infliximab after the first course or subsequently should be made only after discussion with the patient who has been fully informed of the potential risks and benefits of repeated therapy (episodic treatment). 1.3 Infliximab should be prescribed by a gastroenterologist experienced in the management of Crohn's disease. 1.4 Infliximab is not recommended for patients with fistulising Crohn's disease who do not have the other criteria for severe active Crohn's disease as detailed in section 1.1.
Clinical guidelines	None applicable
Public health	None applicable

Appendix C: Literature search for extracorporeal photopheresis for Crohn's disease

Database	Date searched	Version searched
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	12/05/2008	Issue 2, 2008
Database of Abstracts of Reviews of Effects – DARE (CRD website)	12/05/2008	Issue 2, 2008
HTA database (CRD website)	12/05/2008	Issue 2, 2008
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	12/05/2008	Issue 2, 2008
MEDLINE (Ovid)	12 05 2008	01/01/2007 to April Week 5 2008
MEDLINE In-Process (Ovid)	12/05/2008	May 09, 2008
EMBASE (Ovid)	12/05/2008	01/2007 to 2008 Week 19
CINAHL (Dialog DataStar, NLH)	13/05/2008	1982 to present
BLIC (Dialog DataStar)		
National Research Register (NRR) Archive	13/05/2008	–
UK Clinical Research Network (UKCRN) Portfolio Database	13/05/2008	–
Current Controlled Trials *meta*Register of Controlled Trials (*m*RCT)	13/05/2008	–
Clinicaltrials.gov	13/05/2008	–

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 exp Photopheresis/
2 photopheres$.tw.
3 photophores$.tw.
4 exp Photochemotherapy/
5 photochemotherap$.tw.
6 (photo adj3 oxidat$).tw.
7 (extracorpor$ adj3 (photopheres$ or photophores$ or photochemotherap$)).tw.
8 ECP.tw.
9 exp PUVA Therapy/
10 (PUVA adj3 therap$).tw.
11 exp Ultraviolet Therapy/
12 (ultraviolet adj3 therap$).tw.
13 or/1-12
14 exp Crohn Disease/
15 (crohn$ adj3 disease).tw.
16 Ileitis/
17 ileitis.tw.
18 exp Enteritis/
19 enteritis.tw.
20 ileocolit$.tw.

21 exp Inflammatory Bowel Diseases/
22 (inflammator$ adj3 bowel disease).tw.
23 exp Colitis/
24 colit$.tw.
25 or/14-24
26 13 and 25
27 Animals/
28 Humans/
29 27 not (27 and 28)
30 26 not 29