NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedures overview of leukapheresis (white cell apheresis) for inflammatory bowel disease

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 August 2004.

Procedure names

- Leukapheresis
- White cell apheresis.
- Leukocyte removal therapy.
- Selective granulocyte and monocyte adsorption apheresis.
- Leukocytapheresis.

Specialty society

- British Society of Gastroenterology.

Description

Indications

Inflammatory bowel disease.

Ulcerative colitis and Crohn's disease are the most common forms of inflammatory bowel disease. Ulcerative colitis causes inflammation and ulceration of the rectum and sometimes the colon. Symptoms include bloody diarrhoea and rectal bleeding. Crohn's disease usually causes inflammation and ulceration of the small and large intestines, but it can affect any part of the digestive tract. The main symptoms are abdominal pain, diarrhoea and weight loss. Both of these are chronic conditions, characterised by periods of clinical relapse and remission.

The incidence of ulcerative colitis is around 10 to 20 per 100,000 per year in the UK and the incidence of Crohn's disease is approximately 5 to 10 per 100,000 per year.[1]

Current treatment and alternatives

Conservative treatments include dietary measures, and medications to control inflammation. Immunosuppressants may be used if other medical therapies are ineffective at maintaining remission. Patients with ulcerative colitis that does not respond to medical therapy may be treated with surgery to remove the colon.

Although surgery may also be used for patients with Crohn's disease, it may not be curative and the disease often recurs in a different part of the digestive tract.

What the procedure involves

Leukapheresis involves extracorporeal removal of leukocytes from the blood, either by centrifugation or by passage of blood through an adsorptive system. In each system, venous blood is removed in a continuous flow, anticoagulated, processed to deplete the leukocytes, and returned to the circulation. A leukapheresis session takes approximately one to two hours. The procedure is usually carried out once or twice a week, for about 5 to 10 sessions.

Different apheresis systems remove different populations of white blood cells. Leukapheresis using centrifugation removes a proportion of neutrophils and lymphocytes, but it requires specialised and expensive centrifugation equipment. Filter columns, which may contain cellulose acetate beads or a polyester fibre filter, remove a proportion of granulocytes and monocytes (which adhere to the beads or fibre) and some also remove lymphocytes.

How leukapheresis might work in IBD is completely unknown. The procedure removes only a minute fraction of the body's leukocytes in any one session. It is possible that the procedure may cause some leukocytes to be 'activated', perhaps releasing active substances such as cytokines into the plasma, which is returned to the patient.

Efficacy

In one randomised controlled trial of patients with ulcerative colitis, 74% (29/39) of patients treated with leukapheresis had an "excellent" or "moderate" improvement, compared with 38% (14/37) of patients treated with high-dose steroids ($p = 0.005$). In another small randomised controlled trial of patients with Crohn's disease, 100% (12/12) of patients treated with leukapheresis were successfully withdrawn from steroid therapy, compared with 66% (10/15) of patients who were not treated with leukapheresis ($p = 0.074$). 83% (10/12) of patients in the treatment group had recurrence of disease 18 months after steroid weaning, compared with 62% (5/8) patients in the control group (not statistically significant).

In four case series studies, between 55% (24/44) and 82% (32/39) of patients with ulcerative colitis had an initial remission of disease after the treatment. In one study, the proportion of patients in clinical remission dropped from 82% (32/39) at 12 weeks to 67% (26/39) at 12 months after the final treatment. In two further studies, 30% (10/33) and 39% (13/33) of patients relapsed during maintenance therapy after initial complete remission.

The Specialist Advisors stated that there was some uncertainty about the efficacy, due to the lack of data from randomised controlled trials.

Safety

Most studies reported only mild adverse effects such as dizziness, light headedness, headache and flushing. In three studies, the proportion of patients experiencing at least one non-severe adverse effect ranged from 9% (5/53) to 18% (7/39). One study reported adverse effects that were described as moderate or severe in 12% (5/42) of patients treated with leukapheresis: 1 patient had toxic shock, 2 patients had a headache, 1 patient had chest pain and 1 patient had anaemia.

In a randomised controlled trial, the incidence of adverse effects was statistically significantly lower in the patients treated with leukapheresis than in the patients treated with high-dose steroids (24% versus 47%, $p < 0.001$).

The Specialist Advisors did not have any major concerns regarding the safety of the procedure. They stated that potential adverse effects included infection, headache, palpitations, nausea, vomiting, fever, chills, respiratory distress and chest discomfort.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to selective white cell apheresis for inflammatory bowel disease. Searches were conducted via the following databases, covering the period from their commencement to August 2004: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and Science Citation Index. Trial registries and the Internet were also searched. No language restriction was applied to the searches.

The following selection criteria 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.

Characteristic	Criteria
Publication type	Clinical studies 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, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients with inflammatory bowel disease.
Intervention/test	White cell apheresis.
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 seven studies; two randomised controlled trials and five case series. One randomised controlled trial compared patients treated with leukapheresis to patients treated with high-dose steroids.[2] A second small randomised controlled trial treated one group of patients with leukapheresis in addition to their existing treatment while the other group continued on their existing treatment only.[3] Five case series studies have also been summarised in Table 1.[4-8] One study included patients with Crohn's disease.[3] The remaining six studies included patients with ulcerative colitis.

Other studies that are considered to be relevant to this procedure are listed in Appendix A.

Table 1 Summary of key efficacy and safety findings on white cell apheresis for inflammatory bowel disease

Study details	Key efficacy findings	Key safety findings	Comments
Sawada (2003)[2] Prospective randomised controlled trial 1994–1998 Japan 80 patients with active ulcerative colitis: • 52% (42/80) treated with leukapheresis • 48% (38/80) treated with high-dose steroid therapy Inclusion criteria: patients with active-stage moderately severe, severe or fulminant ulcerative colitis. All patients were under total parenteral nutrition and treated with intravenous steroids with or without oral anti-inflammatory medication Exclusion criteria: severe cardiovascular disease within the past 6 months, severe renal failure, hypotension (less than 80 mmHg systolic pressure), weight < 35 kg, age under 12 years, pregnancy, drug abuse, dementia, effective response to current therapy, proctitis, or mild ulcerative colitis. Leukapheresis column used: Cellsorba IBD-94 (Asahi Medical Co. Ltd, Tokyo, Japan) Follow-up: not reported	Primary outcome measures after intensive phase: improvement in clinical symptoms, endoscopic examination, Rachmilewitz clinical activity index (CAI), Lichtiger CAI, Rachmilewitz endoscopic index (EI), Matts endoscopic and pathological classification "Excellent" or "moderate" improvement : • leukapheresis = 74.3% (29/39) • high-dose steroid group = 37.8% (14/37) p = 0.005 No clear change in symptoms or endoscopic findings: • leukapheresis = 20.5% (8/39) • high-dose steroid group = 37.8% (14/37) Worsening in symptoms or endoscopic findings: • leukapheresis = 5.1% (2/39) • high-dose steroid group = 24.3% (9/37) Positive response according to Rachmilewitz CAI: • leukapheresis = 48.7% (19/39) • high-dose steroid group = 27.0% (10/37) p = 0.053 Positive response according to Lichtiger CAI: • leukapheresis = 61.5% (24/39) • high-dose steroid group = 35.1% (13/37) p < 0.05 Positive endoscopic response (Rachmilewitz EI): • leukapheresis = 61.5% (24/39) • high-dose steroid group = 32.4% (12/37) p = 0.005 Positive endoscopic response (Matts criteria): • leukapheresis = 82.1% (32/39) • high-dose steroid group = 37.8% (14/37), p < 0.001 Length of participation in maintenance phase was longer for leukapheresis patients (p = 0.012)	**"Severe" adverse effects** Leukapheresis: • toxic shock = 2.4% (1/42) High-dose steroid therapy: • mental abnormality (such as anxiety) = 2.6% (1/38) **"Moderate" adverse effects** Leukapheresis: • chest pain = 2.4% (1/42) • headache = 4.8% (2/42) • anaemia = 2.4% (1/42) High-dose steroid therapy: • mental abnormality = 2.6% (1/38) • osteoporosis = 2.6% (1/38) • fatty liver = 5.3% (2/38) • acne = 5.3% (2/38) • diabetes = 2.6% (1/38) • subcutaneous haemorrhage = 2.6% (1/38) • hepatic dysfunction = 2.6% (1/38) **"Mild" adverse effects** • Leukapheresis = 14.3% (6/42) • High-dose steroid therapy = 47.4% (18/38) Incidence of adverse effects: • Leukapheresis = 23.8% (10/42) • High-dose steroid therapy = 47.4% (18/38) p < 0.001	Patients were assigned to each group by an independent controller, taking account of severity, extent of lesion, clinical course, and refractoriness. Patients were not blinded to treatment. The trial was conducted in intensive (weeks 1 to 7) and maintenance phases (weeks 8 to 50). Intensive therapy was one session per week for 5 weeks and maintenance therapy was one session every 4 weeks for 11 sessions, ending in week 50. Patients receiving apheresis continued taking steroids at the same dosage as before the study. In the high-dose steroid group, steroid was added to the on-going drug therapy or increased. The initial dose was gradually tapered after 2 weeks, according to improvement in symptoms. Patients in both groups continued to receive the same drug therapy that they were taking before the start of the trial. Four patients were excluded from effectiveness analysis because of dropout or treatment failure (3 in leukapheresis group and 1 in steroid group).

Study details	Key efficacy findings	Key safety findings	Comments
Lerebours E (1994)[3] Prospective randomised controlled trial Date of study not stated France 28 patients with Crohn's disease: • 46% (13/28) treated with lymphapheresis • 54% (15/28) not treated with lymphapheresis (control group) Inclusion criteria: Patients who initially had symptomatic and active Crohn's disease who were in remission after 3 to 7 weeks of steroid therapy. Exclusion criteria: age < 15 years, lymphocyte count < 1500 / mm^3, isolated anoperineal lesions, immunosuppressive therapy during the 2 months before the date of clinical remission, severe cardiopathy, pregnancy, or peripheral access unsuitable for lymphapheresis procedure. Lymphocytes removed using continuous-flow cell separators: CS 3000 (Baxter, USA) or COBE 2997 (Cobe Inc., USA) Mean age: • lymphapheresis group = 29 years • control group = 30 years Follow-up: 18 months	Primary outcome measure = recurrence rate after steroid discontinuation Successful weaning from steroid therapy: • lymphapheresis = 100% (12/12) • control group = 66% (10/15) p = 0.074 (2-sided test) Recurrence after steroid weaning (18-month follow-up): • lymphapheresis = 83% (10/12) • control group = 62% (5/8) p = not significant	No adverse effect of apheresis was noted No patient needed blood transfusion No significant decrease in haemoglobin level was seen in either group 8% (1/13) of patients in the treatment group required a central venous catheter	Method of randomisation not described. Patients were not blinded to treatment. Small patient numbers. Clinical activity was measured by the revised Crohn's Disease Activity Index (CDAI). Active disease was defined by a CDAI ≥ 200. Clinical remission was defined by a CDAI ≤ 150 with a decrease of ≥ 100 points below the initial value. One patient in the lymphapheresis group was excluded because of pregnancy. Nine lymphaphereses were performed within 4 to 5 weeks. All patients in the lymphapheresis group received folic acid and iron intravenously after each treatment, to prevent anaemia. 13% (2/15) of patients in control group were lost to follow-up. Study was prematurely stopped because of failure to recruit enough patients into the treatment group. Many patients refused to participate in the trial.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Hanai H (2003)[4]

Case series

2000–2001

Japan

39 patients with active ulcerative colitis

Inclusion criteria: patients with severe acute relapse of ulcerative colitis who were either corticosteroid naïve or who failed to respond to intensive conventional medication, including high dose corticosteroids.

Granulocyte and monocyte adsorptive apheresis column used: Adacolumn (Japan Immunoresearch Laboratories, Takasaki, Japan)

Mean age: 42 years

Follow-up: 12 months</td>
<td>Main outcomes were based on 2 activity indices: Lichtiger clinical activity index (CAI) and disease activity index (DAI)

Mean CAI score at entry to study = 14
Mean CAI score at 12 weeks = 2, p < 0.001

Mean DAI score at entry to study = 10
Mean DAI score at 12 weeks = 3, p < 0.001

Clinical remission at 12 weeks = 82% (32/39)
Clinical remission at 12 months = 67% (26/39)

<table>
<tr><th>Mean C-reactive protein levels (mg/dL)</th><th>Baseline</th><th>Week 12</th></tr>
<tr><td>Corticosteroid refractory patients who received intravenous steroid therapy (n = 14)</td><td>8.5</td><td>1.4
p ≤ 0.001</td></tr>
<tr><td>Corticosteroid refractory patients who received oral steroids (n = 17)</td><td>5.9</td><td>0.9
p ≤ 0.05</td></tr>
<tr><td>Corticosteroid naïve patients (n = 8)</td><td>6.0</td><td>0.5
p ≤ 0.05</td></tr>
</table>

<table>
<tr><th>Mean haemoglobin (g/dL)</th><th>Baseline</th><th>Week 12</th></tr>
<tr><td>Corticosteroid refractory patients who received intravenous steroid therapy (n = 14)</td><td>9.3</td><td>11.6</td></tr>
<tr><td>Corticosteroid refractory patients who received oral steroids (n = 17)</td><td>10.6</td><td>11.9</td></tr>
<tr><td>Corticosteroid naïve patients (n = 8)</td><td>10.4</td><td>12.7</td></tr>
</table>

13% (4/31) of corticosteroid resistant patients required a colectomy</td>
<td>11 non-severe adverse events were observed in 7 (18%) patients during the study period:
• dizziness / light headedness = 15.4 % (6/39)
• flushing = 7.7% (3/39)
• nausea = 2.6% (1/39)
• mild fever = 2.6% (1/39)</td>
<td>A total of 146 consecutive patients were admitted to the units during the study period.

Patients who failed to respond to anti-inflammatory medication were treated with apheresis (n = 31). Those patients who initially responded to non-steroidal inflammatory medication but then relapsed (n = 8) were also treated with apheresis.

Initial treatment course was five sessions (one per week). If necessary, patients then received an additional five sessions. Patients with severe clinical disease were given two sessions per week for the first 3 weeks and then one session per week, up to a maximum of 11 sessions.

Patients in remission at week 12 continued with non steroidal anti-inflammatory medication as maintenance therapy.</td>
</tr>
</table>

Study details	Key efficacy findings	Key safety findings	Comments
Naganuma M (2004)[5] Case series 2000–2002 Japan 44 patients with active ulcerative colitis Inclusion criteria: patients with moderate or severe ulcerative colitis. Granulocyte and monocyte adsorptive apheresis column used: Adacolumn (Japan Immunoresearch Laboratories, Takasaki, Japan) Mean age: 36 years (range 17 to 64 years) Follow-up: 6 to 33 months	Main outcomes were based on Lichtiger clinical activity index (CAI). A CAI score ≥ 12 was classified as severe Remission (CAI ≤ 4) = 55% (24/44) Clinical response (decrease in CAI ≥ 3 but CAI remained >4) = 20% (9/42) No change/aggravation of disease = 25% (11/44) Maintenance of remission = 61% (20/33) Relapse = 39% (13/33) **Steroid-refractory patients (n = 20)** Remission = 45% (9/20) Clinical response = 15% (3/20) Remission of severe disease = 20% (2/10) Clinical response of severe disease = 10% (1/10) Remission of moderate disease = 70% (7/10) Clinical response of moderate disease = 20% (2/10) **Steroid-dependent patients (n=10)** Remission = 60% (6/10) Clinical response = 30% (3/10) Successful weaning from corticosteroids = 70% (7/10) **Patients who refused re-administration of steroids (n=14)** Remission = 64% (9/14) Clinical response = 21% (3/14)	Mild fever = 2% (1/44) Rash = 2% (1/44) No patient experienced a serious adverse effect	Method of patient recruitment not described. Medical treatment was not altered in the 2 weeks before start of apheresis treatment. There was no change in the dosage of immunosuppressants during treatment but the corticosteroid dosage was allowed to be tapered with improvement of symptoms. Any antidiarrhoeal drug that a patient was receiving prior to treatment could be continued, but no new therapy was permitted. Most patients received five apheresis sessions over 5 consecutive weeks. Six steroid-refractory patients with severe disease received two sessions in the first week and one a week for the next 4 weeks.

Study details	Key efficacy findings	Key safety findings	Comments
Shimoyama T (2001)[6] Case series Date of study not stated Japan 53 patients with active ulcerative colitis Inclusion criteria: patients with active ulcerative colitis Exclusion criteria: age < 12 years or > 76 years, pregnant or lactating women, hypotension (systolic blood pressure 80 mmHg or lower), hypercoagulability, severe anaemia (haemoglobin 8 g/dL or less), or any other serious illness Granulocyte and monocyte adsorptive apheresis column used: Adacolumn (Japan Immunoresearch Laboratories, Takasaki, Japan) Mean age: 30 years Follow-up: 7 weeks	Disease activity was assessed by combining clinical findings, endoscopic findings, and inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) Responders to apheresis treatment = 58.5% (31/53) Mean plasma C-reactive protein levels at baseline = 1.84 mg/dL Mean plasma C-reactive protein levels at end of treatment = 0.95 mg/dL, p = 0.019 Mean erythrocyte sedimentation rate at baseline = 24.6 mm/hour Mean erythrocyte sedimentation rate at end of treatment = 16.7 mm/hour, p = 0.004 Mean haemoglobin value at baseline = 11.1 Mean haemoglobin value at end of treatment = 11.5 Mean platelet counts (10^3/μl) at baseline = 328 Mean platelet counts (10^3/μl) at end of treatment = 292, p = 0.003 Mean daily dose of corticosteroid medication reduced from 24.4 mg at baseline to 14.2 mg at week 7 Mean stool frequency reduced from 7.8 times/day at baseline to 3.6 times/day at week 7, p = 0.0001 Bloody stool at baseline = 84.9% (45/53) Bloody stool at week 7 = 31.6% (12/38)	8 non-severe adverse events were observed in 5 (9%) patients during the study period: • dizziness = 3.8% (2/53) • flushing = 3.8% (2/53) • fever = 3.8% (2/53) • nausea = 1.9% (1/53) • duodenal perforation = 1.9% (1/53)	Method of patient recruitment not described. Corticosteroid therapy was continued during the study, the dose varied according to severity of disease. The number of patients in the trial declined over time because of remission, treatment with medication not indicated in study protocol, or the patient chose to withdraw. The study protocol aimed to treat each patient with one session per week for 5 consecutive weeks. The response to apheresis was better in patients with severe or long duration of ulcerative colitis, and those with a long period of steroid therapy. The authors conclude that granulocyte and monocyte adsorption apheresis could be a useful adjunct to therapy after failure of conventional treatments in patients with active and steroid-resistant ulcerative colitis.

Study details	Key efficacy findings	Key safety findings	Comments
Kohgo K (2002)[7] Case series 1998–1999 Japan 50 patients with ulcerative colitis Inclusion criteria: patients with steroid-refractory active ulcerative colitis, recurrent active disease during steroid tapering, history of repeated steroid administration with a total accumulated dose of 5000 mg prednisolone, or presence of severe adverse effects of steroid administration Exclusion criteria: concurrent systemic infection, heart disease, renal failure, hypotension (systolic blood pressure less than 80 mm Hg), anaemia (haemoglobin less than 9 g/dL), or fulminant disease with impending megacolon, perforation, or massive bleeding Leukocytes removed using centrifugation separation apparatus: Component Collection System (Haemonetics, Braintree, MA, USA) Mean age: 33.5 years Follow-up not reported	Disease activity was assessed by recording changes in symptoms (presence of bloody stool and abdominal pain), bowel habit, body temperature and heart rate. Luminal disease activity was assessed by sigmoidoscopic observations and histological examination within 2 weeks before and after the study period Clinical remission or response = 74% (37/50) After the first apheresis treatment, average stool frequency began to decrease significantly ($p = 0.0002$) Statistically significant improvement in C-reactive protein after 3rd week of treatment ($p = 0.0069$) Bowel movements < 4 times/day after 5 weeks = 68.4% (26/38) C-reactive protein within normal range in patients with an initial level > 0.3 mg/ml = 56.7% (17/30) Histological improvement of inflammation = 54.1% (20/37) Mean haemoglobin concentration decreased slightly but significantly during the study period ($p < 0.0001$)	• Vasovagal reactions = 4% (2/50) • Transient facial or perioral paraesthesia = 14% (7/50) • Progression of anaemia = 8% (4/50)	Study was conducted at 14 centres. Method of patient recruitment not described. Apheresis was performed once a week for 5 weeks. Patients with severely active disease were given an additional session in the first week. Some patients also received additional treatments after 5 weeks, at the doctor's discretion. Analysis was done on an intent-to-treat basis.

Study details	Key efficacy findings	Key safety findings	Comments
Sakata H (2003)[8] Case series 1997–2003 Japan 51 patients with ulcerative colitis Inclusion criteria: patients with active ulcerative colitis who had failed to respond to conventional therapy. Leukapheresis column used: Finecell filter (Asahi Medical Co., Tokyo, Japan) Median age: 38 years (range 13 to 74 years) Follow-up not reported	Main outcomes were based on Rachmilewitz clinical activity index (CAI) and colonoscopic findings. Complete remission was defined as improvement in both CAI and colonoscopic findings Complete remission after first session of remission induction therapy = 64.7% (33/51) Improvement in CAI score only after first session of remission induction therapy = 17.6% (9/51) No change after first session of remission induction therapy = 17.6% (9/51) Mean CAI score at entry to study = 9.2 Mean CAI score after remission induction therapy = 0.2, $p < 0.05$ Relapse during maintenance therapy after initial complete remission = 30.3% (10/33)	No safety data were reported	Eleven patients were excluded from the study because they responded to conventional therapy. 78% (40/51) of patients had previously received steroid therapy. Remission induction therapy was carried out twice a week for 4 to 8 weeks. Maintenance therapy was done once a week for 4 weeks, depending on the patient's condition.

Abbreviations used: CAI = clinical activity index, EI = endoscopic index, DAI = disease activity index

Validity and generalisability of the studies

- The studies varied with regard to inclusion criteria. Five studies included patients with ulcerative colitis and only one study included patients with Crohn's disease.[3] Three studies were restricted to patients with moderately severe or severe ulcerative colitis.[2,4,5] One study included only patients who had failed to respond to conventional therapy.[8]
- Patients were not blinded to treatment in either of the randomised controlled trials.[2,3]
- One randomised controlled trial was very small.[3] This study was stopped prematurely because many patients refused to participate.
- The follow-up for most of the studies was either short or not stated. The three studies that did specify a follow-up period beyond 3 months all reported that a proportion of patients had relapsed during this period.[3,4,5]
- The primary outcome measure of one study was the recurrence rate after successful steroid weaning.[3] The other studies used a combination of clinical indices and endoscopic findings to assess remission or clinical response.
- Different clinical activity indices were used among studies and it is difficult to make comparisons. One study reported results according to two different schemes for measuring clinical activity. [2]
- Anaemia was described as an adverse effect in two studies. In a different study, patients were specifically treated with folic acid and intravenous iron after each apheresis session to prevent this outcome.

Specialist advisors' opinions

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

- The procedure is novel and of uncertain safety and efficacy in the treatment of inflammatory bowel disease.
- The same technique is established practice for a number of other diseases.
- The procedure is widely used in Japan.
- There are several techniques available to perform apheresis.
- More randomised controlled data are needed to compare the efficacy with standard therapy and to confirm whether patients respond to repeated sessions of apheresis.
- There are more data on patients with ulcerative colitis than Crohn's disease.
- The procedure is likely to be carried out in specialist units.

Issues for consideration by IPAC

None other than those described above.

References

1 Carter MJ, Lobo AJ, Travis SPL. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2004; 53: v1–16.

2 Sawada K, Muto T, Shimoyama, et al. Multicenter randomized controlled trial for the treatment of ulcerative colitis with a leukapheresis column. *Current Pharmaceutical Design* 2003; 9: 307–21.

3 Lerebours E, Bussel A, Modigliani R, et al. Treatment of Crohn's disease by lymphocyte apheresis: a randomized controlled trial. *Gastroenterology* 1994; 107: 357–61.

4 Hanai H, Watanabe F, Takeuchi K, et al. Leukocyte adsorptive apheresis for the treatment of active ulcerative colitis: a prospective, uncontrolled, pilot study. *Clinical Gastroenterology and Hepatology* 2003; 1: 28– 35.

5 Naganuma M, Funakoshi S, Sakuraba A, et al. Granulopheresis is useful as an alternative therapy in patients with steroid-refractory or -dependent ulcerative colitis. *Inflammatory Bowel Disease* 2004; 10: 251– 7.

6 Shimoyama T, Sawada K, Hiwatashi N, et al. Safety and efficacy of granulocyte and monocyte adsorption apheresis in patients with active ulcerative colitis: a multicenter study. *Journal of Clinical Apheresis* 2001; 16: 1–9.

7 Kohgo Y, Hibi H, Chiba T, et al. Leukocyte apheresis using a centrifugal cell separator in refractory ulcerative colitis: a multicenter open label trial. *Therapeutic Apheresis* 2002; 6: 255–60.

8 Sakata H, Kawamura N, Horie T, et al. Successful treatment of ulcerative colitis with leukapheresis using non-woven polyester filter. *Therapeutic Apheresis and Dialysis* 2003; 7: 536–9.

Appendix A: Additional papers on white cell apheresis for inflammatory bowel disease not included in the summary tables

Article title	Number of patients/ follow-up	Comments	Direction of conclusions
Ayabe T, Ashida T, Kohgo Y. Centrifugal leukocyte apheresis for ulcerative colitis. *Therapeutic Apheresis* 1998; 2: 125–8.	23 patients	Case series Ulcerative colitis (steroid resistant)	78% (18/23) of patients in remission.
Bicks RO, Groshart KD. Editorial: The current status of T-lymphocyte apheresis (TLA) treatment of Crohn's disease. *Journal of Clinical Gastroenterology* 1989; 11: 136–8.	54 patients	Case series Crohn's disease	94% (51/54) remission.
Ikeda Y, Akbar F, Matsui H, et al. Depletion and decreased function of antigen-presenting dendritic cells caused by lymphopheresis in ulcerative colitis. *Diseases of the Colon and Rectum* 2003; 46: 521–8.	5 patients	Case series Ulcerative colitis	Procedure was safe and caused clinical, endoscopic and histological improvements in all patients.
Nagase K, Sawada K, Ohnishi K, et al. Complications of leukapheresis. *Therapeutic Apheresis* 1998; 2: 120–124.	92 patients	60 ulcerative colitis, 17 Crohn's disease, 15 other conditions.	Side effects in 10% (195/1978) of sessions (51% [47/92] of patients). 'Moderate' reactions in 2% (31/1978) sessions (16% [15/92] of patients).
Sasaki M, Tsujikawa T, Fujiyama Y, et al. Leukapheresis therapy for severe ulcerative colitis. *Therapeutic Apheresis* 1998; 2: 101–4.	9 patients	Case series Ulcerative colitis	67% (6/9) of patients improved, 33% (3/9) in remission.
Suzuki Y, Yoshimura N, Saniabadi AR, et al. Selective granulocyte and monocyte adsorptive apheresis as a first-line treatment for steroid naïve patients with active ulcerative colitis: a prospective uncontrolled study. *Digestive Diseases & Sciences* 2004; 49: 565–71.	20 patients 8 month follow-up	Case series Ulcerative colitis	85% (17/20) of patients in remission. 60% maintained remission at 8m. Significant falls in C-reactive protein.
Tomomasa T, Kobayashi A, Kaneko H, et al. Granulocyte adsorptive apheresis for pediatric patients with ulcerative colitis. *Digestive Diseases & Sciences* 2003; 48: 750–4.	12 patients 23 month follow-up	Children Case series Ulcerative colitis	67% (8/12) of patients in remission. 33% (4/12) relapsed.

Appendix B: Literature search for white cell apheresis for inflammatory bowel disease

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in EMBASE, Current Contents, PreMedline and all EMB databases.

For all other databases a simple search strategy using the key words in the title was employed.

1. apheresis.mp. or Blood Component Removal/
2. Inflammatory Bowel Diseases/
3. Crohn Disease/
4. Colitis, Ulcerative/
5. 3 or 4
6. 2 or 5
7. 1 and 6