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Systematic Review: Granulocyte / Monocyte Adsorptive Apheresis for Ulcerative Colitis

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► **To cite this version:**

Sangeetha Thanaraj, P John Hamlin, Alexander Ford. Systematic Review: Granulocyte / Monocyte Adsorptive Apheresis for Ulcerative Colitis. *Alimentary Pharmacology and Therapeutics*, 2010, 32 (11-12), pp.1297. 10.1111/j.1365-2036.2010.04490.x . hal-00585782

HAL Id: hal-00585782

<https://hal.science/hal-00585782>

Submitted on 14 Apr 2011

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**Systematic Review: Granulocyte / Monocyte Adsorptive
Apheresis for Ulcerative Colitis**

Journal:	<i>Alimentary Pharmacology & Therapeutics</i>
Manuscript ID:	APT-0795-2010.R1
Wiley - Manuscript type:	Systematic Review
Date Submitted by the Author:	30-Sep-2010
Complete List of Authors:	Thanaraj, Sangeetha; Leeds General Infirmary, Leeds Gastroenterology Institute Hamlin, P; Leeds General Infirmary, Leeds Gastroenterology Institute Ford, Alexander; Leeds General Infirmary, Leeds Gastroenterology Institute
Keywords:	Inflammatory bowel disease < Disease-based, Large intestine < Organ-based, Devices < Topics, Inflammation < Topics

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Title: Systematic Review: Granulocyte / Monocyte Adsorptive Apheresis for
Ulcerative Colitis

Short running head: Granulocyte monocyte apheresis for UC

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Abbreviations:

5-ASA	5-aminosalicylic acid
GI	gastrointestinal
GMAA	granulocyte/monocyte adsorptive apheresis
MeSH	medical subject heading
NS	not significant
RCT	randomised controlled trial
UC	ulcerative colitis

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Keywords:

ulcerative colitis

blood component removal

granulocyte

monocyte

Word count:

4079

For Peer Review

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SUMMARY

Background: Patients with ulcerative colitis (UC) that is chronically active despite 5-aminosalicylates or immunomodulators, or who are dependent on corticosteroids to maintain remission, have limited treatment options. Granulocyte/monocyte adsorptive apheresis (GMAA) may have a role in this situation.

Aim: To conduct a systematic review of GMAA in UC.

Methods: MEDLINE, EMBASE, and the Cochrane central register of controlled trials were searched to identify randomised controlled trials (RCTs) comparing GMAA with conventional medical therapy, sham procedure, or “intensive” with “conventional” GMAA regimens in adult UC patients. Studies reported clinical remission or response rates.

Results: Ten RCTs were eligible. **Formal meta-analysis was not undertaken due to concerns about methodological quality of identified studies.** Compared with medical therapy, remission rates with GMAA were generally higher, and corticosteroid-sparing effects were observed. Compared with sham procedure, GMAA did not achieve significantly higher remission rates. “Intensive” GMAA regimens demonstrated generally higher remission rates, and time to remission was shorter compared with “conventional” regimens. Only two RCTs were at low risk of bias. Six were conducted in Japanese patients, which may limit generalisability.

Conclusions: GMAA appears of some benefit in UC. High-quality RCTs comparing GMAA with conventional medical therapy or sham procedure in Western populations, **with disease activity confirmed endoscopically**, are required.

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INTRODUCTION

Ulcerative colitis (UC) is an inflammatory disorder of the gastrointestinal (GI) tract, of unknown aetiology. It causes continuous inflammation affecting the rectum, and usually a variable extent of the colon. The condition is relatively common, with an incidence of 7 to 9 per 100,000 people,^{1, 2} and a prevalence of between 200 and 250 per 100,000 people.¹⁻³ It is a lifelong disease, whose natural history is characterised by a relapsing and remitting course, leading to chronic symptoms that affect quality of life and ability to function.^{4, 5}

As the precise aetiology of UC remains unknown, curative therapy is not possible. However, there are pharmacological agents that are of proven benefit for the condition. Both corticosteroids and 5-aminosalicylic acids (5-ASAs) are more effective than placebo in inducing remission of flare ups of disease activity.⁶⁻⁸ In addition, 5-ASAs and immunosuppressant drugs, such as azathioprine, reduce the risk of subsequent relapse of activity in quiescent disease.⁹⁻¹² Despite this, a proportion of sufferers will go on to develop disease that is resistant to conventional medical therapies, and become corticosteroid-dependent.^{13, 14} These individuals may ultimately require panproctocolectomy, with either end ileostomy or ileal pouch anal anastomosis (IPAA) formation.

However, surgery for UC that is not responsive to conventional medical therapy is not without morbidity, and may carry a mortality in excess of 2%,¹⁵ and quality of life outcomes in patients undergoing IPAA surgery are variable.¹⁶ In addition, surgery may not be suitable for all patients, due to either co-morbidities that make such an approach high-risk, or because individual patients do not find this treatment option acceptable. In this situation the clinician is left with a difficult

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3 decision to make. Long-term corticosteroid use is clearly not desirable, due to the
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5 potentially severe side-effects associated with these drugs, and infliximab, a
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7 monoclonal antibody to tumour necrosis factor- α , is not approved for use in subacute
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9 manifestations of UC by the National Institute for Health and Clinical Excellence in
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11 the UK.¹⁷ Therefore, alternative medical therapies are required, both to reduce the
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13 potential for adverse events associated with long-term corticosteroid use, and to
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15 provide non-surgical alternatives for such patients.
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20 Whilst the exact factors that cause UC are incompletely understood, they are
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22 likely to include environmental triggers in a genetically susceptible individual,
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24 leading to a dysregulation of the immune system of the GI tract. Leukocytes,
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26 including granulocytes and monocytes, are recruited into the GI mucosa in UC,¹⁸ and
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28 have the potential to initiate and amplify inflammation by releasing a cascade of pro-
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30 inflammatory cytokines, proteases, and oxygen derivatives, leading to extensive tissue
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32 injury. These observations have led to the use of granulocyte / monocyte adsorptive
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34 apheresis (GMAA), a technique that removes such activated cells from the peripheral
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36 blood.¹⁹ There have been numerous studies published in the literature that have
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38 reported the efficacy of this technique in patients with UC,²⁰⁻²² but only a limited
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40 number of randomised controlled trials (RCTs). We have performed a systematic
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42 review of RCTs to assess the efficacy of GMAA in the treatment of UC.
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MATERIALS AND METHODS

Search Strategy and Study Selection

A search of the medical literature was conducted using MEDLINE (1950 to August 2010), EMBASE (1946 to August 2010), and the Cochrane central register of controlled trials. Randomised controlled trials examining the efficacy of GMAA in adult patients (> 90% over 16 years of age) with active or corticosteroid-dependent UC were eligible for inclusion. The control arms of these trials were required to receive any of conventional medical therapy, sham apheresis procedure, or an alternative regimen using an active GMAA column. Trials that permitted other concomitant therapies were eligible, as long as these were administered to both the intervention and control arms. The primary outcome studied was remission of disease activity. Secondary outcomes, where reported, included response to therapy, if remission rates were not described, effect of GMAA on endoscopic healing and quality of life, evidence of any corticosteroid-sparing effects, and adverse events arising as a result of GMAA.

Studies of GMAA in UC were identified with the terms *ulcerative colitis*, *inflammatory bowel disease*, *proctitis*, or *colitis* (both as medical subject headings (MeSH) and free text terms). These were combined using the set operator AND with studies identified with the terms: *blood component removal*, *leukapheresis*, *monocytes*, or *granulocytes* (both as MeSH and free text terms), or *granulocyte apheresis*, *monocyte apheresis*, or *adacolumn* (as free text terms).

Abstracts of the papers identified by the initial search were evaluated by the lead investigator for appropriateness to the study question. All potentially relevant papers were obtained and evaluated in detail. The bibliographies of all identified

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3 relevant studies were used to perform a recursive search of the literature. Articles
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5 were assessed independently by two investigators using pre-designed eligibility
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7 forms, according to the eligibility criteria stated previously. Any disagreement
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9 between investigators was resolved by discussion with a third investigator.
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12 13 14 15 **Data Extraction**

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17 All data were extracted independently by two investigators on to a Microsoft
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19 Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as
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21 dichotomous outcomes (i.e. remission / response or failure of remission / response). In
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23 addition, the following clinical data were extracted for each trial, where available:
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25 number of centres, country of origin, geographical region, UC characteristics (severity
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27 of UC activity, presence of corticosteroid-dependence or resistance), schedule of
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29 GMAA used, duration of therapy, primary outcome measure used to define remission
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31 or response following therapy, and duration of follow-up.
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39 **Assessment of Risk of Bias**

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41 This was performed independently by two investigators, with disagreements
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43 resolved by discussion with a third investigator. Risk of bias was assessed as
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45 described in the Cochrane handbook,²³ by recording the method used to generate the
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47 randomization schedule, the method used to conceal allocation, whether blinding was
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49 implemented, what proportion of patients completed follow-up, whether an intention-
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51 to-treat analysis was extractable, and whether there was evidence of selective
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53 reporting of outcomes.
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RESULTS

The search strategy identified a total of 1729 citations, 16 of which appeared to be relevant to the study question, and were therefore retrieved and evaluated in more detail (Figure 1). Nine articles,²⁴⁻³² reporting the results of ten separate RCTs, were eligible for inclusion in the systematic review. **We did not perform a formal meta-analysis due to concerns about the high risk of bias among the RCTs we identified.**

Individual trial characteristics are provided in Table 1. Four trials compared GMAA with conventional medical therapy,^{24, 25, 31, 32} two separate trials (reported in a single article) compared GMAA with sham apheresis,²⁶ and four trials compared “intensive” versus “conventional” GMAA regimens.²⁷⁻³⁰ Only two trials were at low-risk of bias according to our assessment.²⁶ Six studies were conducted entirely in Japan,^{24, 25, 27, 28, 31, 32} two in Europe,^{29, 30} one in the USA and Canada,²⁶ and one in both Europe and Japan.²⁶ Eight of the trials reported remission rates,²⁴⁻³⁰ while the remaining two reported response rates to therapy.^{31, 32} Six RCTs performed a true intention-to-treat analysis, with dropouts assumed to be treatment failures.^{24-26, 28, 31}

Efficacy of GMAA compared with conventional medical therapy in achieving remission or response in UC

We identified four trials making this comparison, all of which were conducted in Japanese centres.^{24, 25, 31, 32} The first,³² published in 1999, randomised 120 patients with UC in equal numbers to receive either five GMAA sessions over 5 weeks or standard medical therapy with corticosteroids. Follow-up was for 7 weeks and 105 patients completed the trial. The authors reported that 31 (58.5%) of 53 patients assigned to GMAA column responded, compared with 23 (44.2%) of 52 allocated to

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3 standard medical therapy ($P = 0.045$). Corticosteroid-sparing effects and adverse
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5 events data were not reported.
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8 In a smaller study, Hanai and colleagues recruited 69 patients with
9
10 corticosteroid-dependent UC.²⁴ The active intervention was 11 sessions of GMAA
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12 given over 10 weeks, while the control arm received a mean dose of 30mg/day of oral
13
14 prednisolone. The primary outcome reported by the authors was clinical remission,
15
16 defined using a clinical activity index of ≤ 4 and a visible mucosal vascular pattern at
17
18 endoscopy. Data were also collected concerning any corticosteroid-sparing effects of
19
20 GMAA therapy, cumulative corticosteroid doses, and mean corticosteroid dose at last
21
22 point of follow-up of the trial, which was 24 weeks. Remission occurred in 39
23
24 (84.8%) of 46 allocated to GMAA, compared with 16 (69.6%) of 23 randomised to
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26 corticosteroids ($P =$ not significant). Overall, 10 (21.7%) of the apheresis patients
27
28 were corticosteroid-free at 24 weeks, compared with 3 (13.0%) of those receiving
29
30 prednisolone ($P =$ not significant). Cumulative corticosteroid doses were significantly
31
32 lower at the end of treatment in the GMAA patients ($P = 0.001$), and mean
33
34 corticosteroid dose was also significantly lower ($P = 0.003$). Adverse events were
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36 reported by 10 patients receiving GMAA, with flushing in six patients. Adverse
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38 events among those assigned to corticosteroids were not reported.
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46 Nakamura and colleagues recruited 20 patients with active UC,³¹ all of whom
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48 were receiving corticosteroids at study commencement, and randomised them in equal
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50 numbers to either GMAA or conventional medical therapy with corticosteroids. They
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52 used a combination of clinical symptoms, endoscopic appearance, and inflammatory
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54 markers to define response to therapy. There was a response rate of 80.0% in the
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56 GMAA arm of the trial, compared with 20.0% in the conventional treatment patients
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58 ($P < 0.05$), and the proportion of patients reporting blood in the stools after
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completion of therapy was significantly lower in those receiving GMAA (10.0% versus 70.0%, $P < 0.01$). Corticosteroid-sparing effects and adverse event rates were not reported by the authors.

The most recent RCT making this comparison was conducted at 5 centres in Japan.²⁵ The investigators randomised 70 patients with severely active UC, most of whom were receiving 5-ASAs in combination with low-dose prednisolone, to receive either twice-weekly GMAA for 3 weeks followed by weekly GMAA, up to a maximum of 11 sessions in total, or intravenous prednisolone at a dose of 40 to 60mg/day for 5 to 10 days, followed by tapered oral prednisolone. Corticosteroid-dependent patients in both treatment arms also received mercaptopurine. Follow-up was at 12 weeks, and the primary outcome measure was clinical remission, defined using a clinical activity index of ≤ 4 . The authors also reported the numbers of patients achieving a corticosteroid-free remission, and adverse events rates. Overall, 26 (74.3%) of 35 in the GMAA arm achieved remission, compared with 16 (48.6%) of 35 receiving prednisolone ($P = 0.02$). In addition, 27 (77.1%) of the GMAA patients were corticosteroid-free at 12 weeks, compared with 5 (14.3%) of the patients receiving prednisolone ($P = 0.008$). Finally, only 5 (14.3%) GMAA patients reported adverse events, compared with 29 (64.4%) of those receiving corticosteroids.

Efficacy of GMAA compared with sham procedure in achieving remission of UC

There were two RCTs comparing GMAA with a sham apheresis procedure, reported in a single article.²⁶ The larger of these two trials was conducted in the USA and Canada, and recruited 168 patients with moderate to severely active UC who were already receiving treatment with at least one of 5-ASA, corticosteroids, azathioprine, or mercaptopurine. Participants were treated for 9 weeks, and the primary outcome of

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3 interest was the number of individuals achieving clinical remission, defined using a
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5 Mayo score of 2 or less, at 12 weeks post-randomisation. Secondary outcome
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8 measures included endoscopic remission, and change in quality of life from baseline.
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10 Overall, 19 (17.0%) of 112 patients were in clinical remission at 12 weeks with
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12 GMAA compared with 6 (10.7%) of 56 receiving the sham apheresis procedure (P =
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14 0.36). The proportion of patients achieving endoscopic remission was very similar in
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16 both treatment arms (12% versus 11%, P = 1.0). The smaller trial was of identical
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18 design, and recruited 47 UC patients from 11 European and 1 Japanese centre.
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20 Clinical remission occurred in 5 (16.1%) of 31 and 3 (18.8%) of 16 in the GMAA and
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22 sham apheresis arms respectively. Changes in quality of life scores from baseline
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24 were not reported in detail, but were said to be comparable between active
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26 intervention and control patients in both trials. Serious adverse events were reported
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28 in 14% of all GMAA and 11% of all sham apheresis patients.
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35 Given the perhaps unexpected finding that GMAA was not significantly
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37 superior to sham apheresis in achieving clinical remission in active UC, the authors
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39 conducted a subgroup analysis, which included only the 63 patients with histological
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41 evidence of mucosal erosions or ulceration at baseline. Clinical remission was
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43 achieved in 11 (24%) of the 46 of these individuals who received GMAA versus 0
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45 (0%) of the 17 randomised to sham apheresis (P = 0.03). **These data suggest that**
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47 **GMAA is of benefit in patients with confirmed endoscopically active disease, and that**
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49 **the treatment effect may have been diluted by the inclusion of patients with much**
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51 **milder disease, or perhaps even functional symptoms.**
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3 **Efficacy of “intensive” GMAA regimens compared with “conventional” GMAA**
4 **regimens in achieving remission of UC**
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8 There were four RCTs that compared “intensive” GMAA regimens with
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10 “conventional” regimens.²⁷⁻³⁰ Ricart *et al.* randomised 20 UC patients with
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12 moderately active disease, all of whom were corticosteroid-dependent, to either 10
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14 apheresis sessions over 10 weeks, or five sessions over 5 weeks.²⁹ The primary
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16 outcome was clinical remission, according to a clinical activity index of ≤ 4 , at week
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18 17. Corticosteroid requirements and quality of life were also recorded. In total, 19
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20 patients completed the study. In the “intensive” arm, 5 (45.5%) of 11 were in
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22 remission, compared with 3 (37.5%) of 8 in the “conventional” arm. All those who
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24 achieved clinical remission were also in endoscopic remission, and all but one of
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26 these patients were corticosteroid-free at week 17. Quality of life scores improved
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28 from baseline in both groups, but these differences were not statistically significant.
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34 There were no serious adverse events observed in either arm of the trial.
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37 In a small Japanese RCT conducted at a single centre,²⁸ 30 patients with
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39 moderately active UC, 50% of whom were corticosteroid-dependent, were
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41 randomised to “intensive” GMAA, consisting of three sessions per week for 2 weeks
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43 followed by one session for 4 weeks, or “conventional” GMAA with 10 weekly
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45 sessions. The primary endpoint was remission 1 week after the end of therapy (7
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47 weeks follow-up for the “intensive” arm, versus 11 weeks for the “conventional”),
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49 defined using a clinical activity index of ≤ 4 , as well as time (in days) to remission.
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52 Changes in quality of life, corticosteroid dose, and endoscopic scores were also
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54 reported. Overall, 12 (80.0%) of 15 in the “intensive” GMAA arm were in remission,
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56 compared with 10 (66.7%) of 15 in the “conventional” GMAA arm, but this
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58 difference was not statistically significant ($P = 0.25$). However, time to remission was
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3 significantly lower in those in the “intensive arm” (10.7 days versus 27.2 days, $P =$
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5 0.04). Again, there was no significant difference observed in quality of life scores,
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7 and there were no significant differences in endoscopic scores between the two arms.
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9 Corticosteroid doses were significantly lower at the end of treatment, compared with
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11 baseline, in both arms ($P = 0.03$ for both). There were four adverse events observed,
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13 two in each group.
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17 A multi-centre Japanese RCT compared twice-weekly with weekly GMAA,
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19 up to a maximum of 10 sessions, in 163 UC patients with mildly to moderately active
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21 disease.²⁷ The primary outcome measure was clinical remission, again defined using
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23 a clinical activity index of ≤ 4 , at 5 weeks in the “intensive” arm and 10 weeks in the
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25 “conventional” arm. Time to remission was also compared between the two treatment
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27 regimens. In total, 149 patients provided analysable data at study end. The remission
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29 rate was higher in the “intensive” therapy arm of the trial, 71.2% (52 of 73) versus
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31 54.0% (41 of 76) in the “conventional” arm ($P = 0.03$), and time to remission was
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33 significantly lower in the “intensive” therapy arm (14.9 days versus 28.1 days, $P <$
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35 0.001). Adverse events occurred in similar numbers of patients in each arm of the trial
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37 (17 in “intensive” versus 14 in “conventional”), but none were serious.
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44 The largest RCT, to date, to compare “intensive” with “conventional” GMAA
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46 was conducted in 42 centres in Europe and recruited 186 patients with moderately to
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48 severely active corticosteroid-dependent or resistant UC.³⁰ The “intensive” arm
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50 received twice-weekly apheresis for 2 weeks followed by a further six sessions over 6
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52 weeks. In the “conventional” arm GMAA was administered weekly for 5 weeks. All
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54 patients were already receiving treatment with one or more of 5-ASA, corticosteroids,
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56 azathioprine, or mercaptopurine, unless previous intolerance or non-response to these
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58 drugs had been demonstrated. The primary outcome of interest was clinical remission
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3 at 12 weeks, according to a clinical activity index ≤ 4 , with 162 patients providing
4 data for this analysis. Time to remission and endoscopic activity were also reported.
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6 Remission rates in the two arms were almost identical (43.9% (36 of 82 patients) with
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8 “intensive” versus 40.0% (32 of 80 patients) with “conventional”), and there was no
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10 statistically significant difference observed in terms of time to remission (39.9 days
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12 versus 46.8 days) or in endoscopic activity. Overall, 6% of the “intensive” therapy
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14 arm and 9% of the “conventional” arm experienced a serious adverse event.
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For Peer Review

DISCUSSION

This systematic review has collected all available published RCT evidence examining the effects of GMAA in both active and corticosteroid-dependent or resistant UC. Compared with conventional medical therapy, in the form of corticosteroids, GMAA appeared superior in several respects. Remission rates in excess of 70% were achieved with GMAA in patients with severely active UC,²⁵ which were significantly higher than those achieved with conventional medical therapy. In corticosteroid-dependent UC, rates of remission with GMAA were as high as 85%.²⁴ There was also evidence for corticosteroid-sparing effects with GMAA, with significantly lower cumulative doses of corticosteroid,²⁴ and significantly higher rates of corticosteroid-free remission in patients allocated to GMAA.²⁵ In addition, adverse event rates were significantly higher in patients assigned to conventional medical therapy.²⁵ Compared with a sham apheresis procedure in patients with moderately to severely active UC,²⁶ GMAA did not achieve significantly higher rates of clinical or endoscopic remission, and adverse events rates were comparable. However, when only individuals with evidence of mucosal erosions or ulceration at baseline histological examination were considered in the analysis, significantly higher remission rates were observed with GMAA. In terms of “intensive” GMAA regimens versus “conventional” regimens, available data were conflicting. Three trials suggested that “intensive” regimens were associated with generally higher rates of remission,²⁷⁻²⁹ and time to achievement of remission was significantly shorter in two RCTs recruiting patients with mildly to moderately active UC.^{27,28} However, the largest RCT to date demonstrated almost identical remission rates with “intensive” and “conventional” regimens in corticosteroid-dependent patients with moderately to

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severely active disease, and no statistically significant difference in the time to remission.³⁰ The effect of GMAA on quality of life was not studied in many of the eligible RCTs but, where reported, there appeared to be no significant benefit of GMAA over conventional medical therapy, sham apheresis procedure, or between the various “intensive” and “conventional” regimens.

Strengths of our study include our rigorous methodology. We described our search strategy, eligibility criteria, and data extraction processes in detail. In addition, independent data extraction was undertaken by two reviewers, and discrepancies were checked and resolved. Finally, the majority of the trials we identified used a validated definition of remission as a clinical endpoint, rather than response to therapy, which we believe is a more clinically useful outcome to the physician who is considering GMAA as a treatment option in a patient with chronic active or corticosteroid-dependent UC who is unsuitable for, or refuses, surgery.

Limitations of the present study, as with any systematic review and meta-analysis, arise from the quality of the trials included. Only two of the ten eligible and included RCTs were at low risk of bias,²⁶ and most trials did not report either the method used to generate the randomisation list, or whether allocation to treatment was concealed. In addition, only three trials reported that investigators were blinded to the assigned therapy.^{25, 26} It has been well-described in the systematic review literature that RCTs that do not adhere to such reporting of their methodology, and trials that are not blinded, tend to overestimate the treatment effect associated with the active intervention.³³ Only six trials reported data using a true intention-to-treat analysis.^{24-26, 28, 31} Again, this may have led to an overestimation of the success rates with active therapy. A final limitation is the fact that six of the ten RCTs were conducted in Japan, meaning that their results may not be generalisable to a Western population,

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3 due to potential underlying differences in patient characteristics, genetics, or
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5 environment.
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8 There has been one previous systematic review to our knowledge, to date, that
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10 has examined the efficacy of GMAA in UC.³⁴ In contrast to the current study, the
11
12 authors felt it appropriate to perform a meta-analysis. They reported a statistically
13
14 significant benefit of GMAA over control therapy, defined using either response to
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16 therapy or clinical remission, with a number needed to treat of 5, and concluded that
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18 homogeneous evidence from seven RCTs uniformly indicated that GMAA was more
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20 successful than drug therapy in achieving response and remission. There are **some**
21
22 **limitations of** this meta-analysis that we have discussed elsewhere,³⁵ **including**
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24 **pooling of** data from RCTs regardless of the control intervention, and **the inclusion of**
25
26 **a pseudo-randomised study in the analysis,**³⁷ a type of study design that is liable to
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28 selection bias. **In addition,** the largest RCT that they identified showed no significant
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30 effect of GMAA on remission or response.²⁶ **There was also statistically significant**
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32 **heterogeneity between studies,**³⁶ **perhaps due to underlying differences in the GMAA**
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34 **regimens used in the various trials.**
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41 Data from the current study demonstrate some evidence for a benefit of
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43 GMAA over conventional medical therapy, in patients with either active or
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45 corticosteroid-dependent UC, in terms of clinical remission, corticosteroid-sparing
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47 effects, and reduced adverse events rates, but no trial to date making this comparison
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49 has been conducted in a Western population. The only study to compare GMAA with
50
51 a sham apheresis procedure, conducted in both Western and Japanese patients, failed
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53 to demonstrate any significant increase in remission rates with GMAA. The authors
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55 speculated that their patient population may have differed from those in previous trials
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60 in terms of disease activity, and that GMAA may only be effective in patients with

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3 severe histological activity, an assertion supported by their *post hoc* analysis
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5 discussed in detail earlier. There seems to be little to choose between various GMAA
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7 regimens in terms of clinical remission rates, though time to remission may be shorter
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9 with a more “intensive” regimen. Adverse events were no higher with GMAA in most
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11 studies, and serious adverse events were rare, suggesting it is a safe treatment option.
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13 Finally, data to support any beneficial effect of GMAA on quality of life are sparse.
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17 Taken together these data tell us that, rather than designing future RCTs to
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19 examine the potential benefit of one GMAA regimen over another, what is actually
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21 required are convincing high-quality data that GMAA is effective in Western patients
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23 with UC. Trials comparing GMAA with conventional medical therapy in
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25 corticosteroid-dependent patients are needed to demonstrate that the results from
26
27 Japanese trials are reproducible. In addition, further rigorous RCTs, of similar design
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29 to that of Sands *et al.*,²⁶ should compare GMAA with sham apheresis in patients with
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31 histological evidence of active disease. One potential niche for GMAA is in patients
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33 with chronic subacute UC refractory to, or intolerant of, 5-ASAs or
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35 immunomodulators, who are corticosteroid-dependent, but who do not have acute
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37 severe disease, and who are therefore unsuitable for either infliximab or ciclosporin.
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39 The only other treatment option at present for this type of patient is surgery, which
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41 may not be suitable, or desirable, for all individuals. Therefore studies that compare
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43 quality of life in patients in this situation who receive GMAA or panproctocolectomy,
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45 followed by either end ileostomy or IPAA, would also be of great interest to both
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47 patients and physicians.
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56 In summary, this systematic review has demonstrated some evidence for a
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58 beneficial effect of GMAA in active or corticosteroid-dependent UC, in terms of both
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60 clinical remission rates and corticosteroid-sparing effects, but more data from trials

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3 conducted in Western patients **with endoscopic evidence of active disease** are required
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6 before its true place in the management of UC is known.
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10 STATEMENTS OF INTEREST

11 12 13 14 15 **Authors' Declaration of Personal Interests:**

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19
20 Sangeetha Thanaraj: none declared. P. John Hamlin: has participated in an advisory
21
22 board for Otsuka Pharmaceuticals. Alexander C. Ford: none declared.
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27 **Declaration of Funding Interests:**

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32 None.
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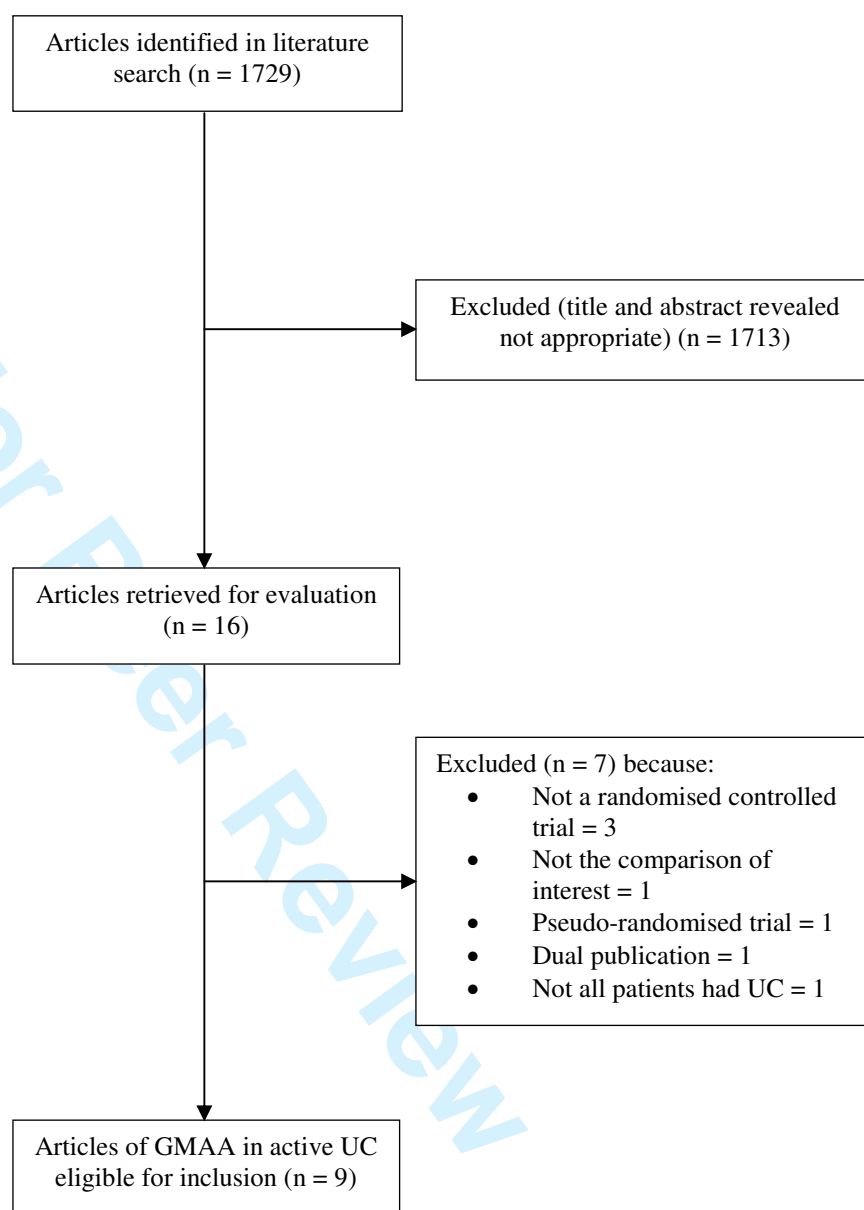
Figure 1. Flow Diagram of Assessment of Studies Identified in the Systematic**Review.**

Table 1. Characteristics of Randomized Controlled Trials of Granulocyte / Monocyte Adsorptive Apheresis in Active or Corticosteroid-dependent UC.

Study and year	Country, setting, and number of centres	Criteria used to define remission or response	Participants	Duration of follow-up	Active intervention and control intervention	Number responding or in remission with active intervention (%)	Number responding or in remission with control intervention (%)	P value reported for the difference in proportions	Methodology
Shimoyama 1999 ³²	Japan, secondary and tertiary care, 14 sites	Clinical symptoms, endoscopic findings, and inflammatory markers	120 patients with moderately to severely active UC	7 weeks	5 apheresis sessions over 5 weeks versus standard medical therapy with corticosteroids	31/53 (58.5)	23/52 (44.2)	0.045	Randomisation and concealment unclear, unblinded

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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16	Hanai 2004 24	Japan, secondary and tertiary care, 7 sites	Clinical activity index \leq 4 and visible mucosal vascular pattern	69 patients with corticosteroid- dependent UC	24 weeks	11 apheresis sessions over 10 weeks versus oral prednisolone (mean dose of 30mg/day)	39/46 (84.8)	16/23 (69.6)	NS	Randomisation, concealment, and blinding unclear
17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47	Nakamura 2004 ³¹	Japan, secondary and tertiary care, 3 sites	Clinical symptoms, endoscopic findings, and inflammatory markers	20 patients with corticosteroid- dependent UC	6 weeks	5 apheresis sessions over 5 weeks versus standard medical therapy with corticosteroids	8/10 (80.0)	2/10 (20.0)	< 0.05	Randomisation, concealment, and blinding unclear

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26	Hanai 2008 ²⁵	Japan, secondary and tertiary care, 5 sites	Clinical activity index \leq 4	70 patients with severely active UC	12 weeks	Twice weekly apheresis sessions for 3 weeks, then up to 5 further apheresis sessions versus intravenous prednisolone (40- 60mg/day) for 5 to 10 days, then tapered oral prednisolone	26/35 (74.3)	16/35 (48.6)	0.02	Randomisation and concealment unclear, investigator- blinded
27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47	Sands 2008a ²⁶	USA and Canada, tertiary care, 36 sites	Mayo score of ≤ 2 , with a score of 0 for rectal bleeding and ≤ 1 for endoscopic activity	168 patients with moderately to severely active UC	12 weeks	10 apheresis sessions over 9 weeks versus 10 sham apheresis sessions over 9 weeks	19/112 (17.0)	6/56 (10.7)	NS	Randomisation and concealment stated, double- blind

Sands 2008b ²⁶	Europe and Japan, tertiary care, 12 sites	Mayo score of ≤ 2 , with a score of 0 for rectal bleeding and ≤ 1 for endoscopic activity	47 patients with moderately to severely active UC	12 weeks	10 apheresis sessions over 9 weeks versus 10 sham apheresis sessions over 9 weeks	5/31 (16.1)	3/16 (18.8)	NS	Randomisation and concealment stated, double- blind
Ricart 2007 ²⁹	Spain, secondary and tertiary care, 5 sites	Clinical activity index \leq 4	20 patients with moderately active corticosteroid- dependent UC	17 weeks	10 apheresis sessions over 10 weeks versus 5 apheresis sessions over 5 weeks	5/11 (54.5)	3/8 (37.5)	NS	Randomisation and concealment unclear, unblinded

For Peer Review

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20	Sakuraba 2008 ²⁸	Japan, tertiary care, 1 site	Clinical activity index \leq 4	30 patients with moderately active UC	7 weeks intervention, 11 weeks control	3 apheresis sessions per week over 2 weeks, then 4 apheresis sessions over 4 weeks versus 10 apheresis sessions over 10 weeks	12/15 (80.0)	10/15 (66.7)	NS	Randomisation and concealment unclear, unblinded
21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47	Sakuraba 2009 ²⁷	Japan, secondary and tertiary care, 24 sites	Clinical activity index \leq 4	163 patients with mildly to moderately active UC	5 weeks intervention, 10 weeks control	2 apheresis sessions per week over 5 weeks versus 10 apheresis sessions over 10 weeks	52/73 (71.2)	41/76 (54.0)	0.03	Randomisation stated, concealment unclear, unblinded

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Dignass 2010 ³⁰	Europe, secondary and tertiary care, 42 sites	Clinical activity index \leq 4	186 patients with moderately to severely active corticosteroid- dependent or resistant UC	12 weeks	2 apheresis sessions per week over 2 weeks, then 6 apheresis sessions over 6 weeks versus 5 apheresis sessions over 5 weeks	36/82 (43.9)	32/80 (40.0)	NS	Randomisation stated, concealment unclear, unblinded
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NS; not significant

For Peer Review

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2 for each meta-analysis).	N/A

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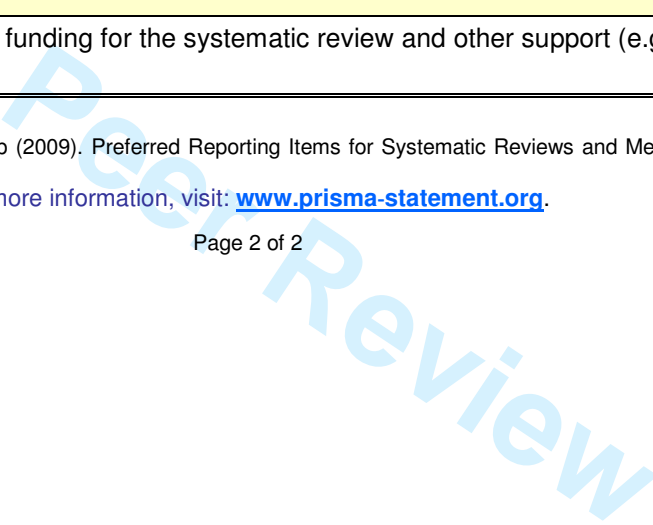
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8 and 26
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	27-32
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	27-32
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8, 27-32
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A

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DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.



EDITOR'S COMMENTS TO AUTHOR:

Please address the reviewers' comments. My personal opinion is that more might be made of the point that the Sands study showed a positive effect of apheresis in patients with greater mucosal ulceration and that future studies should not only be sham controlled but should take care to exclude patients who do not have mucosal ulceration.

We agreed with the editor. We added text to a sentence to the Conclusions section of the Abstract on page 3: "High-quality RCTs comparing GMAA with conventional medical therapy or sham procedure in Western populations, with disease activity confirmed endoscopically, are required."

We added text to the reporting of data from the Sands study in the Results section on page 11: "These data suggest that GMAA is of benefit in patients with confirmed endoscopically active disease, and that the treatment effect may have been diluted by the inclusion of patients with much milder disease, or perhaps even functional symptoms."

We altered a sentence in the Discussion section on pages 17 to 18 to read: "The authors speculated that their patient population may have differed from those in previous trials in terms of disease activity, and that GMAA may only be effective in patients with severe histological activity, an assertion supported by their *post hoc* analysis discussed in detail earlier."

We added text to the final paragraph of the Discussion section on pages 18 and 19, such that it now reads: "In summary, this systematic review has demonstrated some evidence for a beneficial effect of GMAA in active or corticosteroid-dependent UC,

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3 in terms of both clinical remission rates and corticosteroid-sparing effects, but more
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5 data from trials conducted in Western patients with endoscopic evidence of active
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7 disease are required before its true place in the management of UC is known.”
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10 11 12 **REVIEWERS' COMMENTS TO AUTHOR:**

13 14 15 **Reviewer: 1**

16 17 **Comments for Transmission to the Authors**

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20 **This is a descriptive systematic review article on the therapeutic value of**
21
22 **selective granulocyte, monocyte adsorptive apheresis with the Adacolumn device**
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24 **in ulcerative colitis. This review is purely descriptive and no attempt was made**
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26 **to perform a meta-analysis or estimate the size of the effect.**
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34 No response required.
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39 **Major Points:**

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41 **1.It is the authors contention that the available studies are not of sufficient**
42
43 **quality to perform a meta-analysis. Without any statistical tool to objectively**
44
45 **make an assessment of the size of the effect they can merely summarize each**
46
47 **study and let the reader decide on the relative merits of each study. There is a**
48
49 **table of all the studies reviewed but it does not contain just about the most useful**
50
51 **thing: the actual results! The authors must summarise the results in a table for**
52
53 **the readers to make that value judgement. What is the value of reproducing the**
54
55 **PRISMA statement? That could be left out and the trial results, OR and P values**
56
57 **put in.**
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3 We agreed with the reviewer that this was an oversight on our part, and thank them
4
5 for pointing this out. We reported the absolute numbers responding to therapy or in
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7 remission, proportions, and P values reported for these differences in each arm in
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9
10 Table 1 on pages 27 to 32.

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12 The PRISMA statement is required to be submitted online by the journal, which was
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14 our reason for providing it. We apologise if the reviewer was confused as to why this
15
16 had been submitted.
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19 We do not report odds ratios as we did not perform a meta-analysis due to underlying
20
21 differences in study design.
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27 **2.A peer-reviewed meta-analysis have already been published (1). This paper is**
28
29 **imperfect but I think the authors' criticism of it is harsh. Their statistical**
30
31 **analysis is sound and their overall conclusion seems fair. While I agree that there**
32
33 **is considerable heterogeneity in trial design, most of the trials are intervention vs**
34
35 **non-intervention (or sham). The published studies are varied, tend to be small**
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37 **and exactly the scenario to perform a meta-analysis in my view.**
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43 We tempered our criticism of the aforementioned published meta-analysis in the
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45 Discussion section on page 17 to read: “There are some limitations of this meta-
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47 analysis that we have discussed elsewhere,³⁵ including pooling of data from RCTs
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49 regardless of the control intervention, and the inclusion of a pseudo-randomised study
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51 in the analysis,³⁷ a type of study design that is liable to selection bias. In addition, the
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53 largest RCT that they identified showed no significant effect of GMAA on remission
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55 or response.²⁶ There was also statistically significant heterogeneity between studies,
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60 ³⁶ perhaps due to subtle differences in the GMAA regimens used in the various trials.”

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3 **3.The authors have identified 10 RCT. They remark that concealment was “not**
4 **stated” in the non-sham studies, and these studies were rejected as having “risk**
5 **of bias”. Non-sham studies can at best be single-blinded. If they are still unclear**
6 **if the physician is blinded, did the authors attempt to ask the trial authors? (in**
7 **an email age it would be slothful not to).**
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18 We did not reject any studies from the systematic review, but rather reported the
19 findings of each faithfully. We merely pointed out the limitations of the studies as
20 reported in the original publications.
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24 We are confused by the reviewer’s comment. Blinding and concealment of allocation
25 are two separate issues. As the reviewer correctly states, it is not possible to blind
26 patients in a non-sham study as to whether or not they received GMAA or
27 conventional medical therapy. However, in non-sham studies it would still be possible
28 to report whether or not treatment allocation (the order in which treatments were
29 assigned to patients) was concealed. If treatment allocation is not concealed in an
30 RCT, the randomisation process can be subverted (advertently or inadvertently) by the
31 physician who is recruiting patients making (conscious or unconscious) decisions as
32 to whether or not to include a patient in the trial on the basis of their disease
33 characteristics, if he / she knows which therapy is due to be assigned to the next
34 recruited patient.
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50 Only two non-sham studies did not report blinding of physicians. We attempted to
51 obtain information in both cases, but received no response from the authors.
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58 **4.Having rejected these studies, the only admissible study is the Sands study.**
59 **Here the authors conclusions are confused. If they are as rigorous as they claim**
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3 and reject all “risk-of-bias” studies then they only have the Sands study as
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5 admissible for evaluation. Hence their conclusion should be “ There is
6
7 insufficient evidence that GMAA is of any benefit in the treatment of ulcerative
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9 colitis” Instead their statement is: “Remission rates in excess of 70% were
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11 achieved with GMAA in patients with severely active UC,
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13 which were significantly higher than those achieved with conventional medical
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15 therapy. In corticosteroid-dependent UC, rates of remission with GMAA were as
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17 high as 85%.” which is baffling.
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24 Again, we were confused by the reviewer’s comment. We did not reject any studies
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26 from the systematic review, but reported the results of each faithfully in the text (and
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28 Table 1) of the article.
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34 **5. The Sands study (2) itself may be underestimating the true effect of GMAA**
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36 **since only 63/168 (36%) had histological evidence of mucosal inflammation. If a**
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38 **large number of non-inflamed “colitis” patients were recruited this would**
39
40 **dilute the effect of an anti-inflammatory intervention. If the Japanese studies**
41
42 **were overstating the case for GMAA, it could be argued that the Sands study is**
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44 **equally flawed in the opposite direction. This is where a meta-analysis would be**
45
46 **useful in estimating “true” effect size.**
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53 We agreed with the reviewer. The editor also asked us to address this issue. Please see
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55 our response to the editor’s comments above.
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3 **Other Errors:**
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8 **There are other erroneous statements:**
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10 **Pg. 17**“If this trial were to be included at all, it should also have been excluded in
11 **a sensitivity analysis to assess its impact on the bottom-line result of the meta-**
12 **analysis.” No. You either include the study or exclude it both in the meta-**
13 **analysis and results, you cannot pick and choose.**
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22 This part of the text has been removed from the article in line with the reviewer’s
23 second major point above.
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29 **Pg 18** “Data from the current study demonstrate some evidence for a benefit of
30 **GMAA over conventional medical therapy, in patients with either active or**
31 **corticosteroid-dependent UC, in terms of clinical remission, corticosteroid-**
32 **sparing effects, and reduced adverse events rates, but no trial to date making this**
33 **comparison has been conducted in a Western population.” This is at best a**
34 **confusing statement at worse plainly wrong. The Sands study is largely in N**
35 **American populations and compares intervention vs sham, the latter group had**
36 **“conventional medical therapy” except that sham therapy was included to make**
37 **it double-blind.**
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53 We are again unclear as to what the reviewer means by this comment. The Sands
54 study was not a comparison of GMAA with conventional medical therapy, but a trial
55 of GMAA versus sham procedure in UC patients with active disease who were
56 already receiving conventional medical therapy and who had not responded to it, or
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3 were intolerant of it. All medications for UC remained unchanged during the 12
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5 weeks of the trial, so both trial arms received conventional medical therapy. We
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7 therefore left our statement unchanged as it is correct in that, to date, there has been
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9 no comparison of GMAA alone with conventional therapy alone in Western UC
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11 patients.
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17 **Reviewer: 2**

18 **Comments for Transmission to the Authors**

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20 **This is an excellent review article that describes clearly the state or art of the**
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22 **apheresis in UC.**
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29 We thank the reviewer for their kind comments. No response required.
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34 **In the abstract the statement that meta-analysis was not run could be moved into**
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36 **the results section**
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41 The reviewer makes a valid point, which we agreed with. We moved this statement to
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43 the Results section of the Abstract as the reviewer suggested. We also moved this
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45 statement from the last paragraph of the Methods section of the article itself, on page
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47 7, to the first paragraph of the Results section on page 8.
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Reviewer: 3**Comments for Transmission to the Authors**

Could there be some heterogeneity within trials because different techniques of apheresis have been used with likely different mechanisms of action?

We did not report heterogeneity between results of trials we identified in the article as we did not perform a formal meta-analysis. We presumed the reviewer referred to heterogeneity in the meta-analysis by Habermalz and Sauerland, which we had mentioned in the Discussion section. We agreed with the reviewer that this may have been an explanation for some of this heterogeneity, and added this point to our discussion of the aforementioned meta-analysis on page 17 of the Discussion section: “There was also statistically significant heterogeneity between studies,³⁶ perhaps due to underlying differences in the GMAA regimens used in the various trials.”

Peer Review