Supplemetary material

Granulocyte and monocyte apheresis as an adjunctive therapy to induce and maintain clinical remission in ulcerative colitis: A systematic review and meta-analysis

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Search strategy for MEDLINE database

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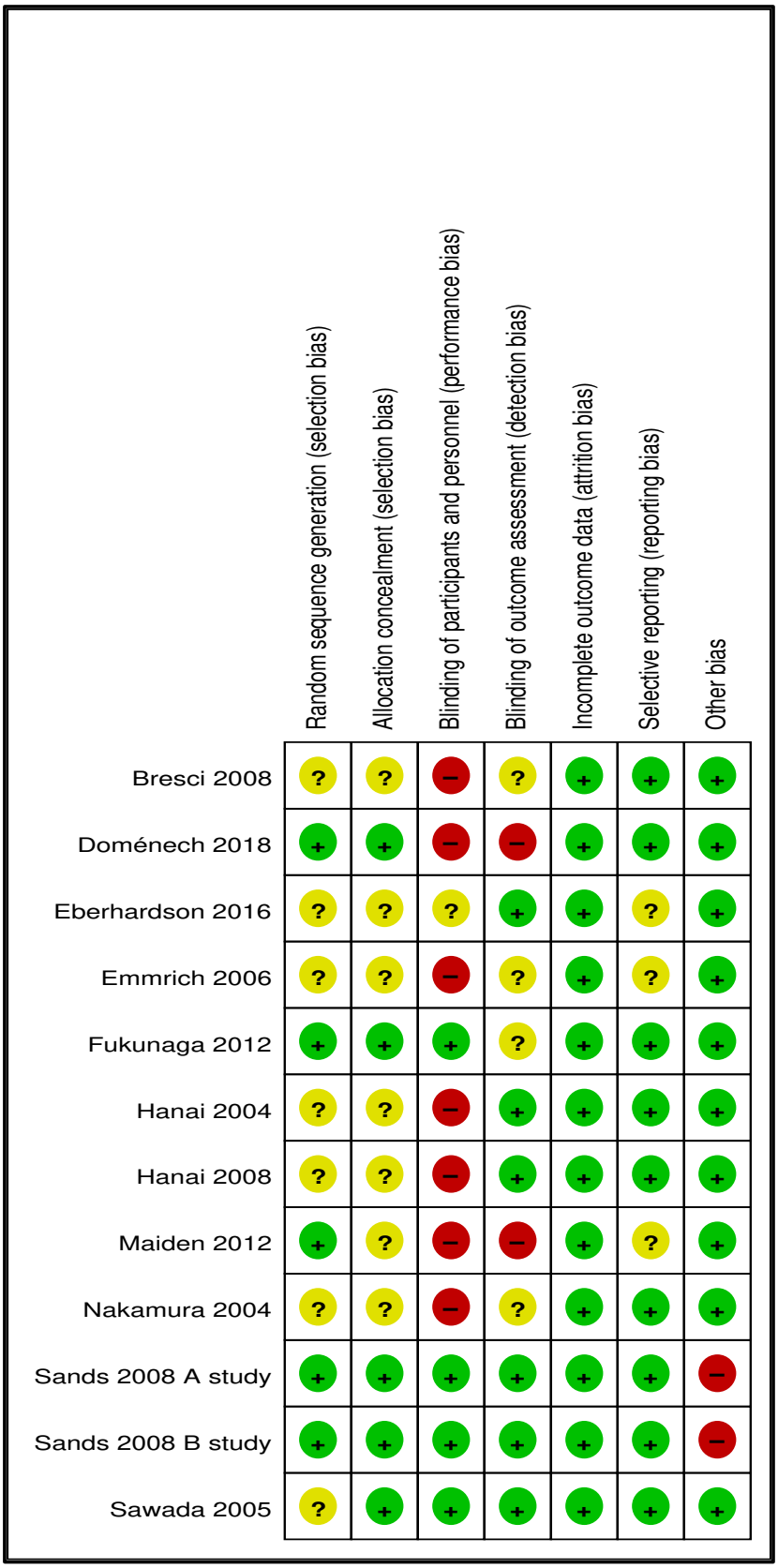
Full query: (gma OR apheresis OR adsorption OR "cell separation" OR leukapher* OR leukopher* OR leukocytapher* OR leukocytopher* OR lymphapher* OR lymphopher* OR lymphocytopher* OR lymphocytapher*) AND ("inflammatory bowel disease" OR "ulcerative colitis") AND (random*)

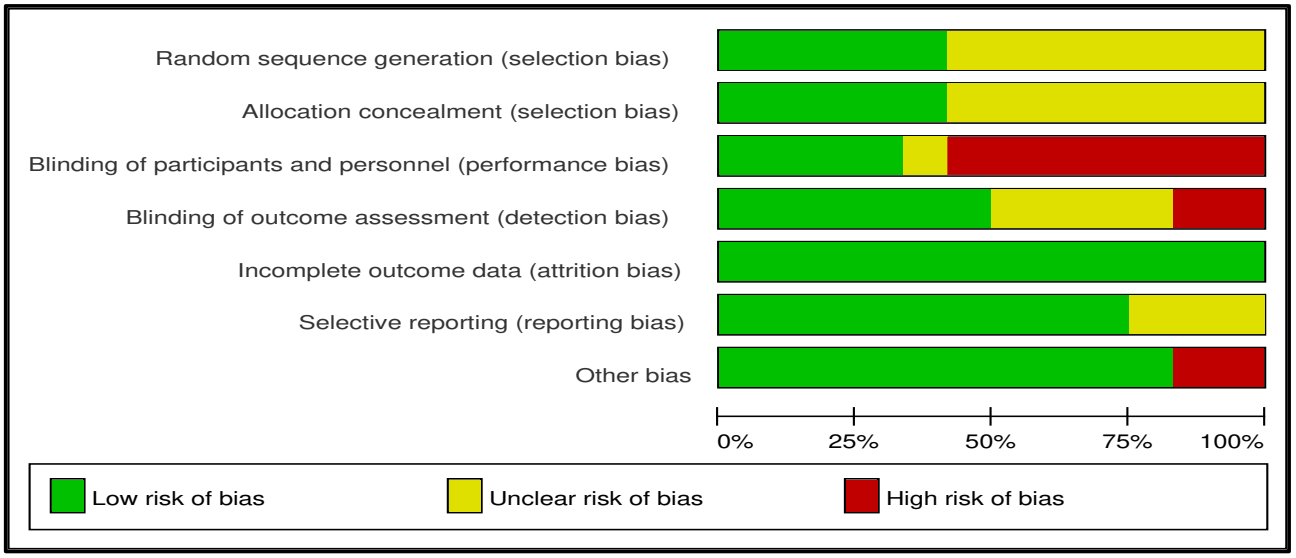
No filters or restrictions were applied.

Search	Query	Automatic explosion
#1	gma OR apheresis OR adsorption OR "cell separation" OR leukapher* OR leukopher* OR leukocytapher* OR leukocytopher* OR lymphapher* OR lymphopher* OR lymphocytopher* OR lymphocytapher*	("gma"[All Fields] OR ("blood component removal"[MeSH Terms] OR ("blood"[All Fields] AND "component"[All Fields] AND "removal"[All Fields]) OR "blood component removal"[All Fields] OR "apheresis"[All Fields]) OR ("adsorption"[MeSH Terms] OR "adsorption"[All Fields] OR "adsorptions"[All Fields] OR "adsorptive"[All Fields] OR "adsorptively"[All Fields] OR "adsorptives"[All Fields] OR "adsorptivities"[All Fields] OR "adsorptivity"[All Fields]) OR "cell separation"[All Fields] OR "leukapher*"[All Fields] OR "leukopher*"[All Fields] OR "leukocytapher*"[All Fields] OR "leukocytopher*"[All Fields] OR "lymphapher*"[All Fields] OR "lymphopher*"[All Fields] OR "lymphocytopher*"[All Fields] OR "lymphocytapher*"[All Fields]
#2	"inflammatory bowel disease" OR "ulcerative colitis"	"inflammatory bowel disease"[All Fields] OR "ulcerative colitis"[All Fields]
#3	random*	"random*"[All Fields]
#4	#1 AND #2	("gma"[All Fields] OR ("blood component removal"[MeSH Terms] OR ("blood"[All Fields] AND "component"[All Fields] AND "removal"[All Fields]) OR "blood component removal"[All Fields] OR "apheresis"[All Fields]) OR ("adsorption"[MeSH Terms] OR "adsorption"[All Fields] OR "adsorptions"[All Fields] OR "adsorptive"[All Fields] OR "adsorptively"[All Fields] OR "adsorptives"[All Fields] OR "adsorptivities"[All Fields] OR "adsorptivity"[All Fields]) OR "cell separation"[All Fields] OR "leukapher*"[All Fields] OR "leukopher*"[All Fields] OR "leukocytapher*"[All Fields] OR "leukocytopher*"[All Fields] OR "lymphapher*"[All Fields] OR "lymphopher*"[All Fields] OR "lymphocytopher*"[All Fields] OR "lymphocytapher*"[All Fields]) AND ("inflammatory bowel disease"[All Fields] OR "ulcerative colitis"[All Fields])
#5	#3 AND #4	("gma"[All Fields] OR ("blood component removal"[MeSH Terms] OR ("blood"[All Fields] AND "component"[All Fields] AND "removal"[All Fields]) OR "blood component removal"[All Fields] OR "apheresis"[All Fields]) OR ("adsorption"[MeSH Terms] OR "adsorption"[All Fields] OR "adsorptions"[All Fields] OR "adsorptive"[All Fields] OR "adsorptively"[All Fields] OR "adsorptives"[All Fields] OR "adsorptivities"[All Fields] OR "adsorptivity"[All Fields]) OR "cell separation"[All Fields] OR "leukapher*"[All Fields] OR "leukopher*"[All Fields] OR "leukocytapher*"[All Fields] OR "leukocytopher*"[All Fields] OR "lymphapher*"[All Fields] OR "lymphopher*"[All Fields] OR "lymphocytopher*"[All Fields] OR "lymphocytapher*"[All Fields]) AND ("inflammatory bowel disease"[All Fields] OR "ulcerative colitis"[All Fields]) AND "random*"[All Fields]

Supplementary Figure 1



Supplementary Figure 2



Detailed risk of bias assessment

Bresci et al. 2008	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated as randomized study, but method was not specified in the manuscript
Allocation concealment (selection bias)	Unclear risk	Not described in the manuscript.
Blinding of participants and personnel (performance bias)	High risk	Not described in the manuscript, but probably not done, because the trial compared an interventional procedure to drug treatment only.
Blinding of outcome assessment (detection bias)	Unclear risk	Not described in the manuscript.
Incomplete outcome data (attrition bias)	Low risk	Number of patients at baseline and at the end of the follow-up are the same.
Selective reporting (reporting bias)	Low risk	Both significant and non-significant data have been reported. Adverse events were adequately reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Doménech et al. 2018	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...randomizaton codes were centerally generated using a computer procedure..." Blocked randomization was used.
Allocation concealment (selection bias)	Low risk	Quote: "...randomizaton codes were centerally generated using a computer procedure..."
Blinding of participants and personnel (performance bias)	High risk.	Open-label.
Blinding of outcome assessment (detection bias)	High risk	Quote: "...the endoscopist was not necessarily blinded..."
Incomplete outcome data (attrition bias)	Low risk	Intention-to-treat method was used. 123/125 patients completed the study.
Selective reporting (reporting bias)	Low risk	Both significant and non-significant results have been reported. Adequate

		description of adverse events.
Other bias	Low risk	The study appears to be free of other sources of bias.

Eberhardson et al. 2017	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Blocked randomization (3:2), but method is fully specified.
Allocation concealment (selection bias)	Unclear risk	Not described in the manuscript.
Blinding of participants and personnel (performance bias)	Unclear risk	Double-blind, but insufficient data to permit judgement (form of placebo treatment was not described).
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The FACS analysis was blinded to the clinical participants and the FACS analyst was also blinded before unblinding day 12."
Incomplete outcome data (attrition bias)	Low risk	1/9 patient from the placebo group was excluded from the study just after the randomization because of SADE (failure to return blood from the column). 2/14 (14%) were excluded from active study group because of adverse event and worsening of the disease, but analysis was conducted on full analyses set basis.
Selective reporting (reporting bias)	Unclear risk	Report of adverse events seems to be inadequate.
Other bias	Low risk	The study appears to be free of other sources of bias.

Hanai et al. 2004	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized study, but method was not specified in the manuscript.
Allocation concealment (selection bias)	Unclear risk	Not described in the manuscript.
Blinding of participants and personnel (performance bias)	High risk	Not described in the manuscript, but other similar article from the authors was stated as unblinded.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Each patient was assessed blindly..."

Incomplete outcome data (attrition bias)	Low risk	Number of patients at baseline and at the end of the follow-up are the same.
Selective reporting (reporting bias)	Low risk	Both significant and non-significant results have been reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Hanai et al. 2008	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized study, but method is not described in the manuscript.
Allocation concealment (selection bias)	Unclear risk	Not described in the manuscript.
Blinding of participants and personnel (performance bias)	High risk	Stated as unblinded.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Each patient was assessed blindly..."
Incomplete outcome data (attrition bias)	Low risk	Number of patients at baseline and at the end of the follow-up are the same
Selective reporting (reporting bias)	Low risk	Both significant and non-significant results have been reported
Other bias	Low risk	The study appears to be free of other sources of bias.

Nakamura et al. 2004	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized, but the method was not specified in the manuscript
Allocation concealment (selection bias)	Unclear risk	Not described in the manuscript.
Blinding of participants and personnel (performance bias)	High risk	Not described in the manuscript, but probably not done, because the trial compared an interventional procedure to drug treatment only.
Blinding of outcome assessment (detection bias)	Unclear risk	No information
Incomplete outcome data (attrition bias)	Low risk	60/66 completed the study; 1 took non-permitted drugs,1 relapsed just after the randomization, further 4 withdrew the consent.

Selective reporting (reporting bias)	Low risk	Both significant and non-significant results have been reported
Other bias	Low risk	The study appears to be free of other sources of bias.

Sands et al. 2008 A study	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...using sealed envelopes with sequential numbers issued in blocks of 3..." and
Allocation concealment (selection bias)	Low risk	Quote: "...using sealed envelopes with sequential numbers issued in blocks of 3..." and
Blinding of participants and personnel (performance bias)	Low risk	Quote: "a polyvinylchloride bypass tube was inserted between the Adacolumn and the Adacircuit to permit bypass of the column among patients undergoing sham procedures."
Blinding of outcome assessment (detection bias)	Low risk	The gastroenterology team was blinded to the treatment assignment.
Incomplete outcome data (attrition bias)	Low risk	Intention-to-treat analysis; however, 66% of patients completed the study (6 patients left the study because of disease flare; 5 from apheresis group, 1 from sham group).
Selective reporting (reporting bias)	Low risk	Both significant and non-significant results have been reported
Other bias	High risk	Quote: "Subjects who withdrew before the week 12 visit were treated as treatment failure for primary end point (clinical remission)." Comment: these imputation of ITT analysis may cause bias.

Sands et al. 2008 B study	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed according to a computer-generated scheme

		that used an integrated voice response system."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed according to a computer-generated scheme that used an integrated voice response system."
Blinding of participants and personnel (performance bias)	Low risk	Quote: "a polyvinylchloride bypass tube was inserted between the Adacolumn and the Adacircuit to permit bypass of the column among patients undergoing sham procedures."
Blinding of outcome assessment (detection bias)	Low risk	The gastroenterology team was blinded to the treatment assignment.
Incomplete outcome data (attrition bias)	Low risk	Intention-to-treat analysis; however, 66% of patients completed the study (6 patients left the study because of disease flare; 5 from apheresis group, 1 from sham group).
Selective reporting (reporting bias)	Low risk	Both significant and non-significant results have been reported
Other bias	High risk	Quote: "Subjects who withdrew before the week 12 visit were treated as treatment failure for primary end point (clinical remission)." Comment: these imputation of ITT analysis may cause bias.

Sawada et al. 2005	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	minimization by an independent controller.
Allocation concealment (selection bias)	Unclear risk	Quote: “The assignment of the enrolled patients to the active group or the sham group was performed by a controller who was independent of the other staff, patients, and relatives.”
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Both columns were covered with an opaque material so that they could

		not be distinguished by the patients."
Blinding of outcome assessment (detection bias)	Low risk	Quote: "To ensure proper blinding within the clinical evaluation, the medical staffs of each institution were separated into two independent groups."
Incomplete outcome data (attrition bias)	Low risk	All of the enrolled eligible patients were evaluated.
Selective reporting (reporting bias)	Low risk	All outcomes of interest were reported.
Other bias	Low risk	The study appears to be free of other sources of bias. Comment: these imputation of ITT analysis may cause bias.

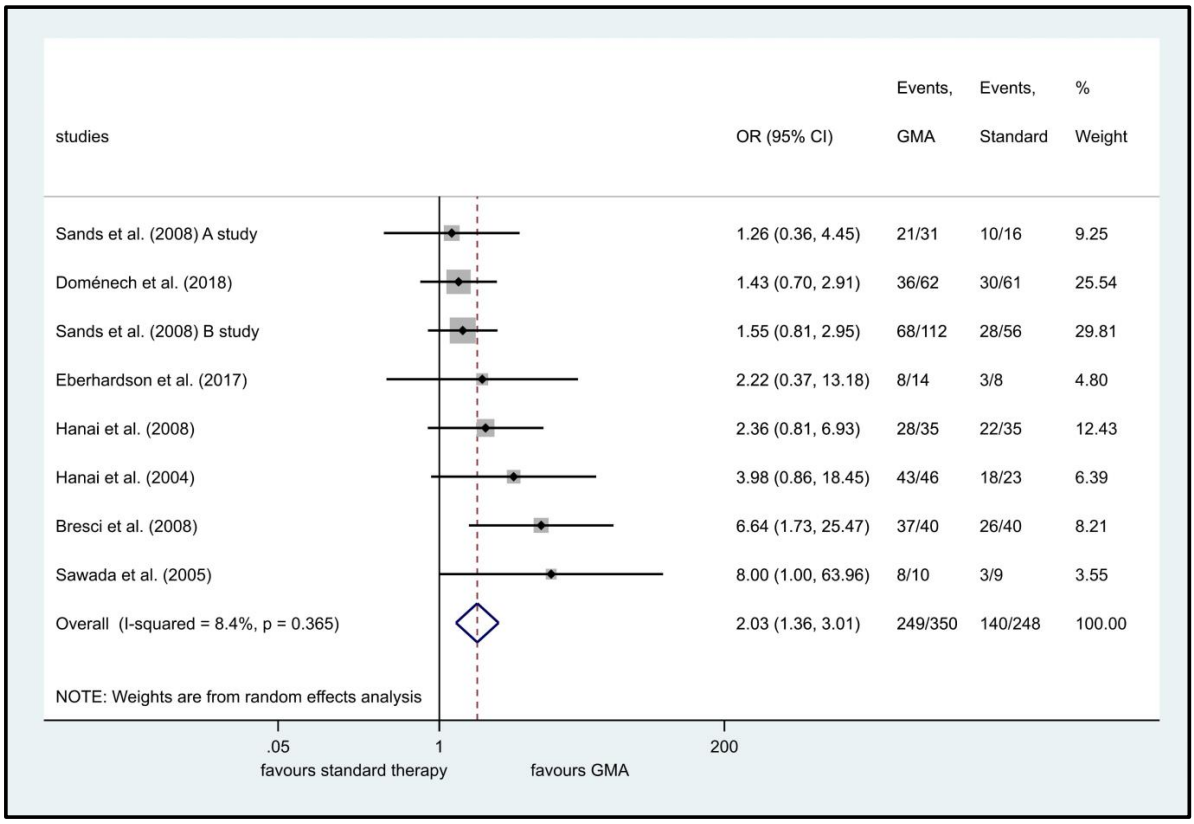
Emmrich et al. 2006	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized, but method is not specified in the manuscript.
Allocation concealment (selection bias)	Unclear risk	Not described in the manuscript.
Blinding of participants and personnel (performance bias)	High risk	Not described in the manuscript, but probably not done, because the trial compared an interventional procedure to drug treatment only.
Blinding of outcome assessment (detection bias)	Unclear risk	Not described in the manuscript.
Incomplete outcome data (attrition bias)	Low risk	Only 1/9 patient from active group discontinued the study.
Selective reporting (reporting bias)	Unclear risk	Report of adverse events seems to be inadequate.
Other bias	Low risk	The study appears to be free of other sources of bias.

Fukunaga et al. 2012	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocked randomization according to a computer-generated scheme.
Allocation concealment (selection bias)	Low risk	Patients were randomized in a 1:1:1 ratio by a statistician at an independent organization.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Both patients and the physician were blinded by a curtain."

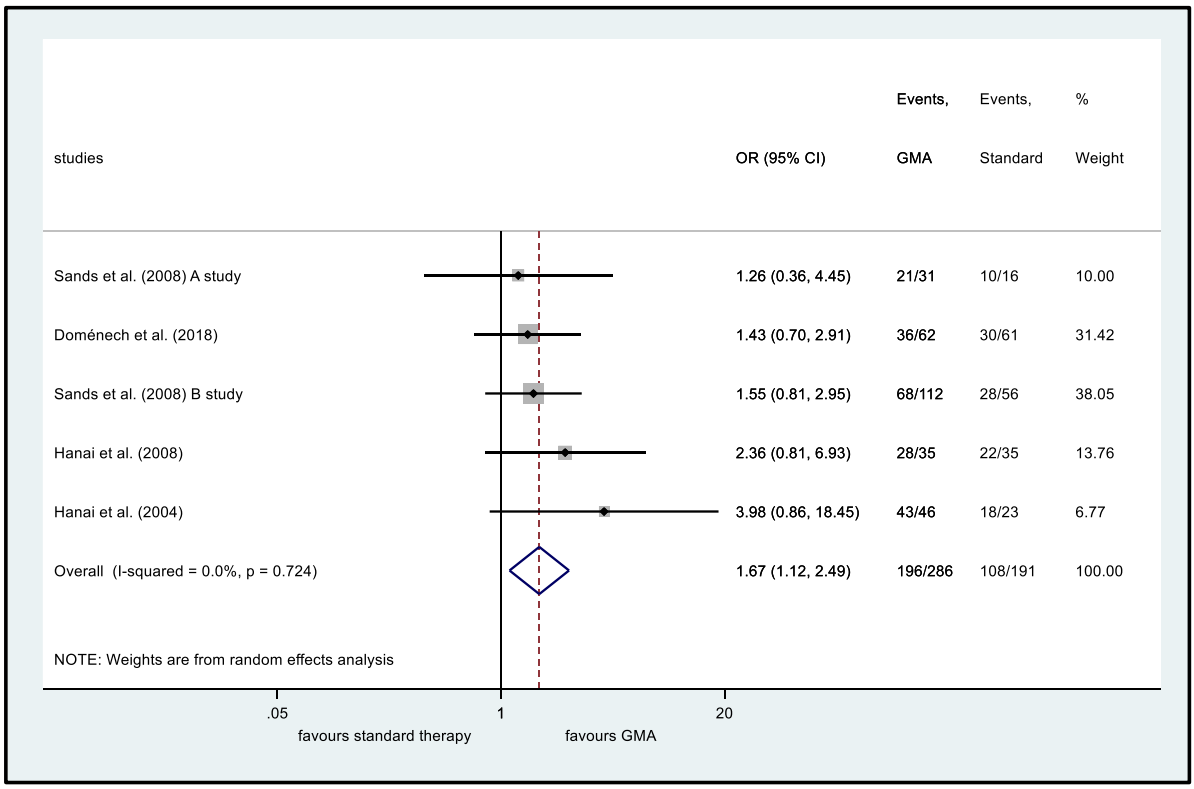
Blinding of outcome assessment (detection bias)	Unclear risk	Not described in the manuscript.
Incomplete outcome data (attrition bias)	Low risk	21/22 completed the study.
Selective reporting (reporting bias)	Low risk	Both significant and non-significant results have been reported.
Other bias	Unclear risk	Concomitant therapeutic regimen was not described clearly, and the authors stated: "a significant fraction of patients in each arm were on concomitant PSL or AZA and this enabled us to assess the contribution of these medications"

Maiden et al. 2008	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was conducted using a linear random number generator of 0 to 1."
Allocation concealment (selection bias)	Unclear risk	Not described in the manuscript.
Blinding of participants and personnel (performance bias)	High risk	Open label
Blinding of outcome assessment (detection bias)	High risk	Open label
Incomplete outcome data (attrition bias)	Low risk	Number of patients at baseline and at the end of the follow-up are the same.
Selective reporting (reporting bias)	Unclear risk	Report of adverse events seems to be inadequate. Number of events in the control group was not described.
Other bias	Low risk	The study appears to be free of other sources of bias.

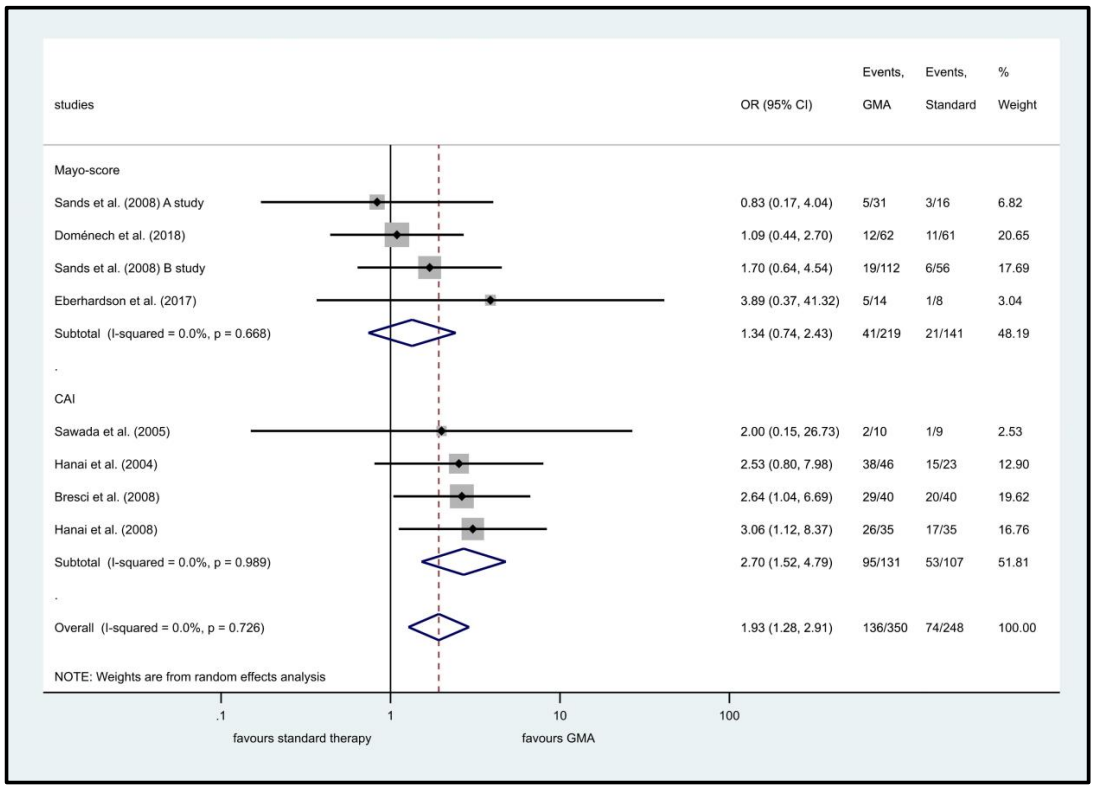
Supplementary Figure 3



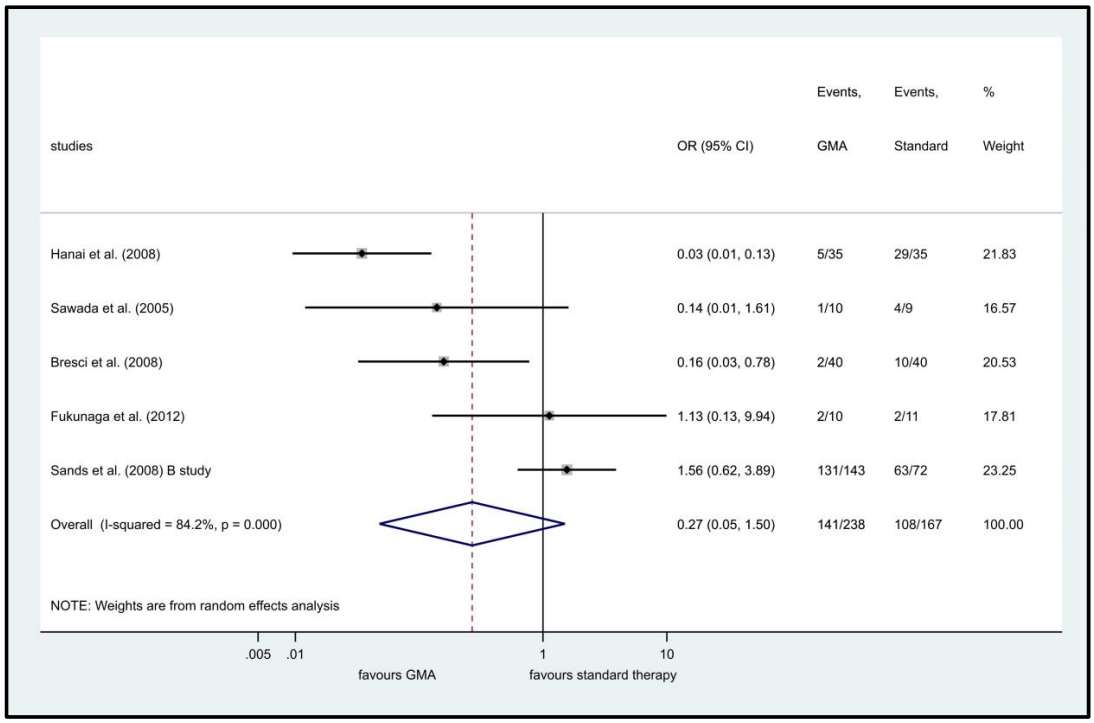
Supplementary Figure 4



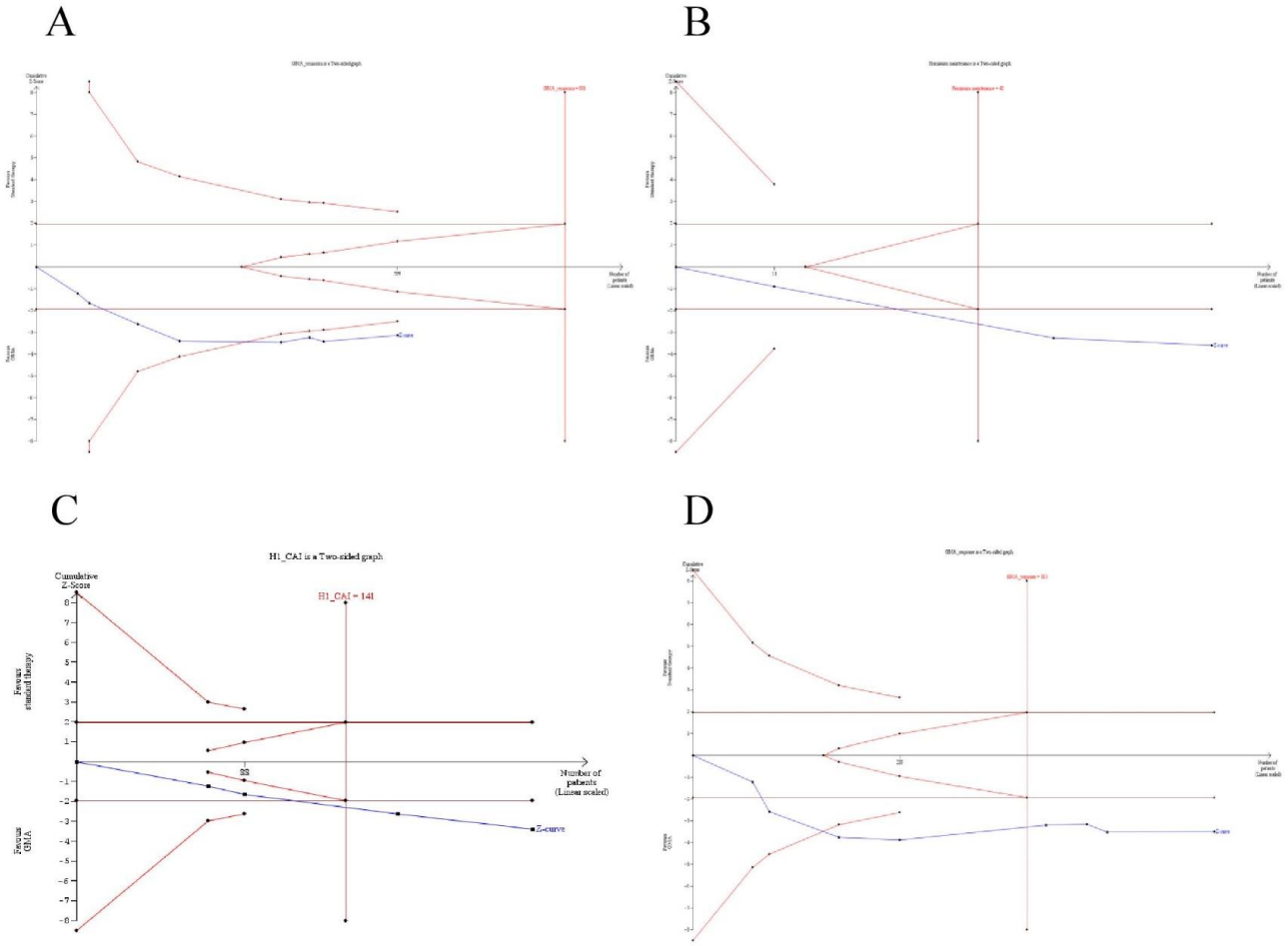
Supplementary Figure 5



Supplementary Figure 6



Supplementary Figure 7



Supplementary Table 1

Study	Reported adverse events
Hanai et al. 2004	flushing, nausea, mild fever
Sawada et al. 2005	fever, skin rash, back pain
Bresci et al. 2008	headache, gastrointestinal intolerance, facies lunaris, vascular hypertension, glucose intolerance
Fukunaga et al. 2012	nausea, skin itchiness
Sands et al. 2008	headache, disease flare-up, decreased diastolic blood pressure, nasopharyngitis, hypotension, nausea, fatigue, post procedure hematoma, abdominal pain, dizziness, vomiting, vessel puncture site bruise, diarrhea, upper respiratory tract infection, flatulence

Supplementary Table 2

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**standard therapy for clinical remission induction and GMA as an adjunctive therapy**	**standard therapy for clinical remission induction**	**Relative (95% CI)**	**Absolute (95% CI)**		
Clinical remission rate (assessed with: CAI or Mayo-score)												
8	randomized trials	very serious	not serious	not serious	serious	none	136/350 (38.9%)	74/249 (29.7%)	**OR 1.94** (1.28 to 2.92)	**153 more per 1 000** (from 54 more to 255 more)	⊕◯◯◯ VERY LOW	CRITICAL
Clinical response and clinical improvement (CAI or Mayo-score)												
8	randomized trials	very serious	not serious	not serious	not serious	none	249/350 (71.1%)	140/249 (56.2%)	**OR 2.05** (1.37 to 3.06)	**162 more per 1 000** (from 75 more to 235 more)	⊕⊕◯◯ LOW	CRITICAL
Clinical remission maintenance rate (assessed with: CAI)												
3	randomized trials	serious	not serious	serious [a]	not serious	none	39/36 (108.3%)	17/35 (48.6%)	**OR 8.34** (2.64 to 26.32)	**402 more per 1 000** (from 228 more to 476 more)	⊕⊕◯◯ LOW	CRITICAL
Adverse events												
5	randomized trials	very serious	not serious	very serious [b]	very serious [c,d]	publication bias strongly suspected	141/238 (59.2%)	108/167 (64.7%)	**OR 0.27** (0.05 to 1.50)	**316 fewer per 1 000** (from 563 fewer to 86 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Steroid-sparing effect												
3	randomized trials	serious	not serious	not serious	very serious [d]	none	66	43	-	WMD **6.83 mg/day lower** (14.47 lower to 0.81 higher)	⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Duration of follow-up differs among studies (6 months or 12 months). b. Pool of adverse events differs among studies. c. The optimal information size criterion is not met. d. TSA could not be carried out.