SUPPLEMENTARY APPENDIX

Comparison of up-front treatments for newly diagnosed immune thrombocytopenia - a systematic review and network meta-analysis

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 doi:10.3324/haematol.2017.174615

Received: June 15, 2017.

Accepted: September 27, 2017.

Pre-published: September 29, 2017

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Supplemental Methods

Data sources and searches

We conducted a literature search to identify all published and unpublished RCTs based on the search strategies suggested in *the Cochrane Handbook for Systematic Reviews of Interventions*. We performed a search of MEDLINE (via PubMed) (1950 to January 2017) and Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2016, Issue 12). The search strategies are outlined in Supplemental Tables 1 and 2. We also searched unpublished clinical trials, using ClinicalTrials.gov as well as conference proceedings of the American Society of Hematology (ASH) (2004 to 2016).

The reference lists of all the included studies and relevant systematic reviews were assessed in order to identify additional studies missed in the original electronic searches. A citation search was also conducted through Web of Science to identify articles citing any of the included studies.

Study selection

We included all relevant RCTs in all languages. We also included abstracts and unpublished data, if sufficient information on the study design, participant characteristics, interventions, and outcomes were available.

Participants could be outpatients or hospital inpatients at the time of enrollment. Any therapeutic interventions (oral, intravenous, or subcutaneous administration) were included, while rare drugs (such as local herbal medicines) were not included.

Role of the funding source

This study received no external funding.

Supplemental Figure Legends

Supplemental Figure 1 Risk of bias summary

Review authors' judgements about each risk of bias item for each included study. Green "-" means low risk, and red "+" means high risk, while yellow "?" indicates unclear risk.

Supplemental Figure 2 Results for the network of severe adverse events comparison

(**A**) The network of comparisons included in the network meta-analysis for severe adverse non-hemorrhagic events (grade 3 or more according to Common Terminology Criteria for Adverse Events version 4.0). The circle size is proportional to the total number of patients in the treatment group. The line width is proportional to the number of trials comparing the treatment groups. (**B**) The summary effect estimate (risk ratio [RR] of adverse events) for each combination of treatments. RRs are indicated by dots, and 95% confidence intervals by bars. (**C**) The surface under the cumulative ranking curve (SUCRA) is shown for each treatment.

Supplemental Figure 3 Funnel Plot of comparison

Risk ratio (RR) for long term sustained response (SR) and short term overall response (OR) and standard error of each study are plotted.

Supplemental Tables

Supplemental Table 1 MEDLINE search strategy (via PubMed)

((((((((randomized controlled trial[pt]) OR controlled clinical trial[pt]) OR randomized[tiab]) OR clinical trials as topic[mesh:noexp]) OR randomly[tiab]) OR trial[ti])) NOT ((animals[mh]) NOT humans[mh])) AND ((((Purpura, Thrombocytopenic, Idiopathic[mh]) OR ITP) OR (purpura AND thrombocytop*)) OR ((autoimmun* OR immun*) AND thrombocytop*))

Supplemental Table 2 CENTRAL search strategy

#1	MeSH descriptor Purpura, Thrombocytopenic, Idiopathic explode all trees
#2	ITP
#3	purpura near thrombocytop*
#4	(autoimmun* or immun*) near thrombocytop*
#5	#1 or #2 or #3 or #4

Supplemental Table 3 Items in data extraction sheet

GENERAL INFORMATIONS
Study ID
Year
STUDY CHARACTERISTICS
Design
Country
Randomization
No. arm
No. pt randomized (each arm)
PATIENTS CHARACTERISTICS
No. of each gender (male / female)
Age (y; median / min / max)
Ethnicity
Diagnosis / Past tx history
Platelet count at dx
Bleeding score at dx
Other complications
COMPONENTS OF THE INTERVENTION
Intervention (dosage, duration, interval, total amounts, tapering)
Additional tx (type, dosage, interval)
OUTCOMES
Early period outcome
Overall response (n; at 7, 14, 28d)
Complete response (n; at 7, 14, 28d)
Platelet counts (at 7, 14, 28d)
Late period outcome
Sustained response (n; at 6, 12, 24m after tx completion)
Relapse (n; at 6, 12, 24m after tx completion)
Platelet counts (at 6, 12, 24m after tx completion)
Total No. Pt (AE measured)
Types of AE (n, grade)
RISK OF BIAS
Random sequence generation
Allocation concealment
Blinding of participants and personnel
Blinding of outcome assessment
Incomplete outcome data (efficacy / safety)

Selective reporting
Other RoB-1 (definition / assessment)
Other RoB-2 (definition / assessment)

Supplemental Table 4 Assessment form for risk of bias

RANDOM SEQUENCE GENERATION

Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.

Criteria for a judgement of 'Low risk' of bias.	The investigators describe a random component in the sequence generation process such as: Referring to a random number table; Using a computer random number generator; Coin tossing; Shuffling cards or envelopes; Throwing dice; Drawing of lots; Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgement of 'High risk' of bias.	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: Sequence generated by odd or even date of birth; Sequence generated by some rule based on date (or day) of admission; Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: Allocation by judgement of the clinician; Allocation by preference of the participant; Allocation based on the results of a laboratory test or a series of tests; Allocation by availability of the intervention.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.

ALLOCATION CONCEALMENT

Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.

Criteria for a judgement of 'Low risk' of bias.	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: Central allocation (including telephone, web-based and pharmacy-controlled randomization); Sequentially numbered drug containers of identical appearance; Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgement of 'High risk' of bias.	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: Using an open random allocation schedule (e.g. a list of random numbers); Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); Alternation or rotation;

	Date of birth; Case record number; Any other explicitly unconcealed procedure.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

BLINDING OF PARTICIPANTS AND PERSONNEL

Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.

Criteria for a judgement of 'Low risk' of bias.	Any one of the following: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: Insufficient information to permit judgement of 'Low risk' or 'High risk'; The study did not address this outcome.

BLINDING OF OUTCOME ASSESSMENT

Detection bias due to knowledge of the allocated interventions by outcome assessors.

Criteria for a judgement of 'Low risk' of bias.	Any one of the following: No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: Insufficient information to permit judgement of 'Low risk' or 'High risk'; The study did not address this outcome.

INCOMPLETE OUTCOME DATA

Attrition bias due to amount, nature or handling of incomplete outcome data.

Criteria for a judgement of 'Low risk' of bias.	Any one of the following: No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias);

	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; Missing data have been imputed using appropriate methods.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; Potentially inappropriate application of simple imputation.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided); The study did not address this outcome.

SELECTIVE REPORTING

Reporting bias due to selective outcome reporting.

Criteria for a judgement of 'Low risk' of bias.	Any of the following: The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Criteria for the judgement of 'High risk' of bias.	Any one of the following: Not all of the study's pre-specified primary outcomes have been reported; One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category.

OTHER BIAS

Bias due to problems not covered elsewhere in the table.

Criteria for a judgement of 'Low risk' of bias.	The study appears to be free of other sources of bias.
Criteria for the judgement of 'High risk' of bias.	There is at least one important risk of bias. For example, the study: Had a potential source of bias related to the specific study design used (cluster-randomized trials and crossover randomized trials); or Had an inappropriate influence of funders due to industry-initiated protocols; or Has been claimed to have been fraudulent; or Had some other problem.
Criteria for the judgement of 'Unclear risk' of bias.	There may be a risk of bias, but there is either: Insufficient information to assess whether an important risk of bias exists; or Insufficient rationale or evidence that an identified problem will introduce bias.

Cited and Revised from *the Cochrane Handbook for Systematic Reviews of Interventions*.

Supplemental Table 5 Definition of SR, and number of patients in total and those achieving SR in each study

	definition	PSL		Dex		RTX+Dex		IVIG±PSL		PSL(LD)		RTX+Dex +PSL		RTX+PSL		mPSL± PSL		rhTPO+ Dex	
ID	*Plt* $\times 10^9/L$	SR	total	SR	total	SR	total	SR	total	SR	total	SR	total	SR	total	SR	total	SR	total
Arnold 2012	*30*	19	27											20	33				
Bae 2010	*30*	27	75	19	76														
Bellucci 1988	*100*	48	112							36	111								
Cui 2011	*30*	7	29	17	30														
Din 2015	*30*	10	29	32	61														
Godeau 2002	*50*							20	56							24	60		
Gudbrandsdottir 2013	*50*			23	71	36	62												
Jacobs 1994	*100*	5	17					3	26										
Li 2011	*50*			12	31	24	31												
Li 2013	*30*	19	49	10	45	29	44												
Mashhadi 2012	*30*	16	30	27	30														
Matschke 2016	*50*	3	9	11	13														
Sun 2016	*30*			6	29													23	30
Wei 2016	*30*	40	97	38	95														
Xing 2013	*30*					23	36					25	38						
Zaja 2010	*50*			19	52	31	49												

Abbreviations are shown in Table 1.

Supplemental Table 6 Definition of OR, and number of patients in total and those achieving OR in each study

	definition	PSL		Dex		RTX+ Dex		HP±PSL		IVIG±PSL		PSL (LD)		RTX+ Dex		mPSL+ PSL		rhTPO +Dex		rhTPO+ PSL	
ID	*Plt* $\times 10^9/L$	OR	total	OR	total	OR	total	OR	total	OR	total	OR	total	OR	total	OR	total	OR	total	OR	total
Bae 2010	*30*	62	75	52	76																
Bellucci 1988	*30*	65	112									41	111								
Cui 2011	*30*	7	29	15	30																
Din 2015	*30*	8	29	25	61																
Godeau 2002	*50*									35	56					33	60				
Gu 2013	*100*	9	31																	27	31
Gudbrandsdottir 2013	*50*			58	71	53	62														
Jacobs 1994	*50*	14	17							19	26										
Kong 2008	*50*	18	35					42	65												
Li 2011	*50*			23	31	25	31														
Li 2013	*30*	34	49	30	45	35	44														
Li 2016	*50*			17	25													21	23		
Mashhadi 2012	*30*	24	31	31	31																
Matschke 2016	*50*	8	9	11	13																
Mazzucconi 1985	*60*	24	37									21	32								
Praituan 2009	*30*	11	18	17	18																
Sun 2016	*30*			15	29													25	30		
Wei 2016	*30*	67	97	78	95																
Xing 2013	*30*					24	36							32	38						
Zaja 2010	*30*			24	52	18	49														

Abbreviations are shown in Table 1.

Supplemental Table 7. Description of severe adverse events in each study

ID	Intervention		Comparison	
	Regimen	Events (*N*)	Regimen	Events (*N*)
Arnold 2012	RTX+PSL	Serum sickness(1)/Accidental fall(1)	PSL	*Adrenal hemorrhage*(1)
Bae 2010	Dex	Hyperglycemia(6)	PSL	Hyperglycemia(5)/Pneumonia(1)/Myalgia(1)
Bellucci 1988	PSL(LD)	ND	PSL	ND
Cui 2011	Dex	none	PSL	none
Din 2015	Dex	Vomit(3)/Hypertension(1)	PSL	none
Godeau 2002	IVIG±PSL	Pulmonary embolism(1)	mPSL±PSL	Diabetes(1)/Hypertension(1)
Gu 2013	rhTPO+PSL	Myocardial infarction(1)	PSL	*Intracranial hemorrhage*(1)
Gudbrandsdottir 2013	RTX+Dex	*Hemorrhage*(2)/Pneumonia(1)/Fever(2)/Pain (1)/Dizziness(1)/Anaphylaxis(1)/Neutropenia (1)/Vasculitis(1)/Cataract(1)	Dex	*Hemorrhage*(1)/Atrial fibrillation(1)/Fever(1)/Pain(1)/Dizziness(1)/Hyper glycemia(1)/Chest pain(1)/ND(2)
Jacobs 1994	IVIG±PSL	ND	PSL	ND
Kong 2008	HP±PSL	ND	PSL	ND
Li 2011	RTX+Dex	ND	Dex	ND
Li 2013	Dex or RTX+Dex	ND	PSL	ND
Li 2016	rhTPO+Dex	none	Dex	none
Mashhadi 2012	Dex	Gastrointestinal distress(1)	PSL	Gastrointestinal distress(2)
Matschke 2016	Dex	*Petechia*(1)/Hypertension(1)	PSL	*Petechia*(2)/Hyperglycemia(1)/Hypokalemia(1)
Mazzucconi 1985	PSL(LD)	ND	PSL	ND
Praituan 2009	Dex	none	PSL	none
Sun 2016	rhTPO+Dex	none	Dex	none
Wei 2016	Dex	none	PSL	Pneumonia(1)/Hyperglycemia(1)
Xing 2013	RTX+Dex+PSL	none	RTX+Dex	none
Zaja 2010	RTX+Dex	*Hemorrhage*(1)/Supraventricular tachycardia(1)/Pneumonia(1)	Dex	Rib fracture(1)

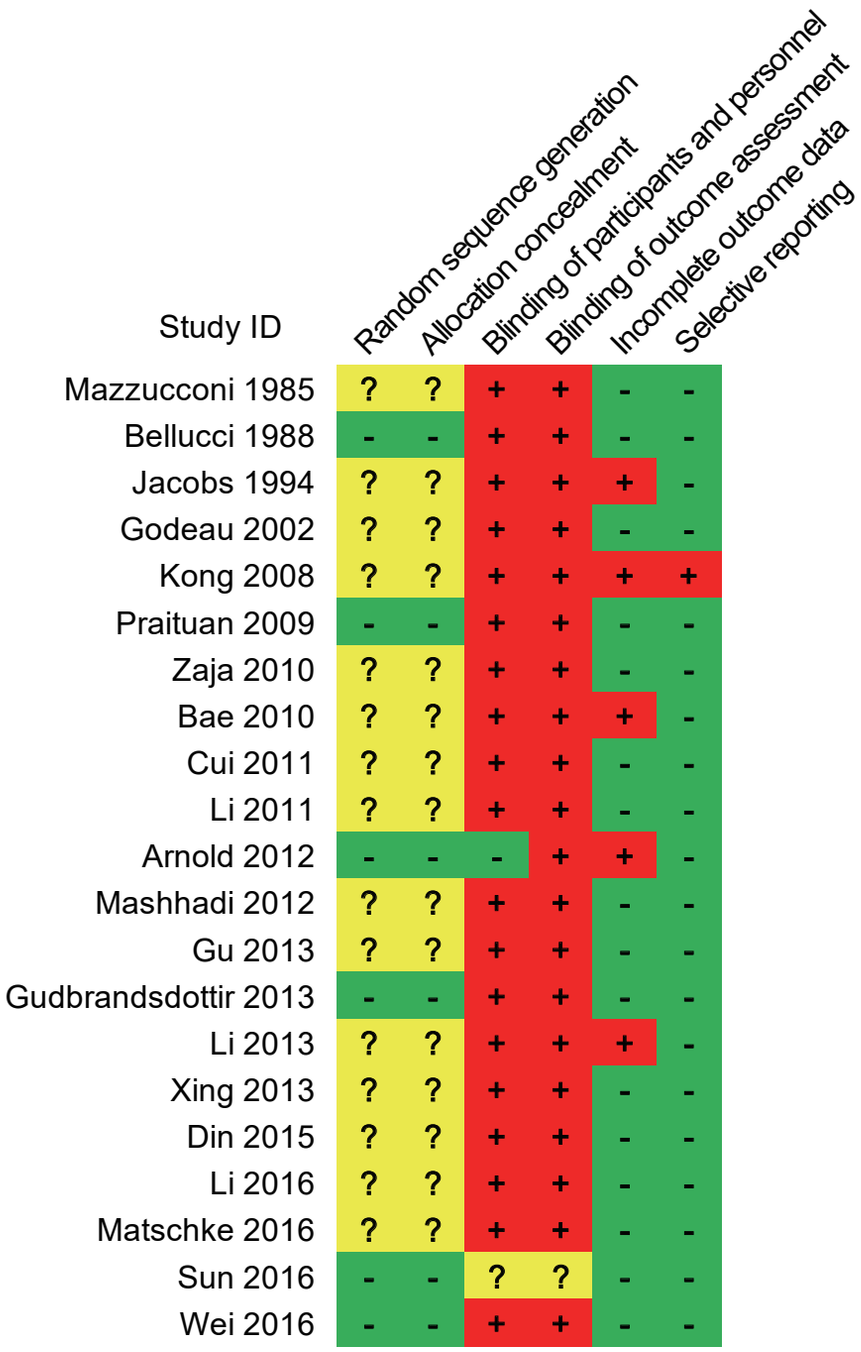
Abbreviations are shown in Table 1. Hemorrhagic events are shown in *Italics*.

Supplemental Table 8. Sensitivity analysis (excluding studies using rhTPO) for SR/OR according to the SUCRA values

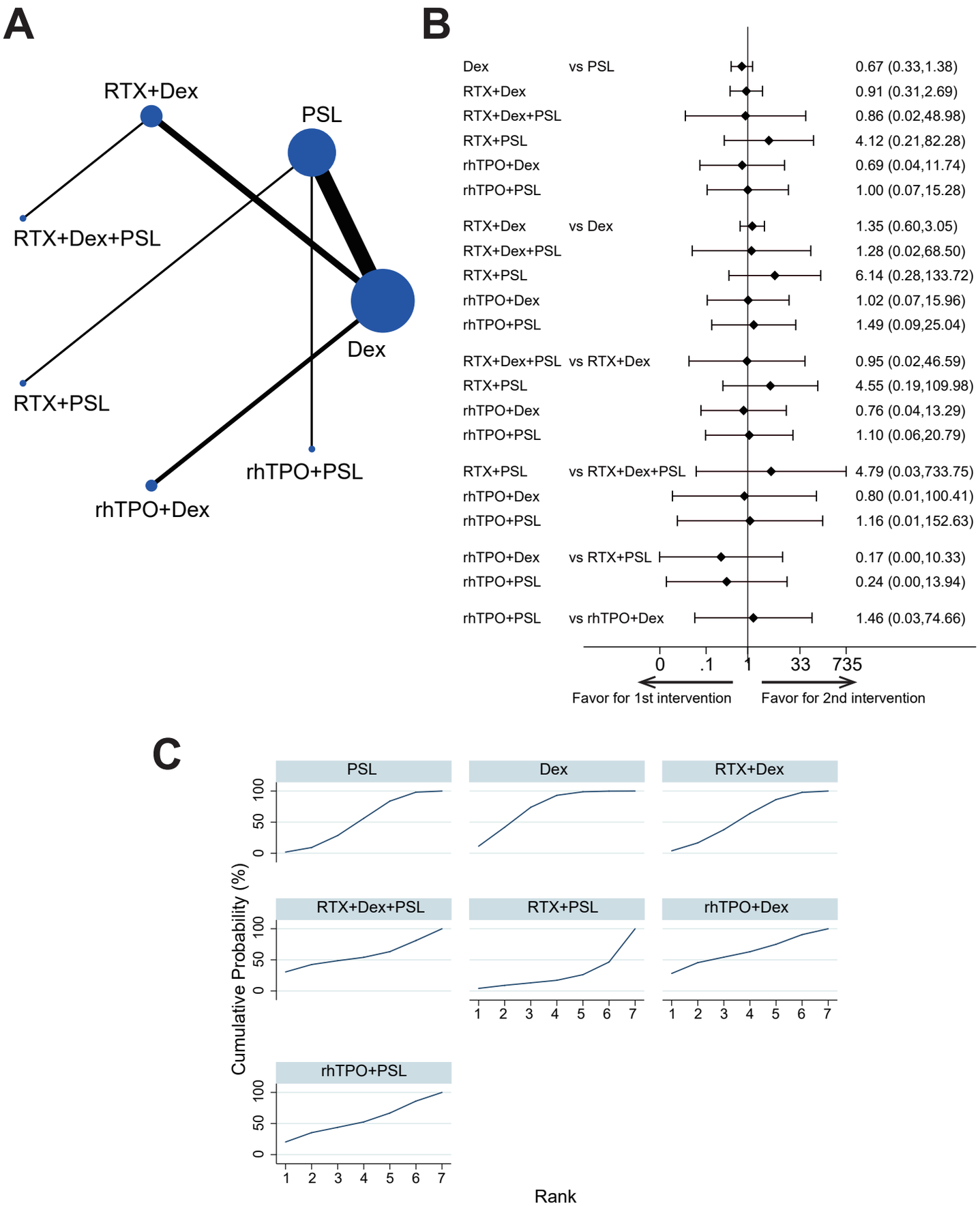
SR			OR		
Ranking	Treatment	SUCRA	Ranking	Treatment	SUCRA
1	RTX+Dex	91.7	1	RTX+Dex+PSL	89.7
2	RTX+Dex+PSL	91.2	2	HP±PSL	72.7
3	Dex	64.3	3	RTX+Dex	69.0
4	PSL	47.7	4	Dex	63.4
5	RTX+PSL	39.2	5	PSL	39.8
6	PSL(LD)	32.1	6	IVIG±PSL	31.0
7	mPSL±PSL	20.6	7	mPSL±PSL	20.2
8	IVIG±PSL	13.2	8	PSL(LD)	14.3

Abbreviations are shown in Table 1 and 2.

Supplemental Figure 1



Supplemental Figure 2



Supplemental Figure 3