推奨作成関連資料 9

■JIA CQ1（JIA 少関節炎型・多関節炎型 1）

■JIA CQ2（JIA 少関節炎型・多関節炎型 2）

■JIA CQ3（JIA 少関節炎型・多関節炎型 3）

■JIA CQ4（JIA 少関節炎型・多関節炎型 4）

■JIA CQ5（JIA 少関節炎型・多関節炎型 5）

■JIA CQ6（JIA 少関節炎型・多関節炎型 6）

※タイトルクリックで該当ページに移動します.

資料A　JIA CQ1　文献検索式（PubMed）

No.	検索式	検索件数
#1	(arthritis, juvenile[MeSH Terms]) OR (arthritis, juvenile[Title/Abstract])	11,682
#2	(((polyarthritis[MeSH Terms]) OR (pauciarthritis[MeSH Terms])) OR (oligoarthritis[MeSH Terms])) OR (monoarthritis[MeSH Terms])	291,695
#3	polyarthritis[Title/Abstract] OR pauciarthritis[Title/Abstract] OR oligoarthritis[Title/Abstract] OR monoarthritis[Title/Abstract]	11,114
#4	(#2) OR (#3)	293,749
#5	(#1) AND (#4)	11,567
#6	"methotrexate "[MeSH Terms] OR "methotrexate"[Title/Abstract]	59,674
#7	(#5) AND (#6)	953
#8	(#5) AND (#6) Filters from2021/1/1 - 2022/12/31	80

データベース：PubMed, ～2022/12/31

検索日　2023/2/12

資料A　JIA CQ1　文献検索式（Cochrane）

No.	検索式	検索件数
#1	Mesh descriptor: [Arthritis, Juvenile] explode all trees	379
#2	(arthritis, juvenile):ti,ab,kw	1,018
#3	#1 or #2	1,018
#4	MeSH descriptor: [Methotrexate] explode all trees	4,737
#5	("methotrecate"):ti,ab,kw	12,676
#6	#4 or #5	12,676
#7	#3 and #6	257
#8	#7 Custom Range: 2021/1/1 - 2022/12/31	19

データベース：Cochrane, ～2022/12/31

検索日　2023/2/12

資料A　JIA CQ1　文献検索式（医中誌）

No.	検索式	検索件数
#1	関節炎-若年性/TH or 若年性特発性関節炎/AL	3,762
#2	関節型/AL or 少関節/AL or 多関節/AL	2,203
#3	#1 and #2	402
#4	Methotrexate/TH or メトトレキサート/AL	22,894
#5	#3 and #4	118
#6	(#5) and (PT=会議録除く)	85
#7	(#6) and (DT=2021/1/1:2022/12/31)	9

データベース：医中誌, ～2022/12/31

検索日　2023/2/12

資料A　JIA CQ1　文献検索式（Embase）

No.	検索式	検索件数
1	('arthritis, juvenile'/exp OR 'arthritis, juvenile':ti,ab,kw) AND ([english]/lim OR [japanese]/lim) AND [abstracts]/lim	16,374
2	(polyarthritis:ti,ab,kw OR pauciarthritis:ti,ab,kw OR oligoarthritis:ti,ab,kw OR monoarthritis:ti,ab,kw) AND ([english]/lim OR [japanese]/lim) AND [abstracts]/lim	137,559
3	methotrexate AND ([english]/lim OR [japanese]/lim) AND [abstracts]/lim	8,040
4	(('arthritis, juvenile'/exp OR 'arthritis, juvenile':ti,ab,kw) AND ([english]/lim OR [japanese]/lim) AND [abstracts]/lim) AND ((polyarthritis:ti,ab,kw OR pauciarthritis:ti,ab,kw OR oligoarthritis:ti,ab,kw OR monoarthritis:ti,ab,kw) AND ([english]/lim OR [japanese]/lim) AND [abstracts]/lim) AND (methotrexate AND ([english]/lim OR [japanese]/lim) AND [abstracts]/lim)	389

データベース：Embase, ～2020/12/28

検索日　2020/12/28

資料B　JIA CQ1　文献検索フローチャート

CQ番号	JIA CQ1

MEDLINE (via Pubmed) から特定した文献数	CENTRALから特定した文献数	Embaseから特定した文献数	医中誌から特定した文献数	その他の情報源から特定した文献数
953	257	389	85	0

↓

重複文献除外後の文献数　（n = 1510 ）　重複文献数　（n= 174 ）

↓

スクリーニングした文献数　（1st Screening）
（n = 1510 ）

→ 除外した文献数
（n = 1468 ）

↓

適格性を評価した論文数　（2nd Screening）
（n = 42 ）

→ 除外した論文数
（n = 24 ）
＜除外理由＞
・Pが基準を満たさず　（n= 0 ）
・I/Cが基準を満たさず　（n= 0 ）
・デザインが異なる　（n= 22 ）
・Oが基準を満たさず　（n= 2 ）
・Ongoing study　（n= 0 ）
・Publication dateが2022/7/1以降　（n= 0 ）
・(TNFのみ)ガイドライン2014/2020にすでに組み込まれている　（n= 0 ）

↓

質的統合に組み入れた研究数/論文数
（n = 18 研究/ 18 論文）

↓

量的統合に加えた研究数　（meta-analysis）
（n = 3 研究）※うち1論文1研究は入手できず

資料C JIA CQ1 バイアスのリスク(活動関節数)

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	JIA CQ1	Giannini	MTX	Placebo	Number of joints with active arthritis	NA	+	+	!	+	+	!
	JIA CQ1-2	Woo	MTX	Placebo	Number of joints with active arthritis	1	+	-	!	+	+	!

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

資料C　JIA CQ1　バイアスのリスク（ACR Pedi 30に類似した治療効果複合指標）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	JIA CQ2	Giannini	MTX	Placebo	Core Variables	1	+	+	!	+	+	!
	JIA CQ2-2	Woo	MTX	Placebo	Core Variables	1	+	-	!	+	+	!

D1　Randomisation process

D2　Deviations from the intended interventions

D3　Missing outcome data

D4　Measurement of the outcome

D5　Selection of the reported result

資料C JIA CQ1 バイアスのリスク(Limited joint range score)

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	JIA CQ3	Giannini	MTX	Placebo	Limited joint range score	1	+	+	!	+	+	!
	JIA CQ3-2	Woo	MTX	Placebo	Limited joint range score	1	+	-	!	+	+	!

D1 Randomisation process

D2 Deviations from the intended interventions

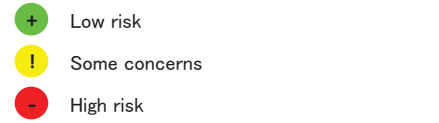
D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C JIA CQ1 バイアスのリスク（Toxicity ）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	JIA CQ5	Giannini	MTX	Placebo	Toxicity	1	+	+	+	+	+	+



D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C JIA CQ1 バイアスのリスク（薬剤継続割合 ）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	JIA CQ7	Giannini	MTX	Placebo	薬剤継続割合	1	+	+	+	+	+	+

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料 D　JIA CQ1　エビデンスプロファイル　Question: MTXpo compared to none/PBO

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTXpo	none/PBO	Relative (95% CI)	Absolute (95% CI)		

Outcomes used for the recommendation

活動関節数

2	randomised trials	not serious	not serious	serious[a]	serious[b]	none	117	81	-	MD 1.96 lower (5.24 lower to 1.32 higher)	⨁⨁◯◯ Low	CRITICAL

ACR Pedi 30 **に類似した治療効果複合指標**

2	randomised trials	not serious	not serious	serious[a]	serious[c]	none	56/118 (47.5%)	22/82 (26.8%)	RR 1.73 (0.94 to 3.18)	196 more per 1,000 (from 16 fewer to 585 more)	⨁⨁◯◯ Low	CRITICAL

Limited joint range score

2	randomised trials	not serious	serious[d]	serious[a]	serious[b]	none	99	63	-	MD 0.67 lower (6.31 lower to 4.97 higher)	⨁◯◯◯ Very low	CRITICAL

Toxicity

1	randomised trials	not serious	not serious	serious[a]	very serious[e]	none	14/86 (16.3%)	5/41 (12.2%)	RR 1.33 (0.52 to 3.45)	40 more per 1,000 (from 59 fewer to 299 more)	⨁◯◯◯ Very low	CRITICAL

薬剤継続割合

1	randomised trials	not serious	not serious	serious[a]	serious[f]	none	74/86 (86.0%)	34/41 (82.9%)	RR 1.04 (0.88 to 1.22)	33 more per 1,000 (from 100 fewer to 182 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; MD: mean difference; RR: risk ratio

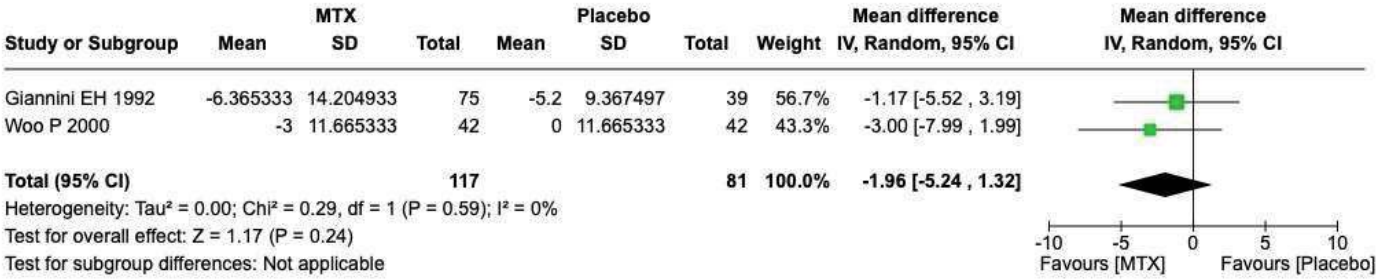
Explanations

a. s-JIA in Giannini1992
b. 95% CI of MD probably crosses one of the MID
c. 95% CI of RR crosses 1.25 of the decision threshold.
d. The results of the two studies are in different directions.
e. 95% CI of RR crosses both 0.75 and 1.25 of the decision thresholds.
f. small sample size

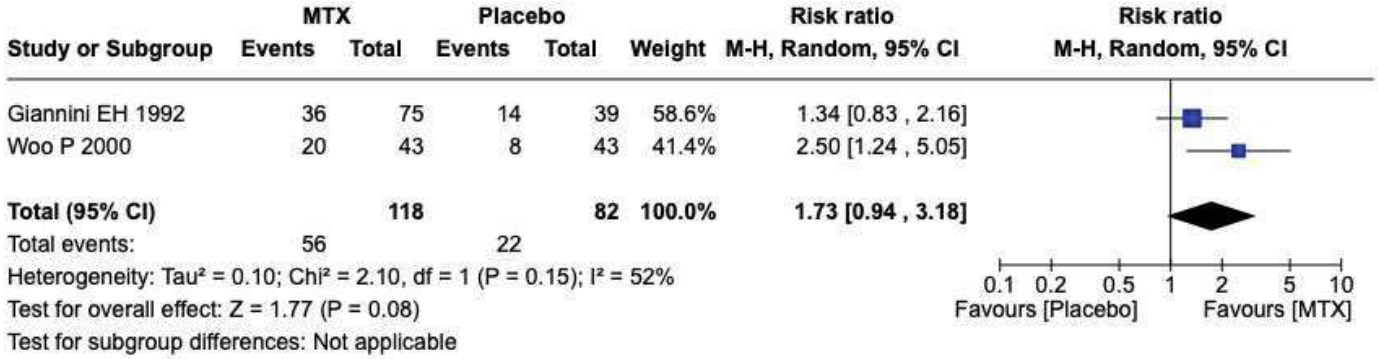
資料 E　JIA CQ1 フォレストプロット

Outcomes used for the recommendation

活動関節数



ACR Pedi 30 に類似した治療効果複合指標



Limited joint range score

Toxicity

薬剤継続割合


MTX
Placebo
Risk ratio
Risk ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Giannini EH 1992 74 86 34 41 100.0% 1.04 [0.88 , 1.22]
Total (95% CI) 86 41 100.0% 1.04 [0.88 , 1.22]
Total events: 74 34
Heterogeneity: Not applicable
Test for overall effect: Z = 0.44 (P = 0.66)
Test for subgroup differences: Not applicable
0.1 0.2 0.5 1 2 5 10
Favours [Placebo]
Favours [MTX]

資料A　JIA CQ2　文献検索式（PubMed）

No.	検索式	検索件数
1	(arthritis, juvenile[MeSH Terms]) OR (arthritis, juvenile[Title/Abstract])	11,814
2	(((polyarthritis[MeSH Terms]) OR (pauciarticular[MeSH Terms])) OR (oligoarthritis[MeSH Terms])) OR (monoarthritis[MeSH Terms])	294,841
3	(((polyarthritis[Title/Abstract]) OR (pauciarticular[Title/Abstract])) OR (oligoarthritis[Title/Abstract])) OR (monoarthritis[Title/Abstract])	11,733
4	#2 OR #3	296,958
5	#1 AND #4	11,696
6	"salazosulfapyridine" OR "sulfasalazine" OR "iguratimod" OR "bucillamine" OR "leflunomide" OR "tacrolimus" OR "mizoribine" OR "azathioprine" OR "cyclosporine"	96,173
7	#5 AND #6	285

データベース：PubMed, ～2022/12/31

検索日　2023/3/21

資料A　JIA CQ2　文献検索式（Cochrane）

No.	検索式	検索件数
1	arthritis, juvenile	1,111
2	polyarthritis OR pauciarticular OR oligoarthritis OR monoarthritis	514
3	#1 AND #2	80
4	salazosulfapyridine OR sulfasalazine OR iguratimod OR bucillamine OR leflunomide OR tacrolimus OR mizoribine OR azathioprine OR cyclosporine	14,846
5	#3 AND #4	14

データベース：Cochrane, ～2022/12/31

検索日　2023/3/21

資料A　JIA CQ2　文献検索式（医中誌）

No.	検索式	検索件数
1	関節炎-若年性/TH or 若年性特発性関節炎/AL	3,769
2	関節型/AL or 少関節/AL or 多関節/AL	2,205
3	#1 and #2	402
4	(Sulfasalazine/TH or サラゾスルファピリジン/AL) or (Sulfasalazine/TH or スルファサラジン/AL) or (Iguratimod/TH or イグラチモド/AL) or (Bucillamine/TH or ブシラミン/AL) or (Leflunomide/TH or レフルノミド/AL) or (Mizoribine/TH or ミゾリビン/AL) or (Tacrolimus/TH or タクロリムス/AL) or (Azathioprine/TH or アザチオプリン/AL) or (Ciclosporin/TH or シクロスポリン/AL)	41,642
5	#3 and #4	28
6	#5 and (PT=会議録除く)	18

データベース：医中誌, ～2022/12/31

検索日　2023/3/12

資料A　JIA CQ2　文献検索式（Embase）

No.	検索式	検索件数
1	('arthritis, juvenile':ab,ti OR 'arthritis, juvenile'/exp OR 'arthritis, juvenile') AND ([english]/lim OR [japanese]/lim) AND [abstracts]/lim	16,397
2	polyarthritis:ab,ti OR pauciarticular:ab,ti OR oligoarthritis:ab,ti OR monoarthritis:ab,ti	8,482
3	salazosulfapyridine OR sulfasalasine OR igratimod OR bucillamine OR leflunomide OR tacrolimus OR mizoribine OR azathioprine OR cyclosporine	72,311
4	#1 AND #2 AND #3	222

データベース：Embase, ～2020/12/31

検索日　2021/1/30

資料B　JIA CQ2　文献検索フローチャート

CQ番号	JIA CQ2

MEDLINE (via Pubmed)から から特定した文献数	CENTRALから 特定した文献数	Embaseから 特定した文献数	医中誌から 特定した文献数
285	14	222	18

その他の情報源から 特定した文献数
4

↓

重複文献除外後の文献数　　重複文献数
（n = 519 ）　（n= 20 ）

↓

その他の情報源から特定した文献数
（n = 4 ）

↓

スクリーニングした文献数　（1st Screening）
（n = 523 ）

→ 除外した文献数
（n = 432 ）

↓

適格性を評価した論文数　（2nd Screening）
（n = 91 ）

→ 除外した論文数
（n = 88 ）
＜除外理由＞
・Pが基準を満たさず　（n= 6 ）
・I/Cが基準を満たさず　（n= 3 ）
・デザインが異なる　（n= 75 ）
・Oが基準を満たさず　（n= 0 ）
・Ongoing study　（n= 0 ）
・Publication dateが2023/1/1以降　（n= 0 ）
・入手できず　（n= 4 ）

↓

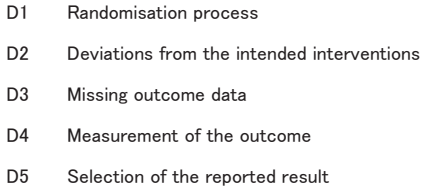
質的統合に組み入れた研究数/論文数
（n = 3 研究/ 3 論文）

↓

量的統合に加えた研究数　（meta-analysis）
（n = 0 研究）

資料C JIA CQ2 バイアスのリスク（Δ Number of active joints）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	61_A	Kvein 1986	AZP	Placebo	Number of active joints	1	+	-	-	+	+	-
	39_B	Silverman 2005	LEF	MTX	Number of active joints	1	+	+	-	+	+	-
	51_B	Rossum 1998	SASP	Placebo	Number of active joints	1	+	+	-	+	+	-



資料C JIA CQ2 バイアスのリスク(ACR Pedi 30)

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	39_A	Silverman 2005	LEF	MTX	ACR Pedi 30	1	+	+	-	+	+	-

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C JIA CQ2 バイアスのリスク（ΔC-HAQ DI）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	39_C	Silverman 2005	LEF	MTX	C-HAQ DI	1	+	+	-	+	+	-

+ Low risk

! Some concerns

- High risk

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C JIA CQ2 バイアスのリスク（Δ Number of limited joints）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	39_D	Silverman 2005	LEF	MTX	Number of limited joints	1	+	+	-	+	+	-
	51_A	Rossum 1998	SASP	Placebo	Number of limited joints	1	+	+	-	+	+	-

! Some concerns

- High risk

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C JIA CQ2 バイアスのリスク（Serious adverse events, Serious infection）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	39_E	Silverman 2005	LEF	MTX	重篤な副作用	1	+	+	+	+	+	+
	39_F	Silverman 2005	LEF	MTX	重篤な感染症	1	+	+	+	+	+	+
	51_C	Rossum 1998	SSZ	Placebo	重篤な副作用	1	+	+	+	+	+	+

+ Low risk

! Some concerns

- High risk

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C JIA CQ2 バイアスのリスク(Drug continuation rate)

Intention-to-treat

Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
61_C	Kvein 1986	AZP	Placebo	Drug continuation rate	1	+	+	+	+	+	+
39_G	Silverman 2005	LEF	MTX	Drug continuation rate	1	+	+	+	+	+	+

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料 D　JIA CQ2　**エビデンスプロファイル**（AZP vs PBO）　Question: AZP compared to placebo for articular JIA

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AZP	placebo	Relative (95% CI)	Absolute (95% CI)		
Outcomes used for the recommendation												
Drug continuation rate (follow-up: 16 weeks)												
1	randomised trials	not serious	not serious	serious[a]	very serious[b]	none	13/17 (76.5%)	11/15 (73.3%)	RR 1.18 (0.24 to 5.86)	132 more per 1,000 (from 557 fewer to 1,000 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; RR: risk ratio

Explanations

a. Differences in population.
b. The 95% confidence interval of the risk ratio include decision thresholds of 0.75 and 1.25.

資料 D　JIA CQ2　エビデンスプロファイル（LEF vs MTX）　Question: LEF compared to MTX for articular JIA

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LEF	MTX	Relative (95% CI)	Absolute (95% CI)		
Outcomes used for the recommendation												
Δ Number of active joints (follow-up: 16 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	serious[c]	none	47	47	-	MD 0.8 higher (0.4 higher to 1.2 higher)	⨁◯◯◯ Very low	CRITICAL
ACR Pedi 30 (follow-up: 16 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	32/47 (68.1%)	42/47 (89.4%)	RR 0.76 (0.61 to 0.95)	214 fewer per 1,000 (from 349 fewer to 45 fewer)	⨁◯◯◯ Very low	CRITICAL
ΔC-HAQ DI (follow-up: 16 weeks)												
1	randomised trials	not serious	not serious	not serious	serious[c]	none	47	47	-	MD 0.05 lower (0.09 lower to 0.01 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Δ Number of limited joints (follow-up: 16 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	serious[c]	none	47	47	-	MD 0.1 higher (0.22 lower to 0.42 higher)	⨁◯◯◯ Very low	CRITICAL
Serious adverse events (follow-up: 16 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious[d]	none	3/47 (6.4%)	0/47 (0.0%) 3.2%[h]	RR 7.00[e] (0.37 o 131.89)	0 fewer per 1,000 (from 0 fewer to 0 fewer) 192 more per 1,000[h] (from 20 fewer to 1,000 more)	⨁⨁◯◯ Low	CRITICAL
Serious infection (follow-up: 16 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious[d]	none	1/47 (2.1%)	0/47 (0.0%) 1.6%[h]	RR 3.00[e] (0.13 to 71.82)	0 fewer per 1,000 (from 0 fewer to 0 fewer) 32 more per 1,000[h] (from 14 fewer to 1,000 more)	⨁⨁◯◯ Low	CRITICAL
Drug continuation rate (follow-up: 16 weeks)												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	44/47 (93.6%)	46/47 (97.9%)	RR 0.96 (0.88 to 1.04)	39 fewer per 1,000 (from 117 fewer to 39 more)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

a. Many missing outcome data may affect the result.
b. The 95% confidence interval of the risk ratio include decision thresholds of 0.75.
c. The total sample size is small.
d. The 95% confidence interval of the risk ratio include decision thresholds of 0.75 and 1.25.
e. Calculated assuming control event count as 0.5.
h. Extrapolated from the paper: Ruperto H, et al. Lancet. 2008; 372: 383-391.

資料 D　JIA CQ2　**エビデンスプロファイル**（SASP vs PBO）　Question: SASP compared to placebo for articular JIA

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SASP	placebo	Relative (95% CI)	Absolute (95% CI)		
Outcomes used for the recommendation												
ΔNumber of active joints (follow-up: 24 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[c,d]	none	35	34	-	MD 4.76 lower (8.06 lower to 1.04 lower)	⨁◯◯◯ Very low	CRITICAL
Δ Number of limited joints (follow-up: 24 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	35	34	-	MD 0.52 lower (3.22 lower to 2.18 higher)	⨁◯◯◯ Very low	CRITICAL
Serious adverse events (follow-up: 24 weeks)												
1	randomised trials	not serious	not serious	not serious	extremely serious[b,e]	none	1/35 (2.9%)	3.2%[g]	RR 2.92[f] (0.12 to 69.20)	61 more per 1,000[g] (from 28 fewer to1,000 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

a. Many missing outcome data may affect the result.
b. The total sample size and the total number of the events are small.
c. The 95% confidence interval of the mean difference includes the minimally important difference of -4.
d. The total sample size is small.
e. The 95% confidence interval of the risk ratio includes both the decision thresholds of 0.75 and 1.25.
f. Calculated assuming control event count as 0.5.
g. Extrapolated from the paper: Ruperto H, et al. Lancet. 2008; 372: 383-391.

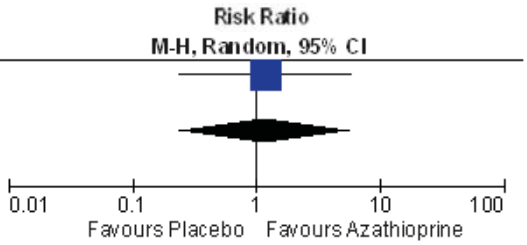
資料 E　JIA CQ2 フォレストプロット（AZP vs PBO）

Outcomes used for the recommendation

Drug continuation rate (follow-up: 16 weeks)

Study or Subgroup	Azathioprine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Kvein 1986	13	17	11	15	100.0%	1.18 [0.24, 5.86]
Total (95% CI)		**17**		**15**	**100.0%**	**1.18 [0.24, 5.86]**
Total events	13		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.20 (P = 0.84)



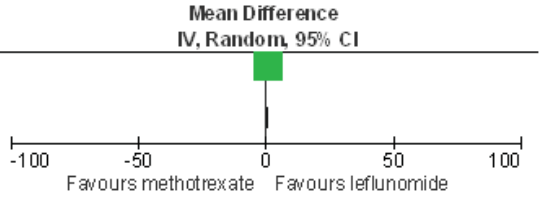
資料 E　JIA CQ2 フォレストプロット（LEF vs MTX）

Outcomes used for the recommendation

Δ Number of active joints (follow-up: 16 weeks)

Study or Subgroup	Leflunomide Mean	SD	Total	Methotrexate Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Silverman 2005	-8.1	1	47	-8.9	1	47	100.0%	0.80 [0.40, 1.20]
Total (95% CI)			**47**			**47**	**100.0%**	**0.80 [0.40, 1.20]**

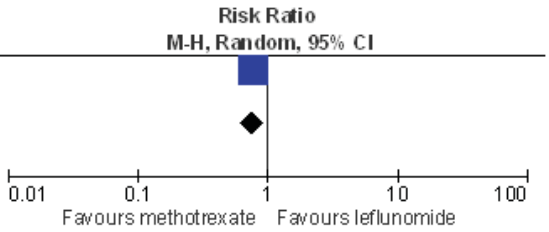
Heterogeneity: Not applicable
Test for overall effect: Z = 3.88 (P = 0.0001)



ACR Pedi 30 (follow-up: 16 weeks)

Study or Subgroup	Leflunomide Events	Total	Methotrexate Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Silverman 2005	32	47	42	47	100.0%	0.76 [0.61, 0.95]
Total (95% CI)		**47**		**47**	**100.0%**	**0.76 [0.61, 0.95]**
Total events	32		42			

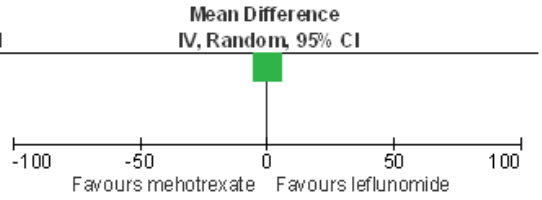
Heterogeneity: Not applicable
Test for overall effect: Z = 2.43 (P = 0.02)



Δ C-HAQ DI (follow-up: 16 weeks)

Study or Subgroup	Leflunomide Mean	SD	Total	Methotrexate Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Silverman 2005	-0.44	0.08	47	-0.39	0.1	47	100.0%	-0.05 [-0.09, -0.01]
Total (95% CI)			**47**			**47**	**100.0%**	**-0.05 [-0.09, -0.01]**

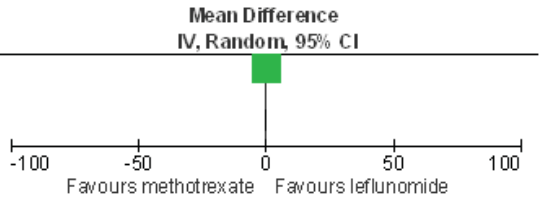
Heterogeneity: Not applicable
Test for overall effect: Z = 2.68 (P = 0.007)



Δ Number of limited joints (follow-up: 16 weeks)

Study or Subgroup	Leflunomide Mean	SD	Total	Methotrexate Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Silverman 2005	-5.2	0.8	47	-5.3	0.8	47	100.0%	0.10 [-0.22, 0.42]
Total (95% CI)			**47**			**47**	**100.0%**	**0.10 [-0.22, 0.42]**

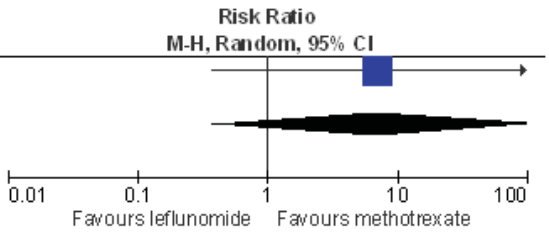
Heterogeneity: Not applicable
Test for overall effect: Z = 0.61 (P = 0.54)



Serious adverse events (follow-up: 16 weeks)

Study or Subgroup	Leflunomide Events	Total	Methotrexate Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Silverman 2005	3	47	0	47	100.0%	7.00 [0.37, 131.89]
Total (95% CI)		**47**		**47**	**100.0%**	**7.00 [0.37, 131.89]**
Total events	3		0			

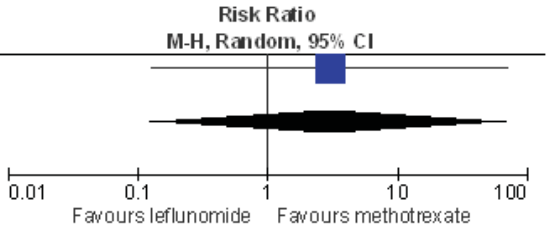
Heterogeneity: Not applicable
Test for overall effect: Z = 1.30 (P = 0.19)



Serious infection (follow-up: 16 weeks)

Study or Subgroup	Leflunomide Events	Leflunomide Total	Methotrexate Events	Methotrexate Total	Weight	Risk Ratio M-H, Random, 95% CI
Silverman 2005	1	47	0	47	100.0%	3.00 [0.13, 71.82]
Total (95% CI)		**47**		**47**	**100.0%**	**3.00 [0.13, 71.82]**
Total events	1		0			

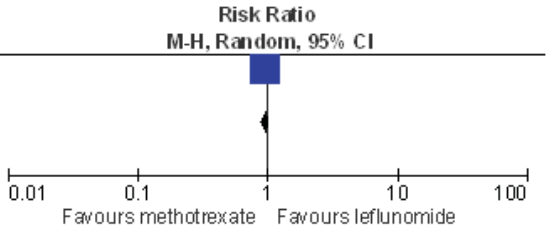
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)



Drug continuation rate (follow-up: 16 weeks)

Study or Subgroup	Leflunomide Events	Leflunomide Total	Methotrexate Events	Methotrexate Total	Weight	Risk Ratio M-H, Random, 95% CI
Silverman 2005	44	47	46	47	100.0%	0.96 [0.88, 1.04]
Total (95% CI)		**47**		**47**	**100.0%**	**0.96 [0.88, 1.04]**
Total events	44		46			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.02 (P = 0.31)



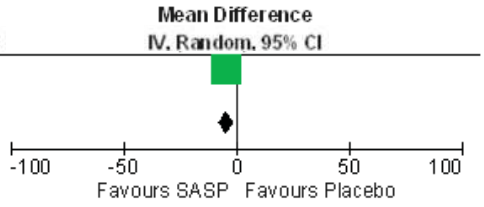
資料 E　JIA CQ2 フォレストプロット（SASP vs PBO）

Outcomes used for the recommendation

Δ Number of active joints (follow-up: 24 weeks)

Study or Subgroup	Salazosulfapyridine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Rossum 1998	-5.54	6.86	35	-0.78	7.11	34	100.0%	-4.76 [-8.06, -1.46]
Total (95% CI)			**35**			**34**	**100.0%**	**-4.76 [-8.06, -1.46]**

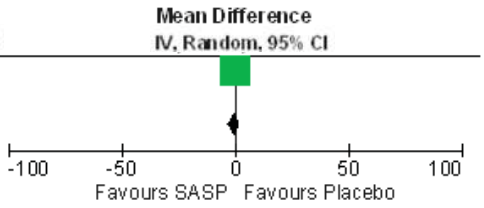
Heterogeneity: Not applicable
Test for overall effect: Z = 2.83 (P = 0.005)



Δ Number of limited joints (follow-up: 24 weeks)

Study or Subgroup	Salazosulfapyridine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Rossum 1998	-2.49	6.62	35	-1.97	4.66	34	100.0%	-0.52 [-3.22, 2.18]
Total (95% CI)			**35**			**34**	**100.0%**	**-0.52 [-3.22, 2.18]**

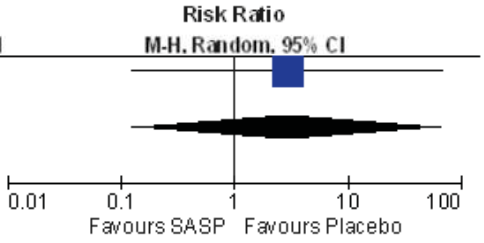
Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.71)



Serious adverse events (follow-up: 24 weeks)

Study or Subgroup	Salazosulfapyridine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Rossum 1998	1	35	0	34	100.0%	2.92 [0.12, 69.20]
Total (95% CI)		**35**		**34**	**100.0%**	**2.92 [0.12, 69.20]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)



資料A　JIA CQ3　文献検索式（Pubmed）

No.	検索式	検索件数
1	(arthritis, juvenile[MeSH Terms]) OR (arthritis, juvenile[Title/Abstract])	11,818
2	(polyarthritis[MeSH Terms]) OR (pauciarticluar[MeSH Terms]) OR (oligoarthritis[MeSH Terms]) OR (monoarthritis[MeSH Terms])	294,929
3	(polyarthritis[Title/Abstract]) OR (pauciarticular[Title/Abstract]) OR (oligoarthritis[Title/Abstract]) OR (monoarthritis[Title/Abstract])	11,733
4	(#2) OR (#3)	297,046
5	(#1) AND (#4)	11,701
6	（corticosteroid [MH]） OR （prednisolone[TIAB]） OR （glucocorticoid [TIAB]） OR （steroid[TIAB]）	469,199
7	(#5) AND (#6)	1,046
8	#7 Filter from 1000/1/1-2022	1,036

データベース：PubMed, ～2022/12/31

検索日　2023/3/1

資料A　JIA CQ3　文献検索式（Cochrane）

No.	検索式	検索件数
1	arthritis, juvenile	1,123
2	(polyarthritis) OR (pauciarticluar) OR (oligoarthritis) OR (monoarthritis)	501
3	(polyarthritis):ti,ab,kw OR (pauciarticular):ti,ab,kw OR (oligoarthritis):ti,ab,kw OR (monoarthritis):ti,ab,kw	437
4	#2 OR #3	517
5	#1 AND #4	80
6	(corticosteroid) OR (prednisolone) OR (glucocorticoid) OR (steroid)	40,042
7	(corticosteroid):ti,ab,kw OR (prednisolone):ti,ab,kw OR (glucocorticoid):ti,ab,kw OR (steroid):ti,ab,kw	38,536
8	#6 OR #7	40,042
9	#5 AND #8	20
10	#9 with Cochrane Library publication date to Dec 2022	20

データベース：Cochrane, ～2022/12/31

検索日　2023/3/1

資料A　JIA CQ3　文献検索式（医中誌）

No.	検索式	検索件数
1	関節炎-若年性/TH　or 少関節炎型若年性特発性関節炎/AL or 多関節炎型若年性特発性関節炎	3,068
2	glucocorticoid/TH or steroid/AL orステロイド/AL or corticosteroid/AL or グルココルチコイド/AL or prednisolone/AL	86,892
3	#1 and #2	354
4	(#3) and (PT=会議録除く)	210
5	#4 and (DT=1900:2022)	210

データベース：医中誌, ～2022/12/31

検索日　2023/3/1

資料A　JIA CQ3　文献検索式（Embase）

No.	検索式	検索件数
1	arthritis, juvenile':ab,ti OR 'arthritis, juvenile'/exp	22,831
2	polyarthritis:ab,ti OR pauciarticular:ab,ti OR oligoarthritis:ab,ti OR monoarthritis:ab,ti	14,657
3	corticosteroid OR prednisolone OR glucocorticoid OR steroid	829,931
4	('arthritis, juvenile':ab,ti OR 'arthritis, juvenile'/exp) AND (polyarthritis:ab,ti OR pauciarticular:ab,ti OR oligoarthritis:ab,ti OR monoarthritis:ab,ti) AND (corticosteroid OR prednisolone OR glucocorticoid OR steroid) AND ([english]/lim OR [japanese]/lim) AND [abstracts]/lim	420

データベース：Embase, ～2020/12/31

検索日　2021/1/11

資料B　JIA CQ3　文献検索フローチャート

CQ番号	JIA CQ3

MEDLINE (via Pubmed)から から特定した文献数	CENTRALから 特定した文献数	Embaseから 特定した文献数	医中誌から 特定した文献数
1036	20	420	210

その他の情報源から 特定した文献数
2

↓

重複文献除外後の文献数　（n = 1685）　重複文献数（n= 1）

↓

その他の情報源から特定した文献数（n = 2）

↓

スクリーニングした文献数（1st Screening）（n = 1687）

→ 除外した文献数（n = 1673）

↓

適格性を評価した論文数（2nd Screening）（n = 14）

→ 除外した論文数（n = 12）

＜除外理由＞

- Pが基準を満たさず（n= 0）
- I/Cが基準を満たさず（n= 0）
- デザインが異なる（n= 12）
- Oが基準を満たさず（n= 0）
- Ongoing study（n= 0）
- Publication dateが2022/7/1以降（n= 0）
- (TNFのみ)ガイドライン2014/2020にすでに組み込まれている（n= 0）

↓

質的統合に組み入れた研究数/論文数（n = 2 研究/ 2 論文）

↓

量的統合に加えた研究数（meta-analysis）（n = 2 研究）

資料C JIA CQ3 バイアスのリスク

SAE

Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
1	Umang.2022	A	B	ACR Pedi 30	1	+	+	+	+	+	+
2	Umang.2022	A	B	ACR Pedi 50	1	+	+	+	+	+	+
3	Umang.2022	A	B	ACR Pedi 70	1	+	+	+	+	+	+
4	Umang.2022	A	B	AE Hyperglycemia	1	+	+	+	+	+	+
5	Umang.2022	A	B	AE Cushing	1	+	+	+	+	+	+
6	Hissink.2017	C	D	ACR Pedi 30	1	!	+	+	+	!	!
7	Hissink.2017	C	D	ACR Pedi 50	1	!	+	+	+	!	!
8	Hissink.2017	C	D	ACR Pedi 70	1	!	+	+	+	!	!
10	Hissink.2017	C	D	AE	1	!	+	+	+	!	!
11	Hissink.2017	C	D	SAE	1	!	+	+	+	!	!

+ Low risk

! Some concerns

- High risk

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

資料 D　JIA CQ3　エビデンスプロファイル（DEX）　Question: Dex versus Placebo for JIA.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTX	placebo	Relative (95% CI)	Absolute (95% CI)		
ACR Pedi30												
1	randomized trials	not serious	not serious	Serious[a]	Serious[b]	none	24/30 (80.0%)	21/28 (75.0%)	RR 1.07 (0.81 to 1.41)	53 more per 1,000 (from 142 fewer to 307 more)	⨁⨁◯◯ low	CRITICAL
ACR Pedi50												
1	randomized trials	not serious	not serious	Serious[a]	Very serious[b]	none	18/30 (60.0%)	17/28 (60.7%)	RR 0.99 (0.65 to 1.50)	6 fewer per 1,000 (from 212 fewer to 304 more)	⨁◯◯◯ very low	IMPORTANT
ACR Pedi70												
1	randomized trials	not serious	not serious	Serious[a]	Very serious[b]	none	11/30 (36.7%)	11/28 (39.3%)	RR 0.93 (0.48 to 1.80)	27 fewer per 1,000 (from 204 fewer to 314 more)	⨁◯◯◯ very low	IMPORTANT
SAE												
1	randomized trials	not serious	not serious	Serious[a]	serious[e]	none	0/30 (0%)	0/28 (0.0%)			⨁⨁◯◯ >ß€	CRITICAL
Cushing												
1	randomized trials	not serious	not serious	Serious[a]	very serious[c]	none	8/30 (26.7%)	4/28 (14.3%)	RR 1.87 (0.63 to 5.52)	124 more per 1,000 (from 53 fewer to 646 more)	⨁◯◯◯ very low	IMPORTANT
Hyperglycemia												
1	randomized trials	not serious	not serious	Serious[a]	Very serious[c]	none	2/30 (6.7%)	0/28 (0.0%)	RR 4.68 (0.23 to 93.37)	d	⨁◯◯◯ very low	IMPORTANT

CI: confidence interval; RR: risk ratio.

Explanations

a. Patients with other types of JIA are included.
b. 95%CI of RR includes the decision thresholds of 1.25
c. 95%CI of RR includes both the decision thresholds of 0.75 and 1.25
d. Unable to extrapolate
e. The total sample size is small.

資料 D　JIA CQ3　エビデンスプロファイル（PSL）　Question: DMARD+PSL versus DMARD for JIA.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTX	placebo	Relative (95% CI)	Absolute (95% CI)		
臨床的非活動状態達成割合（Wallace preliminary criteria）												
1	randomized trials	serious[a]	not serious	not serious	Very serious[b]	none	3/32 (9.4%)	8/32 (25.0%)	RR 0.38 (0.11 to 1.29)	155 fewer per 1,000 (from 223 fewer to 73 more)	⨁◯◯◯ very low	CRITICAL
ACR Pedi30												
1	randomized trials	serious[a]	not serious	not serious	Very serious[b]	none	17/32 (53.1%)	16/32 (50.0%)	RR 1.06 (0.66 to 1.71)	30 more per 1,000 (from 170 fewer to 355 more)	⨁◯◯◯ very low	CRITICAL
ACR Pedi50												
1	randomized trials	serious[a]	not serious	not serious	Very serious[b]	none	12/32 (37.5%)	10/32 (31.3%)	RR 1.20 (0.61 to 2.37)	62 more per 1,000 (from 122 fewer to 428 more)	⨁◯◯◯ very low	IMPORTANT
ACR Pedi70												
1	randomized trials	serious[a]	not serious	not serious	Very serious[b]	none	6/32 (18.8%)	8/32 (25.0%)	RR 0.75 (0.29 to 1.92)	63 fewer per 1,000 (from 178 fewer to 230 more)	⨁◯◯◯ very low	IMPORTANT
SAE												
1	randomized trials	serious[a]	not serious	not serious	Very serious[b]	none	1/32 (3.1%)	2/32 (6.3%)	RR 0.50 (0.05 to 5.24)	31 fewer per 1,000 (from 59 fewer to 265 more)	⨁◯◯◯ very low	CRITICAL
Any AE												
1	randomized trials	serious[a]	not serious	not serious	Very serious[b]	none	9/32 (28.1%)	7/32 (21.9%)	RR 1.29 (0.55 to 3.03)	63 more per 1,000 (from 98 fewer to 444 more)	⨁◯◯◯ very low	IMPORTANT
Gastrointestinal												
1	randomized trials	serious[a]	not serious	not serious	serious[c]	none	14/32 (43.8%)	7/32 (21.9%)	RR 2.00 (0.93 to 4.29)	219 more per 1,000 (from 15 fewer to 720 more)	⨁⨁◯◯ Low	IMPORTANT
Infection												
1	randomized trials	serious[a]	not serious	not serious	Very serious[b]	none	6/32 (18.8%)	8/32 (25.0%)	RR 0.75 (0.29 to 1.92)	63 fewer per 1,000 (from 178 fewer to 230 more)	⨁◯◯◯ very low	IMPORTANT

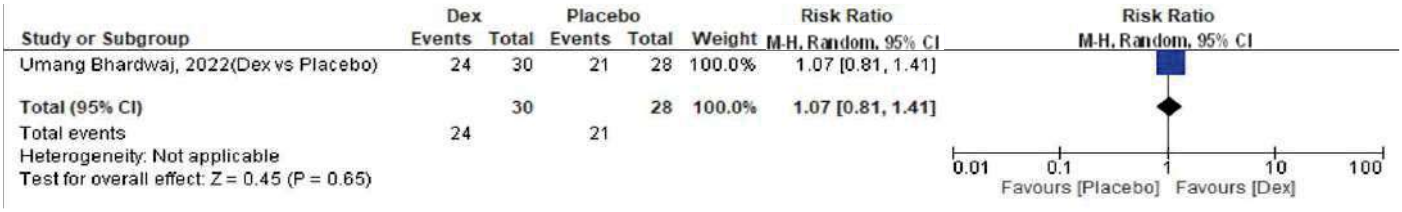
CI: confidence interval; RR: risk ratio.

Explanations

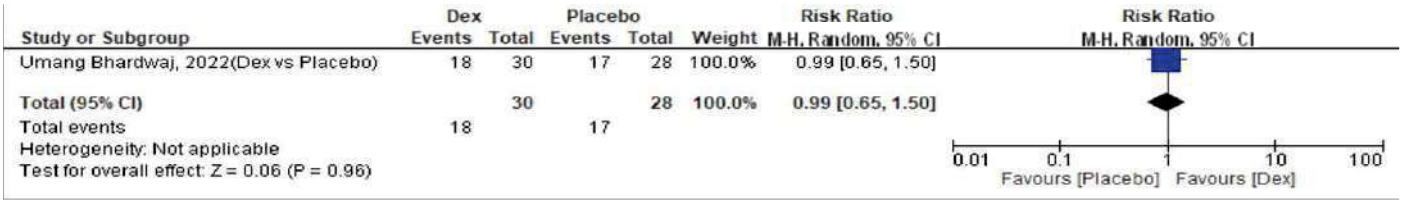
a. Insufficient randomization,
b. The 95% CI of the RR includes both the decision thresholds of 0.75 and 1.25.
c. The 95% CI of the RR includes the decision thresholds of 1.25.

資料 E　JIA CQ3 フォレストプロット（DEX）

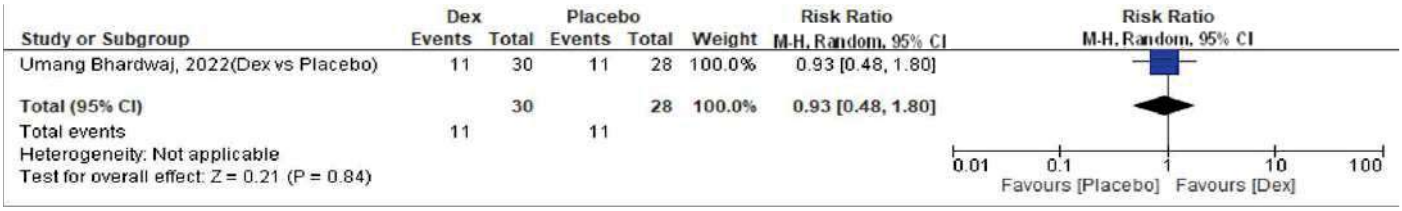
ACR Pedi30



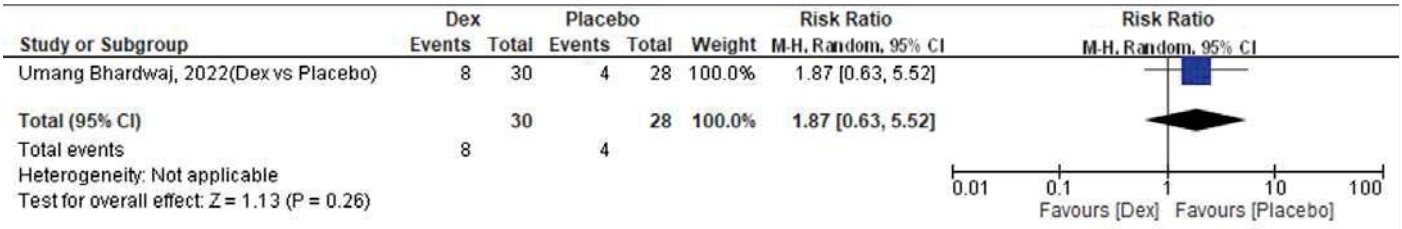
ACR Pedi50



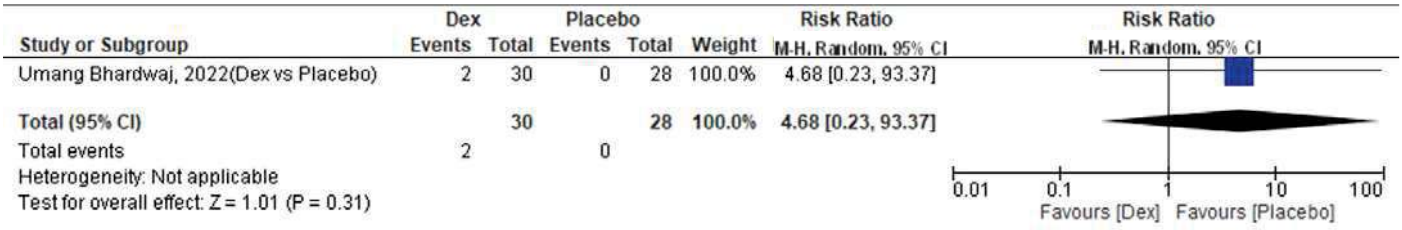
ACR Pedi70



Cushing

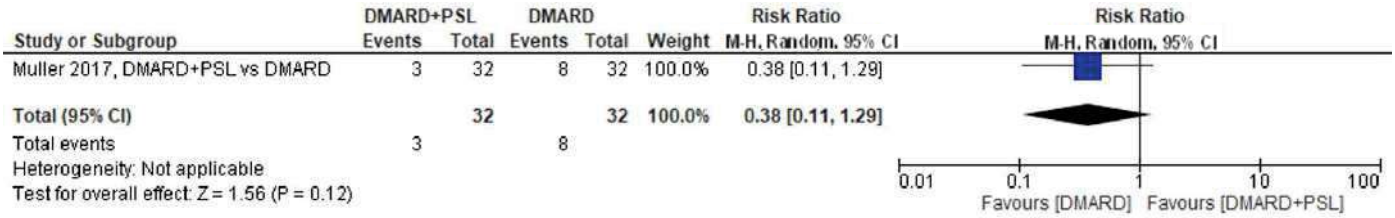


Hyperglycemia

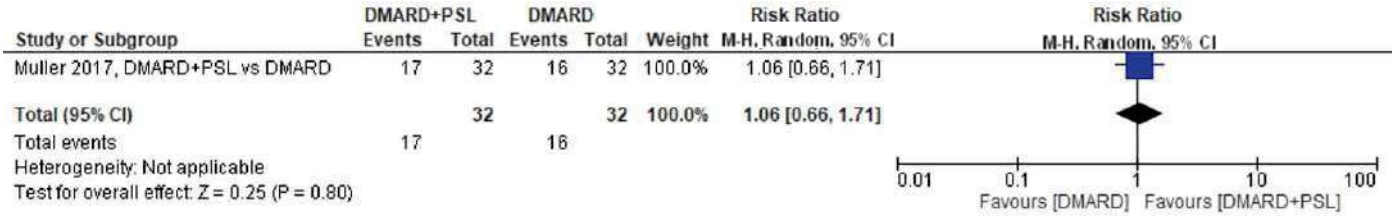


資料 E　JIA CQ3 フォレストプロット（PSL）

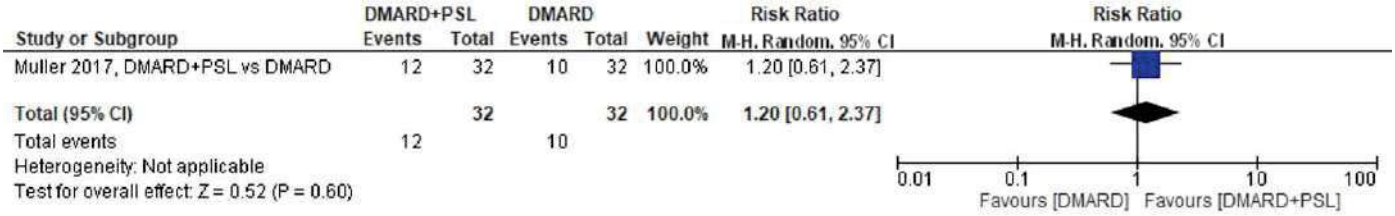
臨床的非活動状態達成割合（Wallace preliminary criteria）



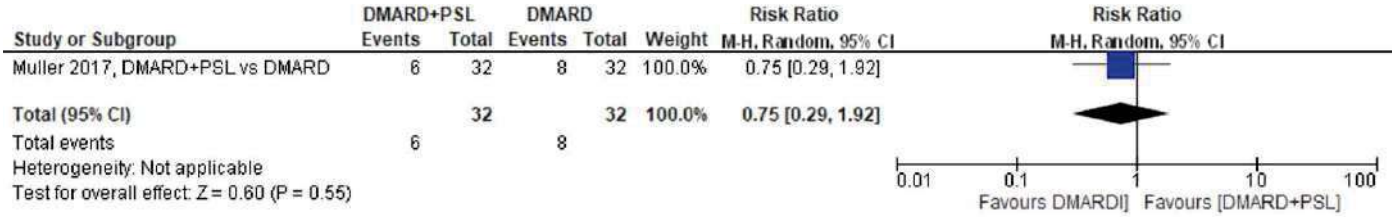
ACR Pedi30



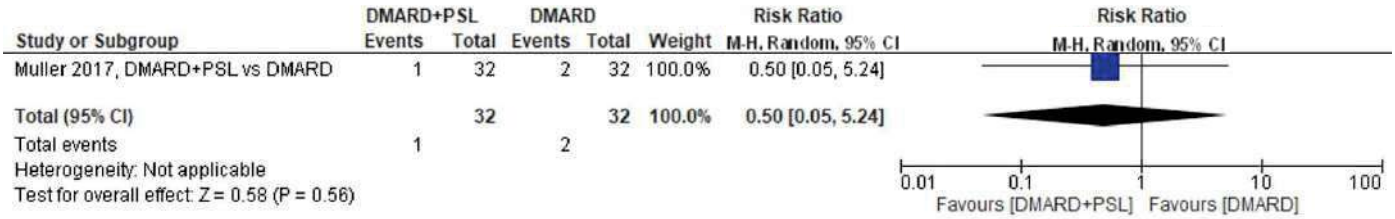
ACR Pedi50



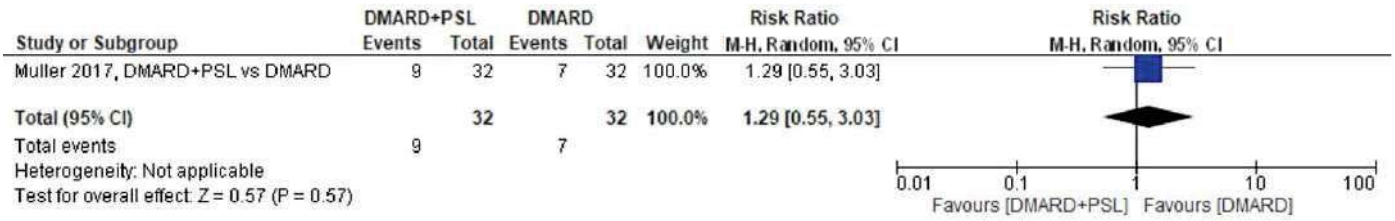
ACR Pedi70



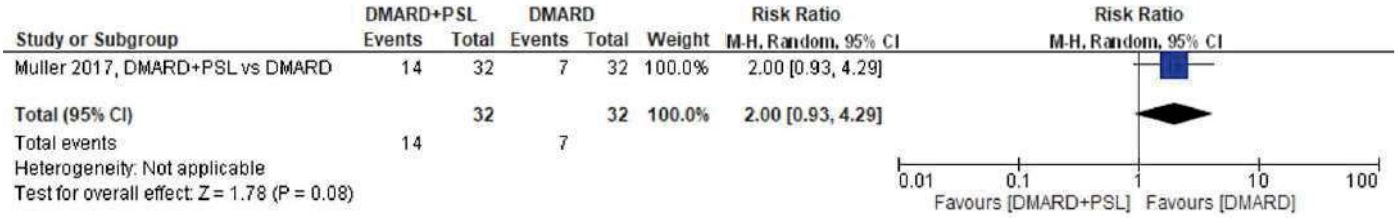
SAE



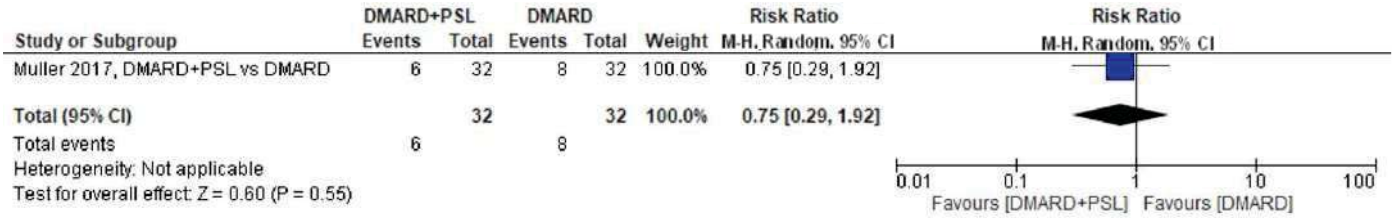
Any AE



Gastrointestinal



Infection



資料A　JIA CQ4　文献検索式（PubMed）

No.	検索式	検索件数
1	(arthritis, juvenile[MeSH Terms]) OR (arthritis, juvenile[Title/Abstract])	11,631
2	(polyarthritis[MeSH Terms]) OR (pauciarticular[MeSH Terms]) OR (oligoarthritis[MeSH Terms]) OR (monoarthritis[MeSH Terms])	290,608
3	(polyarthritis[Title/Abstract]) OR (pauciarticular[Title/Abstract]) OR (oligoarthritis[Title/Abstract]) OR (monoarthritis[Title/Abstract])	11,646
4	(#2) OR (#3)	292,689
5	(#1) AND (#4)	11,518
6	etanercept OR adalimumab OR infliximab OR golimumab OR certolizumab OR TNF inhibitor OR TNF blockage	82,337
7	(#5) AND (#6)	875

データベース：PubMed, ～2022/12/31

検索日　2023/1/9

No.	検索式	検索件数
1	(arthritis, juvenile):ti,ab,kw	1,013
2	(etanercept OR adalimumab OR infliximab OR golimumab OR certolizumab OR TNF inhibitor OR TNF blockage)	9,691
3	(#1) AND (#2)	242

データベース：Cochrane, ～2022/12/31

検索日　2023/1/9

資料A　JIA CQ4　文献検索式（医中誌）

No.	検索式	検索件数
1	(関節炎-若年性/TH or 若年性特発性関節炎/AL)	3,748
2	関節型/AL or 少関節/AL or 多関節/AL	2,200
3	#1 and #2	402
4	(Etanercept/TH or エタネルセプト/AL) or (Adalimumab/TH or アダリムマブ/AL) or (Infliximab/TH or インフリキシマブ/AL) or (Golimumab/TH or ゴリムマブ/AL) or (("Certolizumab Pegol"/TH or Certolizumab/AL) and Pegol/TH or セルトリズマブ/AL) or ((腫瘍壊死因子アルファ/TH or TNF/AL) and inhibitor/AL or (腫瘍壊死因子アルファ/TH or TNF/AL) and blockage/AL or (腫瘍壊死因子アルファ/TH or TNF/AL) and blockade/AL or (腫瘍壊死因子アルファ/TH or TNF/AL) and blocker/AL and or腫瘍壊死因子阻害薬/AL)	16,537
5	#3 and #4	80
6	#5 and (PT=会議録除く)	46

データベース：医中誌, ～2022/12/31

検索日　2023/1/9

資料A　JIA CQ4　文献検索式（Embase）

No.	検索式	検索件数
1	arthritis, juvenile':ab,ti OR 'arthritis, juvenile'/exp	22,831
2	juvenile rheumatoid arthritis':ab,ti OR 'juvenile rheumatoid arthritis'/exp	23,359
3	polyarthritis:ab,ti OR pauciarticular:ab,ti OR oligoarthritis:ab,ti OR monoarthritis:ab,ti	14,657
4	etanercept OR adalimumab OR golimumab OR tocilizumab OR abatacept OR infliximab OR biosimilar	96,414
5	('arthritis, juvenile':ab,ti OR 'arthritis, juvenile'/exp) AND (polyarthritis:ab,ti OR pauciarticular:ab,ti OR oligoarthritis:ab,ti OR monoarthritis:ab,ti) AND (etanercept OR adalimumab OR golimumab OR tocilizumab OR abatacept OR infliximab OR biosimilar) AND ([english]/lim OR [japanese]/lim) AND [abstracts]/lim	281

データベース：Embase, ～2020/12/31

検索日　2021/1/10

資料B　JIA CQ4　文献検索フローチャート

CQ番号	JIA CQ4

MEDLINE（via Pubmed）から特定した文献数	CENTRALから特定した文献数	Embaseから特定した文献数	医中誌から特定した文献数	その他の情報源から特定した文献数
875	242	281	46	0

↓

重複文献除外後の文献数　（n = 1397）　重複文献数　（n= 47）

↓

その他の情報源から特定した文献数　（n = 0）

↓

スクリーニングした文献数（1st Screening）　（n = 1397）

→ 除外した文献数　（n = 1102）

↓

適格性を評価した論文数（2nd Screening）　（n = 61）

→ 除外した論文数　（n = 41）

＜除外理由＞

- Pが基準を満たさず　（n= 3）
- I/Cが基準を満たさず　（n= 18）
- デザインが異なる　（n= 9）
- Oが基準を満たさず　（n= 11）
- Ongoing study　（n= 0）
- Publication dateが2022/7/1以降　（n= 0）

↓

質的統合に組み入れた研究数/論文数　（n = 19 研究/ 20 論文）

↓

量的統合に加えた研究数（meta-analysis）　（n = 4 研究

資料C　JIA CQ4　バイアスのリスク（parallel_ACRpedi30）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	17	Ruperto, 2007	IFX+MTX	MTX	ACR pedi 30	NA	+	+	+	+	+	+

+ Low risk

! Some concerns

- High risk

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C JIA CQ4 バイアスのリスク(parallel_ACRpedi50)

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	18	Ruperto, 2007	IFX+MTX	MTX	ACR pedi 50	NA	+	+	+	+	+	+

+ Low risk

! Some concerns

- High risk

D1 Randomisation process

D2 Deviations from the intended interventions

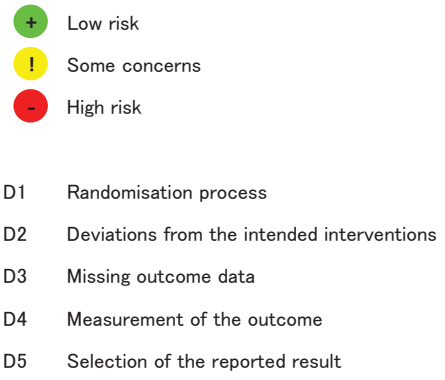
D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C JIA CQ4 バイアスのリスク（parallel_ACRpedi70）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	19	Ruperto, 2007	IFX+MTX	MTX	ACR pedi 70	NA	+	+	+	+	+	+



資料C　JIA CQ4　バイアスのリスク（parallel_CHAQ-DI変化量 ）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	20	Ruperto, 2007	IFX+MTX	MTX	CHAQ	NA	+	+	+	+	+	+

+ Low risk

! Some concerns

- High risk

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C JIA CQ4 バイアスのリスク（withdrawal〈vs.MTX〉_Flare）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	39	Lovell, 2008	ADA+MTX	MTX	Flare	NA	+	+	+	+	+	+
	45	Brunner, 2018	GOL+MTX	MTX	Flare	NA	+	+	+	+	+	+

+ Low risk

! Some concerns

- High risk

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C JIA CQ4 バイアスのリスク（withdrawal〈vs.MTX〉_ACRpedi30）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	35	Lovell, 2008	ADA+MTX	MTX	ACR pedi 30	NA	+	+	+	+	+	+
	41	Brunner, 2018	GOL+MTX	MTX	ACR pedi 30	NA	+	+	+	+	+	+

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C　JIA CQ4　バイアスのリスク（withdrawal〈vs.MTX〉_ACRpedi50）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	36	Lovell, 2008	ADA+MTX	MTX	ACR pedi 50	NA	+	+	+	+	+	+
	42	Brunner, 2018	GOL+MTX	MTX	ACR pedi 50	NA	+	+	+	+	+	+

D1　Randomisation process

D2　Deviations from the intended interventions

D3　Missing outcome data

D4　Measurement of the outcome

D5　Selection of the reported result

資料C JIA CQ4 バイアスのリスク(withdrawal〈vs.MTX〉_ACRpedi70)

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	37	Lovell, 2008	ADA+MTX	MTX	ACR pedi 70	NA	+	+	+	+	+	+
	43	Brunner, 2018	GOL+MTX	MTX	ACR pedi 70	NA	+	+	+	+	+	+

D1 Randomisation process

D2 Deviations from the intended interventions

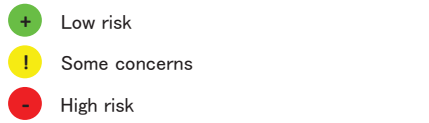
D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C JIA CQ4 バイアスのリスク（withdrawal〈vs.MTX〉_ACR Pedi90 ）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	38	Lovell, 2008	ADA+MTX	MTX	ACR pedi 90	NA	+	+	+	+	+	+
	44	Brunner, 2018	GOL+MTX	MTX	ACR pedi 90	NA	+	+	+	+	+	+



D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C JIA CQ4 バイアスのリスク（withdrawal〈vs.MTX〉_SAE）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	40	Lovell, 2008	ADA+MTX	MTX	SAE	NA	+	+	+	+	+	+
	46	Brunner, 2018	GOL+MTX	MTX	SAE	NA	+	+	+	+	+	+

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C JIA CQ4 バイアスのリスク（withdrawal〈vs.PBO〉_Flare）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	27	Lovell, 2000	ETA	Placebo	Flare	NA	!	+	+	+	+	!

+ Low risk
! Some concerns
- High risk

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

資料C JIA CQ4 バイアスのリスク（withdrawal〈vs.PBO〉_ACRpedi30）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	24	Lovell, 2000	ETA	Placebo	ACR pedi 30	NA	!	+	+	+	+	!

+ Low risk
! Some concerns
- High risk

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

資料C JIA CQ4 バイアスのリスク（withdrawal〈vs.PBO〉_ACRpedi50 ）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	25	Lovell, 2000	ETA	Placebo	ACR pedi 50	NA	!	+	+	+	+	!

+ Low risk

! Some concerns

- High risk

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C JIA CQ4 バイアスのリスク（withdrawal〈vs.PBO〉_ACRpedi70 ）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	26	Lovell, 2000	ETA	Placebo	ACR pedi 70	NA	!	+	+	+	+	!

+ Low risk
! Some concerns
- High risk

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

資料C JIA CQ4 バイアスのリスク（withdrawal〈vs.PBO〉_SAE）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	28	Lovell, 2000	ETA	Placebo	SAE	NA	!	+	+	+	+	+

+ Low risk
! Some concerns
- High risk

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

資料 D　JIA CQ4　エビデンスプロファイル（parallel）　Question: TNFi + MTX compared to MTX for JIA

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi+MTX	MTX	Relative (95% CI)	Absolute (95% CI)		
ACRpedi30												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	37/58 (63.8%)	29/59 (49.2%)	RR 1.30 (0.94 to 1.79)	147 more per 1,000 (from 29 fewer to 388 more)	⨁⨁◯◯ Low	CRITICAL
ACRpedi50												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	29/58 (50.0%)	20/59 (33.9%)	RR 1.48 (0.95 to 2.29)	163 more per 1,000 (from 17 fewer to 437 more)	⨁⨁◯◯ Low	IMPORTANT
ACRpedi70												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	13/58 (22.4%)	7/59 (11.9%)	RR 1.89 (0.81 to 4.40)	106 more per 1,000 (from 23 fewer to 403 more)	⨁⨁◯◯ Low	IMPORTANT
CHAQ-DI 変化量												
1	randomised trials	not serious	not serious	serious[a]	serious[c]	none	58	59	-	MD 0.12 lower (0.37 lower to 0.13 higher)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

a. Patients with other types of JIA are included.
b. The 95% confidence interval of risk ratio includes decision threshold of 1.25.
c. The 95% confidence interval of risk ratio includes decision threshold of -0.22.

資料 D　JIA CQ4　エビデンスプロファイル（withdrawal（vs. MTX））Question: TNFi + MTX compared to MTX for JIA

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi+MTX	MTX	Relative (95% CI)	Absolute (95% CI)		
flare												
2	randomised trials	not serious	serious[a]	not serious	serious[c]	none	46/116 (39.7%)	60/113 (53.1%)	RR 0.75 (0.56 to 0.99)	133 fewer per 1,000 (from 234 fewer to 5 fewer)	⨁⨁◯◯ Low	CRITICAL
ACRpedi30												
2	randomised trials	not serious	serious[a]	not serious	serious[b]	none	65/116 (56.0%)	56/113 (49.6%)	RR 1.13 (0.88 to 1.45)	64 more per 1,000 (from 59 fewer to 223 more)	⨁⨁◯◯ Low	CRITICAL
ACRpedi50												
2	randomised trials	not serious	serious[a]	not serious	serious[b]	none	64/116 (55.2%)	55/113 (48.7%)	RR 1.13 (0.88 to 1.46)	63 more per 1,000 (from 58 fewer to 224 more)	⨁⨁◯◯ Low	IMPORTANT
ACRpedi70												
2	randomised trials	not serious	serious[a]	not serious	serious[b]	none	61/116 (52.6%)	46/113 (40.7%)	RR 1.29 (0.97 to 1.72)	118 more per 1,000 (from 12 fewer to 293 more)	⨁⨁◯◯ Low	IMPORTANT
ACRpedi90												
2	randomised trials	not serious	not serious	not serious	serious[b]	none	46/116 (39.7%)	34/113 (30.1%)	RR 1.32 (0.92 to 1.89)	96 more per 1,000 (from 24 fewer to 268 more)	⨁⨁⨁◯ Moderate	IMPORTANT
SAE												
2	randomised trials	not serious	not serious	not serious	very serious[b,c]	none	8/116 (6.9%)	11/113 (9.7%)	RR 0.72 (0.31 to 1.67)	27 fewer per 1,000 (from 67 fewer to 65 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; RR: risk ratio

Explanations

a. I2 is more than 40%.
b. The 95% confidence interval of risk ratio includes decision threshold of 1.25.
c. The 95% confidence interval of risk ratio includes decision threshold of 0.75.

資料 D　JIA CQ4　**エビデンスプロファイル（withdrawal (vs.PBO)）**　Question: TNFi compared to placebo for JIA

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi	placebo	Relative (95% CI)	Absolute (95% CI)		
Flare(16w)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	7/25 (28.0%)	21/26 (80.8%)	RR 0.35 (0.18 to 0.67)	525 fewer per 1,000 (from 662 fewer to 267 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
ACRpedi30(16w)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	20/25 (80.0%)	9/26 (34.6%)	RR 2.31 (1.32 to 4.06)	453 more per 1,000 (from 111 more to 1,000 more)	⨁⨁⨁◯ Moderate	CRITICAL
ACRpedi50(16w)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	18/25 (72.0%)	6/26 (23.1%)	RR 3.12 (1.48 to 6.56)	489 more per 1,000 (from 111 more to 1,000 more)	⨁⨁⨁◯ Moderate	IMPORTANT
ACRpedi70(16w)												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	11/25 (44.0%)	5/26 (19.2%)	RR 2.29 (0.93 to 5.65)	248 more per 1,000 (from 13 fewer to 894 more)	⨁⨁⨁◯ Moderate	IMPORTANT
SAE(16wk)												
1	randomised trials	not serious	not serious	not serious	very serious[c]	none	2/25 (8.0%)	0/26 (0.0%)	RR 5.19 (0.26 to 103.07)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; RR: risk ratio

Explanations

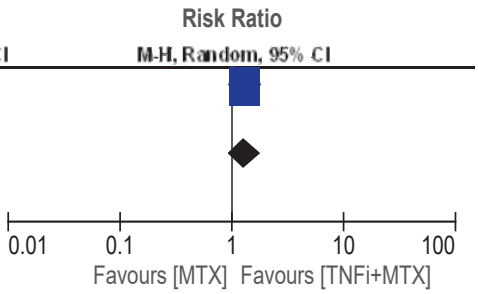
a. Sample size is small.
b. The 95% confidence interval of risk ratio includes decision threshold of 1.25.
c. The 95% confidence interval of risk ratio includes decision thresholds of 0.75 and 1.25.

資料 E　JIA CQ4　フォレストプロット（parallel）

ACRpedi30

Study or Subgroup	TNFi+MTX Events	Total	MTX Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ruperto,2007 (IFX+MTXvsMTX)	37	58	29	59	100.0%	1.30 [0.94, 1.79]
Total (95% CI)		**58**		**59**	**100.0%**	**1.30 [0.94, 1.79]**
Total events	37		29			

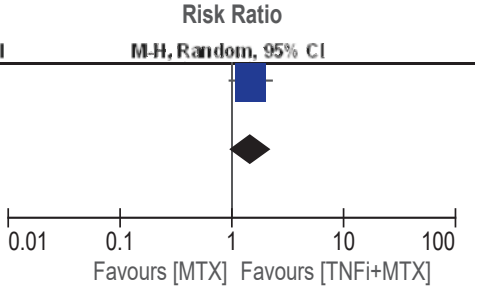
Heterogeneity: Not applicable
Test for overall effect: Z = 1.58 (P = 0.11)



ACRpedi50

Study or Subgroup	TNFi+MTX Events	Total	MTX Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ruperto,2007 (IFX+MTXvsMTX)	29	58	20	59	100.0%	1.48 [0.95, 2.29]
Total (95% CI)		**58**		**59**	**100.0%**	**1.48 [0.95, 2.29]**
Total events	29		20			

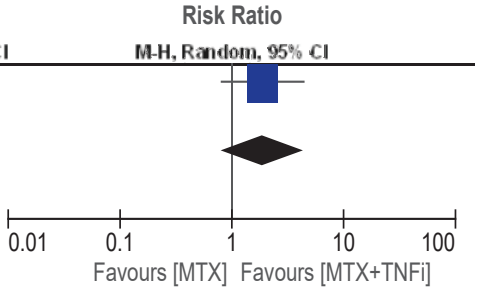
Heterogeneity: Not applicable
Test for overall effect: Z = 1.73 (P = 0.08)



ACRpedi70

Study or Subgroup	TNFi+MTX Events	Total	MTX Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ruperto,2007 (IFX+MTXvsMTX)	13	58	7	59	100.0%	1.89 [0.81, 4.40]
Total (95% CI)		**58**		**59**	**100.0%**	**1.89 [0.81, 4.40]**
Total events	13		7			

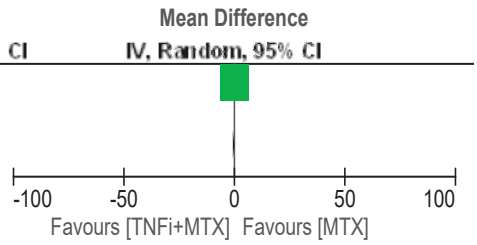
Heterogeneity: Not applicable
Test for overall effect: Z = 1.48 (P = 0.14)



CHAQ-DI 変化量

Study or Subgroup	TNFi+MTX Mean	SD	Total	MTX Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ruperto,2007 (IFX+MTXvsMTX)	0.92	0.76	58	1.04	0.61	59	100.0%	-0.12 [-0.37, 0.13]
Total (95% CI)			**58**			**59**	**100.0%**	**-0.12 [-0.37, 0.13]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.94 (P = 0.35)

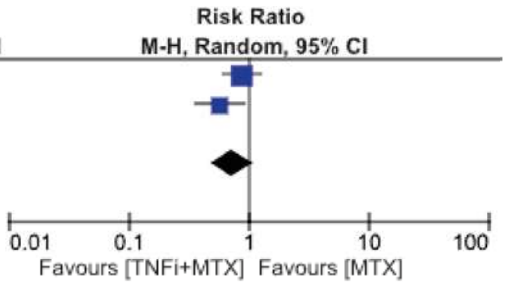


資料 E　JIA CQ4　フォレストプロット（withdrawal (vs.MTX)）

Flare

Study or Subgroup	TNFi+MTX Events	Total	MTX Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Brunner 2018	32	78	36	76	57.5%	0.87 [0.61, 1.24]
Lovvel 2008	14	38	24	37	42.5%	0.57 [0.35, 0.92]
Total (95% CI)		**116**		**113**	**100.0%**	**0.72 [0.48, 1.09]**
Total events	46		60			

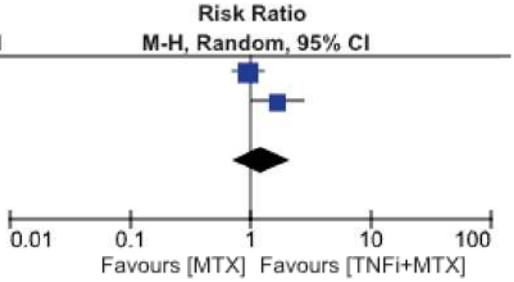
Heterogeneity: Tau² = 0.04; Chi² = 1.92, df = 1 (P = 0.17); I² = 48%
Test for overall effect: Z = 1.55 (P = 0.12)



ACRpedi30

Study or Subgroup	TNFi+MTX Events	Total	MTX Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Brunner 2018	41	78	42	76	55.9%	0.95 [0.71, 1.27]
Lovvel 2008	24	38	14	37	44.1%	1.67 [1.03, 2.70]
Total (95% CI)		**116**		**113**	**100.0%**	**1.22 [0.70, 2.11]**
Total events	65		56			

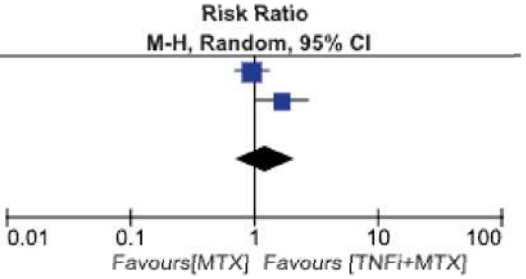
Heterogeneity: Tau² = 0.12; Chi² = 3.88, df = 1 (P = 0.05); I² = 74%
Test for overall effect: Z = 0.71 (P = 0.48)



ACRpedi50

Study or Subgroup	TNFi+MTX Events	Total	MTX Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Brunner 2018	40	78	41	76	55.7%	0.95 [0.70, 1.28]
Lovvel 2008	24	38	14	37	44.3%	1.67 [1.03, 2.70]
Total (95% CI)		**116**		**113**	**100.0%**	**1.22 [0.70, 2.11]**
Total events	64		55			

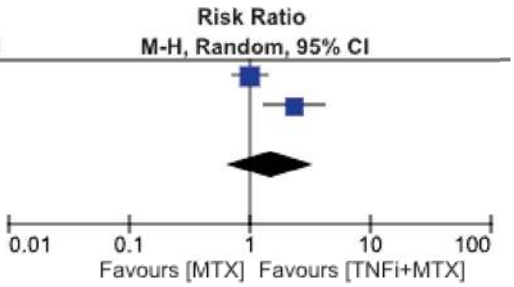
Heterogeneity: Tau² = 0.12; Chi² = 3.83, df = 1 (P = 0.05); I² = 74%
Test for overall effect: Z = 0.71 (P = 0.48)



ACRpedi70

Study or Subgroup	TNFi+MTX Events	Total	MTX Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Brunner 2018	37	78	36	76	54.1%	1.00 [0.72, 1.40]
Lovvel 2008	24	38	10	37	45.9%	2.34 [1.31, 4.18]
Total (95% CI)		**116**		**113**	**100.0%**	**1.48 [0.64, 3.40]**
Total events	61		46			

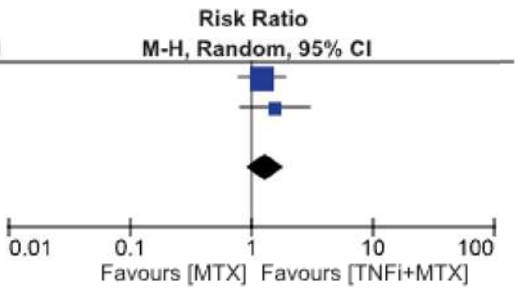
Heterogeneity: Tau² = 0.31; Chi² = 6.23, df = 1 (P = 0.01); I² = 84%
Test for overall effect: Z = 0.92 (P = 0.36)



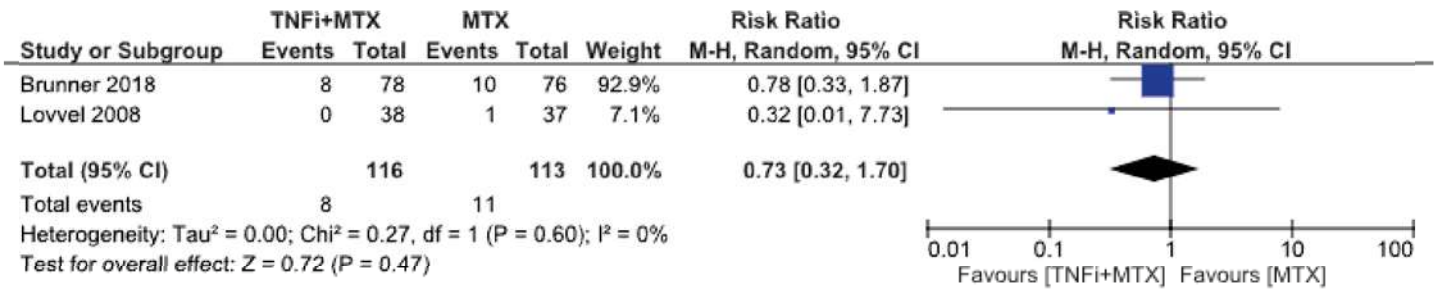
ACRpedi90

Study or Subgroup	TNFi+MTX Events	Total	MTX Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Brunner 2018	30	78	24	76	69.0%	1.22 [0.79, 1.88]
Lovvel 2008	16	38	10	37	31.0%	1.56 [0.82, 2.98]
Total (95% CI)		**116**		**113**	**100.0%**	**1.31 [0.92, 1.89]**
Total events	46		34			

Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 1.49 (P = 0.14)



SAE

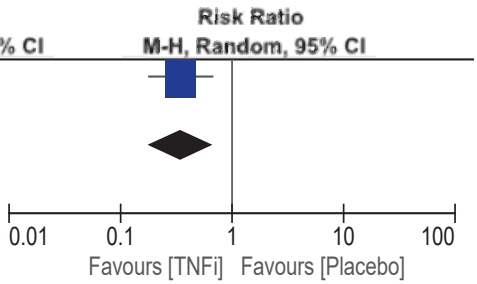

TNFi+MTX
MTX
Risk Ratio
Risk Ratio
Study or Subgroup
Events Total Events Total Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
Brunner 2018 8 78 10 76 92.9% 0.78 [0.33, 1.87]
Lovvel 2008 0 38 1 37 7.1% 0.32 [0.01, 7.73]
Total (95% CI) 116 113 100.0% 0.73 [0.32, 1.70]
Total events 8 11
Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 1 (P = 0.60); I² = 0%
Test for overall effect: Z = 0.72 (P = 0.47)
0.01
0.1
1
10
100
Favours [TNFi+MTX]
Favours [MTX]

資料 E　JIA CQ4　フォレストプロット（withdrawal (vs.PBO)）

Flare(16w)

Study or Subgroup	TNFi Events	TNFi Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Lovell, 2000 (ETN vs PLA)	7	25	21	26	100.0%	0.35 [0.18, 0.67]
Total (95% CI)		**25**		**26**	**100.0%**	**0.35 [0.18, 0.67]**
Total events	7		21			

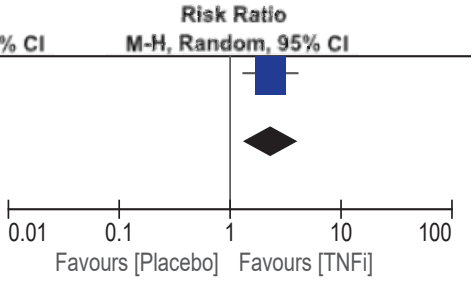
Heterogeneity: Not applicable
Test for overall effect: Z = 3.17 (P = 0.002)



ACRpedi30(16w)

Study or Subgroup	TNFi Events	TNFi Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Lovell, 2000 (ETN vs PLA)	20	25	9	26	100.0%	2.31 [1.32, 4.06]
Total (95% CI)		**25**		**26**	**100.0%**	**2.31 [1.32, 4.06]**
Total events	20		9			

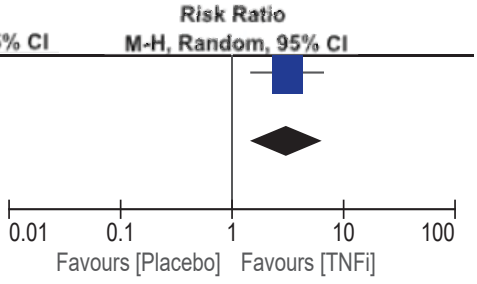
Heterogeneity: Not applicable
Test for overall effect: Z = 2.91 (P = 0.004)



ACRpedi50(16w)

Study or Subgroup	TNFi Events	TNFi Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Lovell, 2000 (ETN vs PLA)	18	25	6	26	100.0%	3.12 [1.48, 6.56]
Total (95% CI)		**25**		**26**	**100.0%**	**3.12 [1.48, 6.56]**
Total events	18		6			

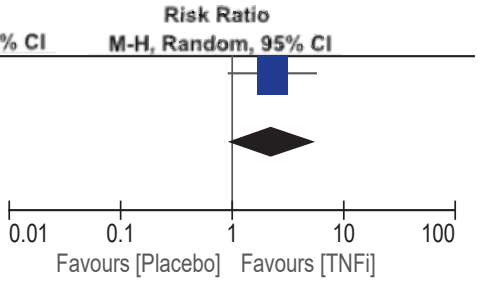
Heterogeneity: Not applicable
Test for overall effect: Z = 3.00 (P = 0.003)



ACRpedi70(16w)

Study or Subgroup	TNFi Events	TNFi Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Lovell, 2000 (ETN vs PLA)	11	25	5	26	100.0%	2.29 [0.93, 5.65]
Total (95% CI)		**25**		**26**	**100.0%**	**2.29 [0.93, 5.65]**
Total events	11		5			

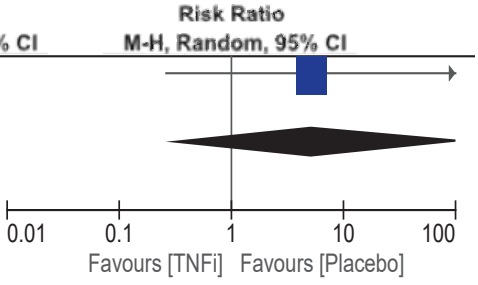
Heterogeneity: Not applicable
Test for overall effect: Z = 1.80 (P = 0.07)



SAE(16w)

Study or Subgroup	TNFi Events	TNFi Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Lovell, 2000 (ETN vs PLA)	2	25	0	26	100.0%	5.19 [0.26, 103.07]
Total (95% CI)		**25**		**26**	**100.0%**	**5.19 [0.26, 103.07]**
Total events	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.08 (P = 0.28)



資料A　JIA CQ5　文献検索式（PubMed）

No.	検索式	検索件数
1	(arthritis, juvenile[MeSH Terms]) OR (arthritis, juvenile[Title/Abstract])	11,667
2	(polyarthritis[MeSH Terms]) OR (pauciarticular[MeSH Terms]) OR (oligoarthritis[MeSH Terms]) OR (monoarthritis[MeSH Terms])	291,339
3	(polyarthritis[Title/Abstract]) OR (pauciarticular[Title/Abstract]) OR (oligoarthritis[Title/Abstract]) OR (monoarthritis[Title/Abstract])	11,668
4	(#2) OR (#3)	293,428
5	(#1) AND (#4)	11,553
6	tocilizumab OR sarilumab OR IL-6 inhibitor OR IL-6 blockage OR IL-6 blockade OR IL-6 blocker	38,694
7	(#5) AND (#6)	319

データベース：PubMed, ～2022/12/31

検索日　2023/2/1

資料A　JIA CQ5　文献検索式（Cochrane）

No.	検索式	検索件数
1	(arthritis, juvenile):ti,ab,kw	1018
2	(tocilizumab OR sarilumab OR IL-6 inhibitor OR IL-6 blockage OR IL-6 blockade OR IL-6 blocker)	16,007
3	(#1) AND (#2)	128

データベース：Cochrane, ～2022/12/31

検索日　2023/2/1

資料A　JIA CQ5　文献検索式（医中誌）

No.	検索式	検索件数
1	(関節炎-若年性/TH or 若年性特発性関節炎/AL)	3,762
2	関節型/AL or 少関節/AL or 多関節/AL	2,203
3	#1 and #2	402
4	(Tocilizumab/TH or トシリズマブ/AL) or (Sarilumab/TH or サリルマブ/AL) or (IL-6 inhibitor/AL or IL-6 blockage/AL or IL-6 blockade/AL or IL-6 blocker/AL orインターロイキン6阻害薬/AL)	5,678
5	#3 and #4	73
6	#5 and (PT=会議録除く)	36

データベース：医中誌, ～2022/12/31

検索日　2023/2/1

資料A　JIA CQ5　文献検索式（Embase）

No.	検索式	検索件数
1	arthritis, juvenile':ab,ti OR 'arthritis, juvenile'/exp	22,831
2	juvenile rheumatoid arthritis':ab,ti OR 'juvenile rheumatoid arthritis'/exp	23,359
3	polyarthritis:ab,ti OR pauciarticular:ab,ti OR oligoarthritis:ab,ti OR monoarthritis:ab,ti	14,657
4	etanercept OR adalimumab OR golimumab OR tocilizumab OR abatacept OR infliximab OR biosimilar	96,414
5	('arthritis, juvenile':ab,ti OR 'arthritis, juvenile'/exp) AND (polyarthritis:ab,ti OR pauciarticular:ab,ti OR oligoarthritis:ab,ti OR monoarthritis:ab,ti) AND (etanercept OR adalimumab OR golimumab OR tocilizumab OR abatacept OR infliximab OR biosimilar) AND ([english]/lim OR [japanese]/lim) AND [abstracts]/lim	281

データベース：Embase, ～2020/12/31

検索日　2021/1/10

資料B　JIA CQ5　文献検索フローチャート

CQ番号	JIA CQ5

MEDLINE (via Pubmed)から から特定した文献数	CENTRALから 特定した文献数	Embaseから 特定した文献数	医中誌から 特定した文献数	その他の情報源から 特定した文献数
319	128	281	36	1

↓

重複文献除外後の文献数　（n = 756 ）　重複文献数　（n= 8 ）

↓

スクリーニングした文献数　（1st Screening）
（n = 757 ）

→ 除外した文献数
（n = 740 ）

↓

適格性を評価した論文数　（2nd Screening）
（n = 16 ）

→ 除外した論文数
（n = 12 ）
＜除外理由＞
・Pが基準を満たさず　（n= 1 ）
・I/Cが基準を満たさず　（n= 5 ）
・デザインが異なる　（n= 5 ）
・Oが基準を満たさず　（n= 1 ）
・Ongoing study　（n= 0 ）
・Publication dateが2022/7/1以降　（n= 0 ）
・(TNFのみ)ガイドライン2014/2020に すでに組み込まれている　（n= 0 ）

↓

質的統合に組み入れた研究数/論文数
（n = 4 研究/ 4 論文）

↓

量的統合に加えた研究数　（meta-analysis）
（n = 1 研究

資料C JIA CQ5 バイアスのリスク(flare)

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	1	Brunner, 2015	TCZ+MTX	MTX	Flare	NA	+	+	+	+	+	+

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C JIA CQ5 バイアスのリスク（ACR pedi 30 ）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	1	Brunner, 2015	TCZ+MTX	MTX	ACR pedi 30	NA	+	+	+	+	+	+

+ Low risk

! Some concerns

- High risk

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C JIA CQ5 バイアスのリスク（ACR pedi 50 ）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	1	Brunner, 2015	TCZ+MTX	MTX	ACR pedi 50	NA	+	+	+	+	+	+

+ Low risk

! Some concerns

- High risk

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C JIA CQ5 バイアスのリスク（ACR pedi 70 ）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	1	Brunner, 2015	TCZ+MTX	MTX	ACR pedi 70	NA	+	+	+	+	+	+

+ Low risk

! Some concerns

- High risk

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C JIA CQ5 バイアスのリスク（ACR pedi 90 ）

Intention-to-treat

Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
1	Brunner, 2015	TCZ+MTX	MTX	ACR pedi 90	NA	+	+	+	+	+	+

+ Low risk

! Some concerns

- High risk

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C　JIA CQ5　バイアスのリスク（CHAQ-DI変化量）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	1	Brunner, 2015	TCZ+MTX	MTX	HAQ	NA	+	+	+	+	+	+

+ Low risk

! Some concerns

- High risk

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C JIA CQ5 バイアスのリスク（SAE ）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	1	Brunner, 2015	TCZ+MTX	MTX	SAE	NA	+	+	+	+	+	+

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料 D　JIA CQ5　エビデンスプロファイル　Question: IL-6i＋MTX compared to placebo+MTX for pJIA

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IL-6i＋MTX	placebo+MTX	Relative (95% CI)	Absolute (95% CI)		
flare												
1	randomised trials	not serious	not serious	not serious	serious[a,c]	none	21/82 (25.6%)	39/81 (48.1%)	RR 0.53 (0.35 to 0.82)	226 fewer per 1,000 (from 313 fewer to 87 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
ACR pedi 30												
1	randomised trials	not serious	not serious	not serious	serious[a,b]	none	61/82 (74.4%)	44/81 (54.3%)	RR 1.37 (1.08 to 1.74)	201 more per 1,000 (from 43 more to 402 more)	⨁⨁⨁◯ Moderate	CRITICAL
ACR pedi 50												
1	randomised trials	not serious	not serious	not serious	serious[a,b]	none	60/82 (73.2%)	42/81 (51.9%)	RR 1.41 (1.10 to 1.81)	213 more per 1,000 (from 52 more to 420 more)	⨁⨁⨁◯ Moderate	IMPORTANT
ACR pedi 70												
1	randomised trials	not serious	not serious	not serious	serious[a,b]	none	53/82 (64.6%)	34/81 (42.0%)	RR 1.54 (1.14 to 2.08)	227 more per 1,000 (from 59 more to 453 more)	⨁⨁⨁◯ Moderate	IMPORTANT
ACR pedi 90												
1	randomised trials	not serious	not serious	not serious	serious[a,b]	none	37/82 (45.1%)	19/81 (23.5%)	RR 2.68 (1.37 to 5.26)	394 more per 1,000 (from 87 more to 999 more)	⨁⨁⨁◯ Moderate	IMPORTANT
CHAQ-DI 変化量												
1	randomised trials	not serious	not serious	not serious	serious[a,d]	none	82	81	-	MD 0.08 lower (0.29 lower to 0.13 higher)	⨁⨁⨁◯ Moderate	CRITICAL
SAE												
1	randomised trials	not serious	not serious	not serious	very serious[a,e]	none	3/82 (3.7%)	3/81 (3.7%)	RR 0.99 (0.21 to 4.75)	0 fewer per 1,000 (from 29 fewer to 117 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; MD: mean difference; OR: odds ratio; RR: risk ratio

Explanations

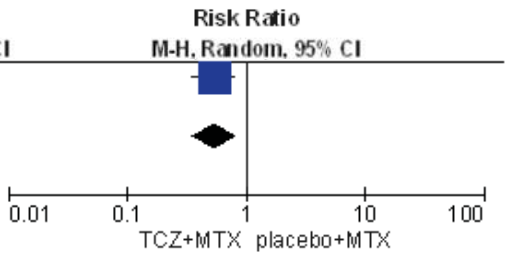
a. Sample size is small
b. The 95% confidence interval of risk ratio includes decision threshold of 1.25.
c. The 95% confidence interval of risk ratio includes decision threshold of 0.75.
d. The 95% confidence interval of risk ratio includes decision threshold of -0.22
e. The 95% confidence interval of risk ratio includes decision thresholds of 0.75 and 1.25.

資料 E　JIA CQ5　フォレストプロット

flare

Study or Subgroup	TCZ+MTX Events	Total	placebo+MTX Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Brunner 2015	21	82	39	81	100.0%	0.53 [0.35, 0.82]
Total (95% CI)		**82**		**81**	**100.0%**	**0.53 [0.35, 0.82]**
Total events	21		39			

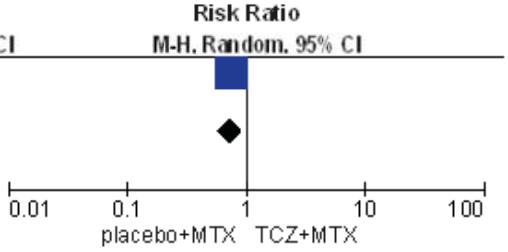
Heterogeneity: Not applicable
Test for overall effect: Z = 2.86 (P = 0.004)



ACR pedi 30

Study or Subgroup	placebo+MTX Events	Total	TCZ+MTX Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Brunner 2015	44	81	61	82	100.0%	0.73 [0.58, 0.93]
Total (95% CI)		**81**		**82**	**100.0%**	**0.73 [0.58, 0.93]**
Total events	44		61			

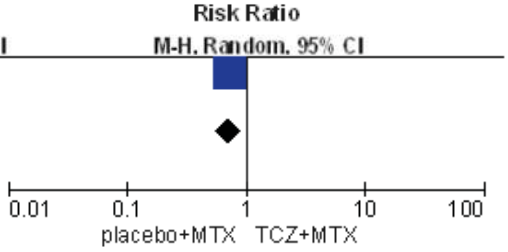
Heterogeneity: Not applicable
Test for overall effect: Z = 2.60 (P = 0.009)



ACR pedi 50

Study or Subgroup	placebo+MTX Events	Total	TCZ+MTX Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Brunner 2015	42	81	60	82	100.0%	0.71 [0.55, 0.91]
Total (95% CI)		**81**		**82**	**100.0%**	**0.71 [0.55, 0.91]**
Total events	42		60			

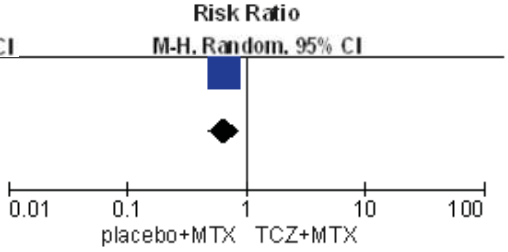
Heterogeneity: Not applicable
Test for overall effect: Z = 2.73 (P = 0.006)



ACR pedi 70

Study or Subgroup	placebo+MTX Events	Total	TCZ+MTX Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Brunner 2015	34	81	53	82	100.0%	0.65 [0.48, 0.88]
Total (95% CI)		**81**		**82**	**100.0%**	**0.65 [0.48, 0.88]**
Total events	34		53			

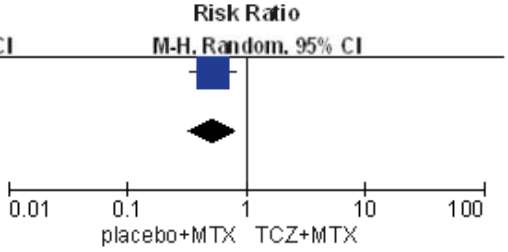
Heterogeneity: Not applicable
Test for overall effect: Z = 2.80 (P = 0.005)



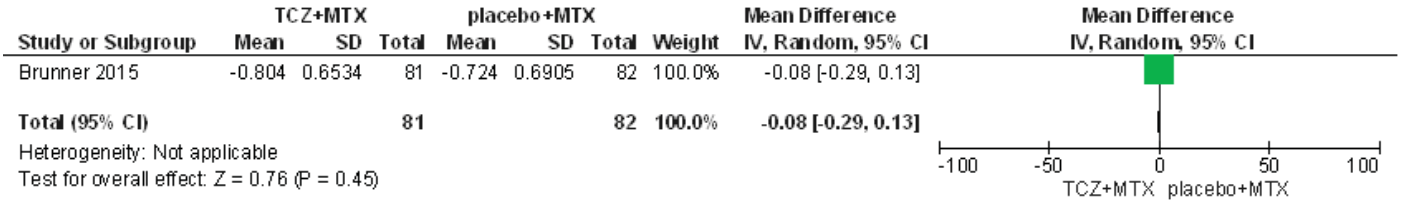
ACR pedi 90

Study or Subgroup	placebo+MTX Events	Total	TCZ+MTX Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Brunner 2015	19	81	37	82	100.0%	0.52 [0.33, 0.82]
Total (95% CI)		**81**		**82**	**100.0%**	**0.52 [0.33, 0.82]**
Total events	19		37			

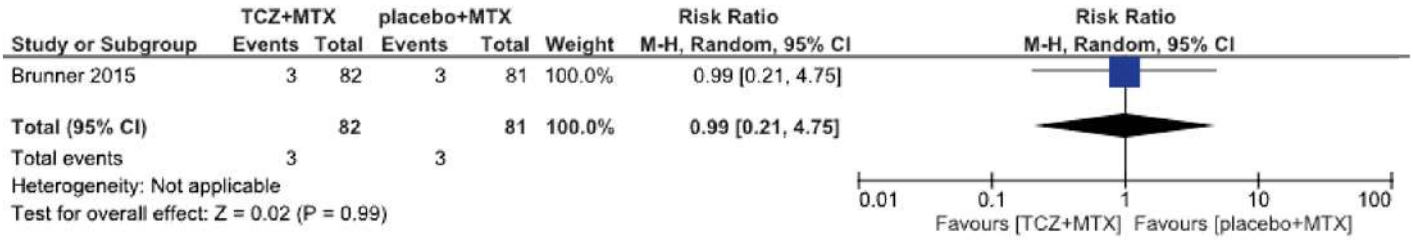
Heterogeneity: Not applicable
Test for overall effect: Z = 2.79 (P = 0.005)



CHAQ-DI 変化量



SAE



No.	検索式	検索件数
#1	(("oligoarthritis"[Title/Abstract] OR "polyarthritis"[Title/Abstract] OR "arthritis"[Title/Abstract]) AND ("pediat*"[Title/Abstract] OR "paediat*"[Title/Abstract] OR "child*"[Title/Abstract] OR "juvenile"[Title/Abstract])) OR "arthritis, juvenile"[MeSH Terms]	20,700
#2	“janus kinase inhibitors”[mh] OR "janus kinases"[mh] OR “janus kinase inhibitor*”[tiab] OR “JAK inhibitor*”[tiab] OR JAK1*[tiab] OR JAK2*[tiab] OR JAK3*[tiab] OR TYK2*[tiab] OR tsDMARD*[tiab] OR “ts DMARD*”[tiab] OR ”targeted synthetic DMARD*”[tiab] OR jakinib*[tiab]	24,392
#3	tofacitinib[nm] OR tofacitinib[tiab] OR tasocitinib[tiab] OR Xeljanz[tiab] OR Jakvinus[tiab] OR CP690*[tiab] OR CP-690*[tiab]	2,513
#4	baricitinib[nm] OR baricitinib[tiab] OR “baricitinib phosphate”[tiab] OR “baricitinib phosphate salt” [tiab] OR Olumiant[tiab] OR INCB028050[tiab] OR INCB-28050[tiab] OR LY3009104[tiab] OR LY-3009104[tiab]	1,016
#5	peficitinib[nm] OR peficitinib[tiab] OR Smyraf[tiab] OR ASP015K[tiab] OR ASP-015K[tiab] OR AS1940150BR[tiab] OR AS-1940150BR[tiab] OR JKT201A[tiab] OR JKT-201A[tiab]	97
#6	upadacitinib[nm] OR upadacitinib[tiab] OR Rinvoq[tiab] OR ABT494[tiab] OR ABT-494[tiab] OR A1293543[tiab] OR A-1293543[tiab]	403
#7	filgotinib [nm] OR filgotinib[tiab] OR Jyseleca[tiab] OR GS6034[tiab] OR GS-6034[tiab] OR GLPG0634[tiab] OR GLPG-0634[tiab]	233
#8	#2 OR #3 OR #4 OR #5 OR #6 OR #7	25,954
#9	(“randomized controlled trial”[pt] OR “controlled clinical trial”[pt] OR “clinical trial”[pt] OR “drug therapy”[sh] OR randomly[tiab] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR trial[tiab] OR groups[tiab]) NOT ("case reports"[pt] OR "case report*"[tiab] OR "case series"[tiab]) NOT (animals[mh] NOT humans[mh])	4,625,695
#10	1900/1/1:2022/6/30[dp]	34,291,273
#11	#1 AND #8 AND #9 AND #10	43

データベース：PubMed, ～2022/6/30

検索日　2022/10/25

No.	検索式	検索件数
#1	((oligoarthritis:ti,ab OR polyarthritis:ti,ab OR arthritis:ti,ab) AND (pediat*:ti,ab OR paediat*:ti,ab OR child*:ti,ab OR juvenile:ti,ab)) OR [mh "arthritis, juvenile"]	1,376
#2	(MeSH descriptor: [Janus Kinase Inhibitors] explode all trees)	102
#3	(MeSH descriptor: [Janus Kinases] explode all trees)	159
#4	("janus kinase" NEXT inhibitor*):ti,ab OR ("JAK" NEXT inhibitor*):ti,ab OR JAK1*:ti,ab OR JAK2*:ti,ab OR JAK3*:ti,ab OR TYK2*:ti,ab OR tsDMARD*:ti,ab OR ("ts" NEXT DMARD*):ti,ab OR ("targeted synthetic" NEXT DMARD*):ti,ab OR jakinib*:ti,ab	2,157
#5	tofacitinib:ti,ab OR tasocitinib:ti,ab OR Xeljanz:ti,ab OR Jakvinus:ti,ab OR CP690*:ti,ab OR CP-690*:ti,ab	1,008
#6	baricitinib:ti,ab OR "baricitinib phosphate":ti,ab OR "baricitinib phosphate salt":ti,ab OR Olumiant:ti,ab OR INCB028050:ti,ab OR INCB-28050:ti,ab OR LY3009104:ti,ab OR LY-3009104:ti,ab	573
#7	peficitinib:ti,ab OR Smyraf:ti,ab OR ASP015K:ti,ab OR ASP-015K:ti,ab OR AS1940150BR:ti,ab OR AS-1940150BR:ti,ab OR JKT201A:ti,ab OR JKT-201A:ti,ab	53
#8	upadacitinib:ti,ab OR Rinvoq:ti,ab OR ABT494:ti,ab OR ABT-494:ti,ab OR A1293543:ti,ab OR A-1293543:ti,ab	555
#9	filgotinib:ti,ab OR Jyseleca:ti,ab OR GS6034:ti,ab OR GS-6034:ti,ab OR GLPG0634:ti,ab OR GLPG-0634:ti,ab	310
#10	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	3,390
#11	#1 AND #10	42
#12	("randomized controlled trial":pt OR "controlled clinical trial":pt OR "clinical trial":pt OR [mh "drug therapy"] OR randomly:ti,ab OR randomized:ti,ab OR " randomised":ti,ab OR placebo:ti,ab OR trial:ti,ab OR groups:ti,ab) NOT ("case reports":pt OR "case" NEXT report*:ti,ab OR "case series":ti,ab) NOT ([mh animals] NOT [mh humans])	1,524,399
#13	#11 AND #12 with Publication Year from 1900 to 2022, in Trials	42

データベース：Cochrane, ～2022/6/30

検索日　2022/10/11

資料A　JIA CQ6　文献検索式（医中誌）

No.	検索式	検索件数
#1	関節炎-若年性/TH OR 若年性特発性関節炎/TA OR 若年性関節炎/TA OR 若年性関節リウマチ/TA OR "juvenile idiopathic arthritis"/TA	4,189
#2	"Janus Kinase Inhibitors"/TH OR "Janus Kinase"/TA OR JAK/TA OR tsDMARD/TA OR “ts DMARD”/TA OR “targeted synthetic DMARD”/TA OR 標的合成疾患修飾性抗リウマチ薬/TA	5,862
#3	Tofacitinib/TH orトファシチニブ/TA or tofacitinib/TA or tasocitinib/TA or ゼルヤンツ/TA or Xeljanz/TA or Jakvinus/TA	193
#4	Baricitinib/TH or バリシチニブ/TA or baricitinib/TA or オルミエント/TA or Olumiant/TA	545
#5	Peficitinib/TH or ペフィシチニブ/TA or peficitinib/TA or スマイラフ/TA or Smyraf/TA	85
#6	Upadacitinib/TH or ウパダシチニブ/TA or upadacitinib/TA or リンヴォック/TA or Rinvoq/TA	176
#7	Filgotinib/TH or フィルゴチニブ/TA or filgotinib/TA or ジセレカ/TA or Jyseleca/TA	118
#8	#2 OR #3 OR #4 OR #5 OR #6 OR #7	6,023
#9	DT=1900:2022	15,068,613
#10	#1 AND #8 AND #9	6
#11	#10 and (メタアナリシス/TH or システマティックレビュー/TH or 診療ガイドライン/TH)	1
#12	#10 and (RD=メタアナリシス,診療ガイドライン)	0
#13	#10 and (メタアナリシス/TA or システマティックレビュー/ TA or 診療ガイドライン/ TA)	0
#14	#11 or #12 or #13	1
#15	#10 and 介入研究/TH	0
#16	#10 and (RD=ランダム化比較試験)	0
#17	#10 and (介入研究/TA or 臨床試験/TA or ランダム化比較試験/TA or 無作為化比較試験/TA or 第I相試験/TA or 第 II 相試験/TA or 第III相試験/TA or 第IV相試験/TA or 非劣性試験/TA or 同等性試験/TA or ランダム割付/TA)	0
#18	(#15 or #16 or #17) not #14	0

データベース：医中誌, ～2022/6/30

検索日　2022/10/10

No.	検索式	検索件数
#1	((oligoarthritis:ti,ab OR polyarthritis:ti,ab OR arthritis:ti,ab) AND (pediat*:ti,ab OR paediat*:ti,ab OR child*:ti,ab OR juvenile:ti,ab)) OR 'arthritis, juvenile'/exp	37,424
#2	janus kinase inhibitors'/exp OR 'janus kinase inhibitor*':ti,ab OR 'JAK inhibitor*':ti,ab OR JAK1*:ti,ab OR JAK2*:ti,ab OR JAK3*:ti,ab OR TYK2*:ti,ab OR tsDMARD*:ti,ab OR 'ts DMARD*':ti,ab OR 'targeted synthetic DMARD*':ti,ab OR jakinib*:ti,ab	49,224
#3	tofacitinib:tn OR tofacitinib:ti,ab OR tasocitinib:ti,ab OR Xeljanz:ti,ab OR Jakvinus:ti,ab OR CP690*:ti,ab OR CP-690*:ti,ab	4,924
#4	baricitinib:tn OR baricitinib:ti,ab OR 'baricitinib phosphate':ti,ab OR 'baricitinib phosphate salt':ti,ab OR Olumiant:ti,ab OR INCB028050:ti,ab OR INCB-28050:ti,ab OR LY3009104:ti,ab OR LY-3009104:ti,ab	1,809
#5	peficitinib:tn OR peficitinib:ti,ab OR Smyraf:ti,ab OR ASP015K:ti,ab OR ASP-015K:ti,ab OR AS1940150BR:ti,ab OR AS-1940150BR:ti,ab OR JKT201A:ti,ab OR JKT-201A:ti,ab	140
#6	upadacitinib:tn OR upadacitinib:ti,ab OR Rinvoq:ti,ab OR ABT494:ti,ab OR ABT-494:ti,ab OR A1293543:ti,ab OR A-1293543:ti,ab	976
#7	filgotinib:tn OR filgotinib:ti,ab OR Jyseleca:ti,ab OR GS6034:ti,ab OR GS-6034:ti,ab OR GLPG0634:ti,ab OR GLPG-0634:ti,ab	541
#8	#2 OR #3 OR #4 OR #5 OR #6 OR #7	49,404
#9	'randomized controlled trial'/de	735,552
#10	'controlled clinical trial'/de	438,345
#11	random*:ti,ab,tt	1,849,306
#12	'randomization'/de	95,295
#13	'intermethod comparison'/de	291,161
#14	placebo:ti,ab,tt	349,537
#15	compare:ti,tt OR compared:ti,tt OR comparison:ti,tt	601,137
#16	(evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)	2,589,181
#17	(open NEXT/1 label):ti,ab,tt	101,025
#18	((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt	264,092
#19	'double blind procedure'/de	200,651
#20	(parallel NEXT/1 group*):ti,ab,tt	30,304
#21	(crossover:ti,ab,tt OR 'cross over':ti,ab,tt)	119,146
#22	((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt	431,551
#23	(assigned:ti,ab,tt OR allocated:ti,ab,tt)	461,190
#24	(controlled NEAR/8 (study OR design OR trial)):ti,ab,tt	430,331
#25	(volunteer:ti,ab,tt OR volunteers:ti,ab,tt)	274,346
#26	'human experiment'/de	599,592
#27	trial:ti,tt	379,107
#28	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27	5,997,888
#29	(((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database or databases)):ti,ab,tt) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'randomly assigned':ti,ab,tt))	2,943
#30	('cross - sectional study'/de NOT ('randomized controlled trial'/de OR 'controlled clinical study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'control group':ti,ab,tt OR 'control groups':ti,ab,tt))	347,318
#31	('case control*':ti,ab,tt AND random*:ti,ab,tt NOT ('randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt))	20,323
#32	'systematic review':ti,tt NOT (trial:ti,tt OR study:ti,tt)	225,437
#33	(nonrandom*:ti,ab,tt NOT random*:ti,ab,tt)	18,184
#34	'random field*':ti,ab,tt	2,763
#35	('random cluster' NEAR/4 sampl*):ti,ab,tt	1,598
#36	(review:ab AND review:it) NOT trial:ti,tt	1,024,858
#37	'we searched':ab AND (review:ti,tt OR review:it)	44,237
#38	'update review':ab	127
#39	(databases NEAR/5 searched):ab	58,399
#40	((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de)	1,178,732
#41	('animal experiment'/de NOT ('human experiment'/de OR 'human'/de))	2,473,859
#42	#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41	4,104,523
#43	#28 NOT #42	5,308,246
#44	[1900-2022]/py	42,068,901
#45	#1 AND #8 AND #43 AND #44	61

データベース：Embase, ～2022/6/30

検索日　2022/10/27

資料B　JIA CQ6　文献検索フローチャート

CQ番号	JIA CQ6

MEDLINE (via Pubmed)から から特定した文献数	CENTRALから 特定した文献数	Embaseから 特定した文献数	医中誌から 特定した文献数
43	42	61	0

その他の情報源から 特定した文献数
0

↓

重複文献除外後の文献数　（n = 133 ）　重複文献数　（n= 13 ）

↓

その他の情報源から特定した文献数　（n = 0 ）

↓

スクリーニングした文献数　（1st Screening）　（n = 133 ）

→ 除外した文献数　（n = 120 ）

↓

適格性を評価した論文数　（2nd Screening）　（n = 13 ）

→ 除外した論文数　（n = 4 ）

＜除外理由＞

- Pが基準を満たさず　（n= 2 ）
- I/Cが基準を満たさず　（n= 0 ）
- デザインが異なる　（n= 2 ）
- Oが基準を満たさず　（n= 0 ）
- Ongoing study　（n= 0 ）
- Publication dateが2022/7/1以降　（n= 0 ）
- (TNFのみ)ガイドライン2014/2020にすでに組み込まれている　（n= 0 ）

↓

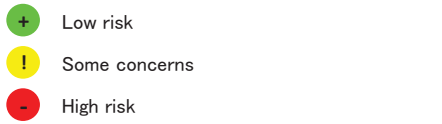
質的統合に組み入れた研究数/論文数　（n = 2 研究/ 9 論文）

↓

量的統合に加えた研究数　（meta-analysis）　（n = 2 研究）

資料C JIA CQ6 バイアスのリスク（Flare ）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	7	JUVE-BASIS	Bari→Bari	Bari→PBO	flare rate	1	+	+	+	+	+	+
	1	Ruperto, N.	Tofa→Tofa	Tofa→PBO	flare rate	1	+	+	+	+	+	+



D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C JIA CQ6 バイアスのリスク（ACR Pedi 30, JADAS-27-CRP）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	8	JUVE-BASIS	Bari→Bari	Bari→PBO	composite measure	1	+	+	+	+	+	+
	2	Ruperto, N.	Tofa→Tofa	Tofa→PBO	composite measure	1	+	+	!	+	+	!

+ Low risk

! Some concerns

- High risk

D1 Randomisation process

D2 Deviations from the intended interventions

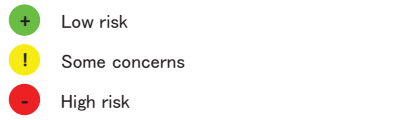
D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C JIA CQ6 バイアスのリスク(参考:ACR Pedi 30, JADAS-27-CRP)

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	11	JUVE-BASIS	Bari→Bari	Bari→PBO	composite measure	1	+	+	+	+	+	+
	6	Ruperto, N.	Tofa→Tofa	Tofa→PBO	composite measure	1	+	+	+	+	+	+



D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C JIA CQ6 バイアスのリスク（ΔC-HAQ DI）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	3	Ruperto, N.	Tofa→Tofa	Tofa→PBO	ΔC-HAQ DI	1	+	+	!	+	+	!

+ Low risk

! Some concerns

- High risk

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料C JIA CQ6 バイアスのリスク（Serious adverse event ）

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	9	JUVE-BASIS	Bari→Bari	Bari→PBO	SAE	1	+	+	+	+	+	+
	4	Ruperto, N.	Tofa→Tofa	Tofa→PBO	SAE	1	+	+	+	+	+	+

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

資料 D　JIA CQ6　エビデンスプロファイル　Question: JAKi compared to PBO for JIA

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JAKi	PBO	Relative (95% CI)	Absolute (95% CI)		
Outcomes used for the recommendation												
Flare												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	35/154 (22.7%)	79/151 (52.3%)	RR 0.44 (0.28 to 0.69)	293 fewer per 1,000 (from 377 fewer to 162 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
ΔJADAS-27-CRP												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	49	32	-	MD 4.36 lower (4.79 lower to 3.93 lower)	⨁⨁⨁◯ Moderate	CRITICAL
ACR pedi 30												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	106/154 (68.8%)	64/151 (42.4%)	RR 1.61 (1.30 to 1.99)	259 more per 1,000 (from 127 more to 420 more)	⨁⨁⨁◯ Moderate	CRITICAL
臨床的非活動状態達成割合（JIA/ACR inactive disease）												
2	randomised trials	not serious	not serious	not serious	serious[c]	none	32/154 (20.8%)	18/151 (11.9%)	RR 1.74 (1.03 to 2.97)	88 more per 1,000 (from 4 more to 235 more)	⨁⨁⨁◯ Moderate	CRITICAL
ΔC-HAQ DI												
1	randomised trials	not serious	not serious	not serious	serious[d]	none	49	33	-	MD 0.12 lower (0.14 lower to 0.1 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Serious adverse event												
2	randomised trials	not serious	not serious	not serious	very serious[e]	none	5/170 (2.9%)	3/166 (1.8%)	RR 1.51 (0.40 to 5.72)	9 more per 1,000 (from 11 fewer to 85 more)	⨁⨁◯◯ Low	CRITICAL
Serious infection												
2	randomised trials	not serious	not serious	not serious	very serious[e]	none	3/170 (1.8%)	0/166 (0.0%) 6.5%[f]	RR 3.84 (0.43 to 34.38)	165 more per 1,000 (from 37 fewer to 1,000 more)	⨁⨁◯◯ Low	CRITICAL

Outcomes related to the recommendation

ACR pedi 50

2	randomised trials	not serious	not serious	not serious	serious[c]	none	100/154 (64.9%)	63/151 (41.7%)	RR 1.54 (1.24 to 1.92)	225 more per 1,000 (from 100 more to 384 more)	⨁⨁⨁◯ Moderate	CRITICAL

ACR pedi 70

2	randomised trials	not serious	not serious	not serious	serious[c]	none	83/154 (53.9%)	55/151 (36.4%)	RR 1.48 (1.14 to 1.91)	175 more per 1,000 (from 51 more to 331 more)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; MD: mean difference; RR: risk ratio

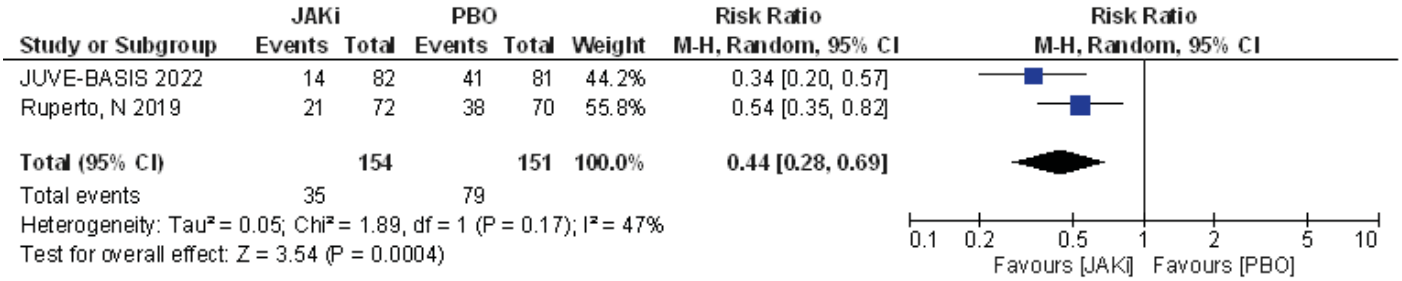
Explanations

a. The total sample size and the total number of the events are small.
b. The 95% confidence interval of the mean difference includes the minimally important difference of -5.5.
c. The 95% confidence interval of the risk ratio includes the decision threshold of 1.25.
d. The total sample size is small.
e. The 95% confidence interval of the risk ratio includes both the decision thresholds of 0.75 and 1.25.
f. Extrapolated from the paper: Ruperto H, et al. Lancet. 2008; 372: 383-391.

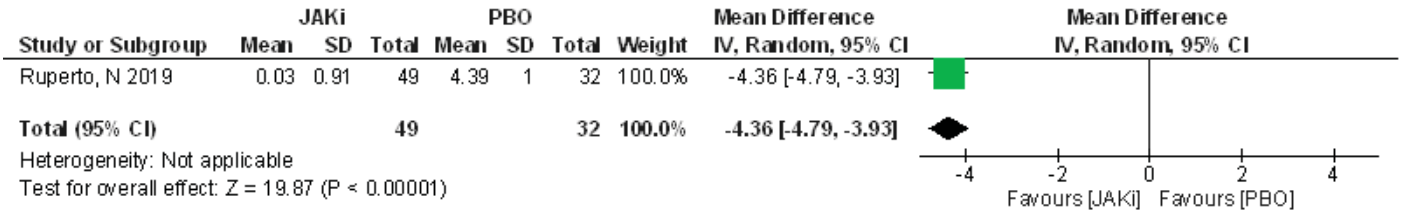
資料 E　JIA CQ6 フォレストプロット

Outcomes used for the recommendation

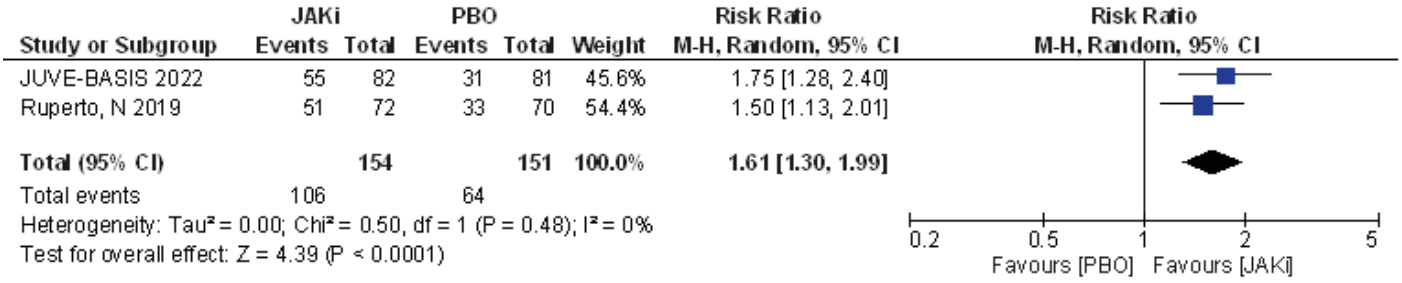
Flare



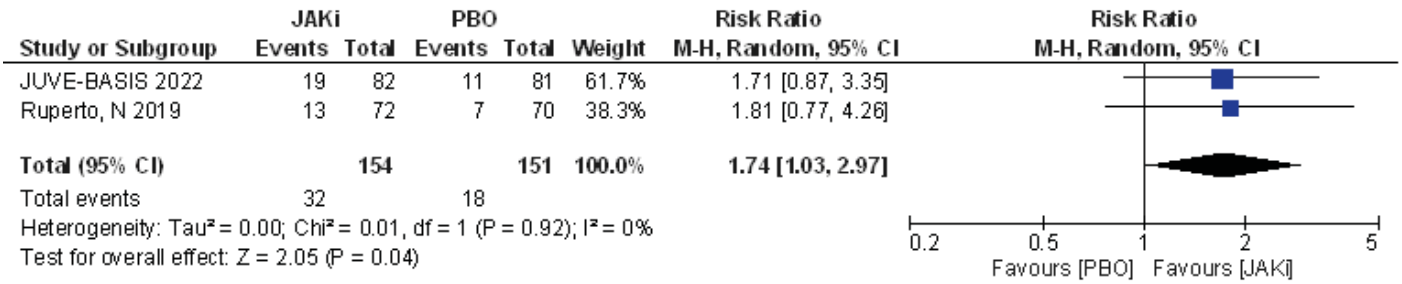
ΔJADAS-27-CRP



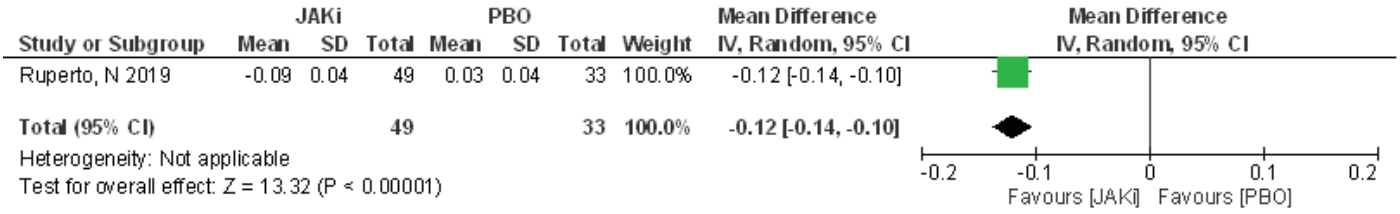
ACRpedi30



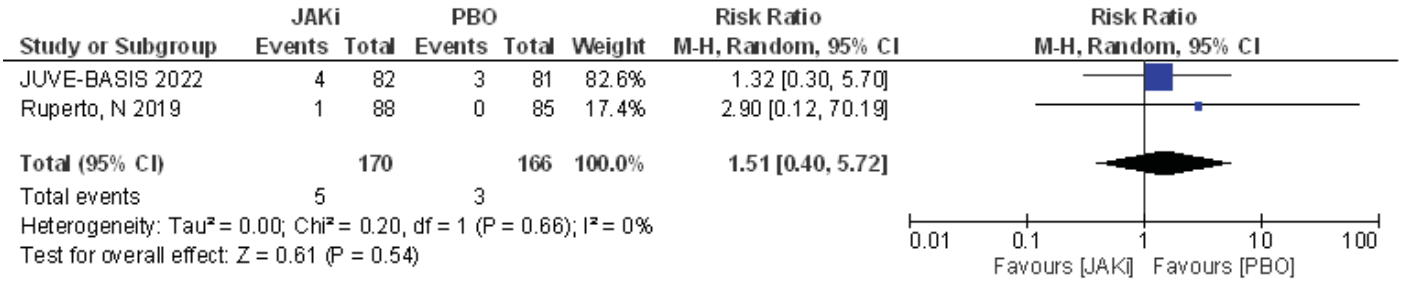
臨床的非活動状態達成割合（JIA/ACR inactive disease）



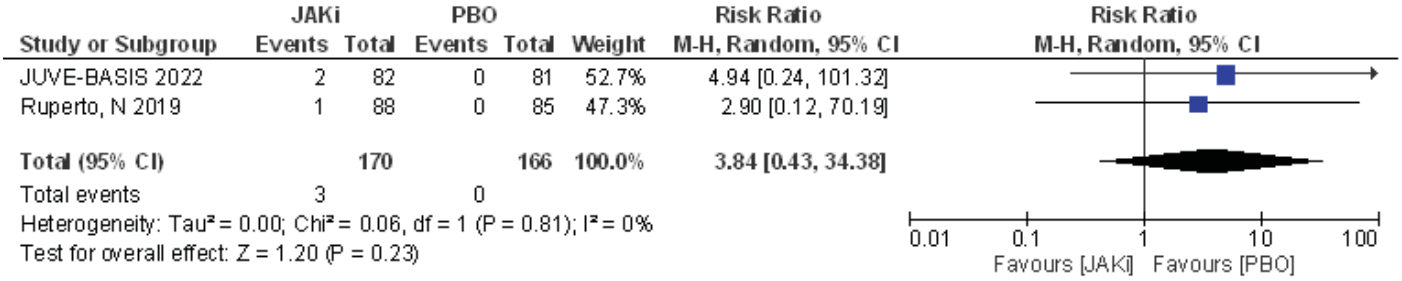
Δ C-HAQ DI



Serious adverse event



Serious infection

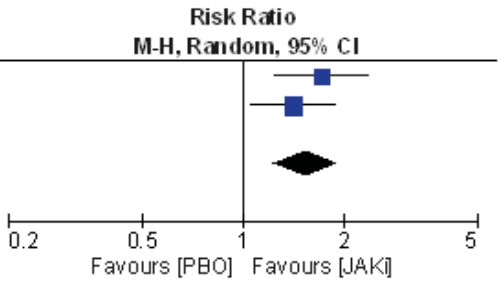


Outcomes used for the recommendation

ACR pedi 50

Study or Subgroup	JAKi Events	JAKi Total	PBO Events	PBO Total	Weight	Risk Ratio M-H, Random, 95% CI
JUVE-BASIS 2022	52	82	30	81	45.0%	1.71 [1.23, 2.38]
Ruperto, N 2019	48	72	33	70	55.0%	1.41 [1.05, 1.90]
Total (95% CI)		**154**		**151**	**100.0%**	**1.54 [1.24, 1.92]**
Total events	100		63			

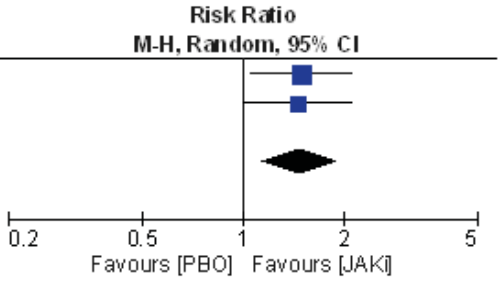
Heterogeneity: Tau² = 0.00; Chi² = 0.72, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 3.85 (P = 0.0001)



ACR pedi 70

Study or Subgroup	JAKi Events	JAKi Total	PBO Events	PBO Total	Weight	Risk Ratio M-H, Random, 95% CI
JUVE-BASIS 2022	44	82	29	81	52.4%	1.50 [1.05, 2.14]
Ruperto, N 2019	39	72	26	70	47.6%	1.46 [1.01, 2.11]
Total (95% CI)		**154**		**151**	**100.0%**	**1.48 [1.14, 1.91]**
Total events	83		55			

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 2.99 (P = 0.003)



資料 F　JIA CQ6　Evidence to Decision テーブル

CQ (No.PICO)

JIA CQ6：JIA 少関節炎型または多関節炎型の患者（児）に，JAK 阻害薬は有用か？

患者：JAK 阻害薬で JIA/ACR pedi 30 response を達成した関節型 JIA 患者

介入：JAK 阻害薬継続

対照：JAK 阻害薬を PBO へ切り替え

主要アウトカム(重大)：JIA の再燃率、JADAS-27-CRP、JIA/ACR pedi 30、寛解率(ID 達成率) 、C-HAQ DI、重篤な副作用頻度、重篤な感染症頻度

副次アウトカム(重要)：JIA/ACR pedi 50，70 達成率

背景：関節型 JIA の現在の標準治療は、まず MTX で治療を開始し、効果不十分な場合に追加治療を検討する。関節型 JIA 患者に対して、JAK 阻害薬が推奨されるかを検討することは、治療方針決定に重要である。

基準 1. 問題　この問題は優先事項か？		
判断	**リサーチエビデンス**	**追加的考察**
○ いいえ ○ おそらく，いいえ ○ おそらく，はい ● はい ○ さまざま ○ 分からない	JMDC claim データベースの解析では 30 歳未満の関節型 JIA の 40-54%、指定難病データベースの解析では 20 歳代の関節型 JIA の約 85%で生物学的製剤を使用されており、MTX による治療コントロールが不十分な JIA 患者が多く存在すると考えられる(1)。これらの患者に対して JAK 阻害薬の追加治療が有用かを検討することは、治療方針の決定に重要である。	日本で関節リウマチに承認された JAK 阻害薬は 5 種類あるが、関節型 JIA に対する JAK 阻害薬の有用性についてはこれまで検討されていない。JIA に対する JAK 阻害薬の治験は行われているものの、2023 年 6 月現在で保険適用外となっている。
基準 2. 望ましい効果　予期される望ましい効果はどの程度のものか？		
判断	**リサーチエビデンス**	**追加的考察**
○ わずか ● 小さい ○ 中 ○ 大きい ○ さまざま ○ 分からない	26~32 週の MTX+JAK 阻害薬は、MTX との比較で 重大なアウトカムとして 1. 再燃阻止の絶対効果(26-32 週時)は、再燃が 1000 人あたり 293(－162～－377)人減少 、相対効果は RR 0.44(0.28～0.69)	

	2. ΔJADAS-27-CRP の絶対効果(26-32 週時)は－4.36 (－3.93～－4.79) 3. JIA/ACR pedi 30 (26-32 週時) 達成に関する絶対効果は 1000 人あたり 259(127～420)人増加 、相対効果 RR 1.61(1.30～1.99) 4. Inactive disease(44 週)の絶対効果は 1000 人あたり 88(4～235)人増加、相対効果は RR 1.74(1.03～2.94) 5. ΔC-HAQ DI(44 週)の絶対効果は－0.12(－0.14～－0.10) 以上より、JAK 阻害により関節型 JIA の関節炎は抑制されると考えられ、望ましい効果は「小さい」と判断した。	

基準 3. 望ましくない効果　予期される望ましくない効果はどの程度のものか？

判断	リサーチエビデンス	追加的考察
○ 大きい ● 中 ○ 小さい ○ わずか ○ さまざま ○ 分からない	26~32 週の MTX+JAK 阻害薬は、MTX との比較で 重大なアウトカムとして 1. JAK 阻害薬による重篤な副作用の絶対効果は 1000 人あたり 27 (7～103) 人増加、相対効果 RR 1.51(0.40～5.72) 2. 重篤な感染症の絶対効果は 1000 人あたり 250 (－28～1000) 人増加、相対効果 RR 3.84(0.43～34.38) 以上より、JAK 阻害薬による、重症副作用や重症感染症の望ましくない効果は「中」と判断した。	

基準 4. エビデンスの確実性　効果に関する全体的なエビデンスの確実性はどの程度か？

判断	リサーチエビデンス	追加的考察
○ 非常に低 ● 低 ○ 中 ○ 高 ○ 採用研究なし	重大なアウトカムに関する介入の効果は益が増加、害が増加しており、異なる方向となるため、重大なアウトカムの中でエビデンスレベルの最も低い「低」とした。	

基準 5.　価値観　人々が主要なアウトカムをどの程度重視するかについて重要な不確実性やばらつきはあるか？

判断	リサーチエビデンス	追加的考察
○ 重要な不確実性またはばらつきあり ○ 重要な不確実性またはばらつきの可能性あり ● 重要な不確実性またはばらつきはおそらくなし ○ 重要な不確実性またはばらつきはなし	なし	JIA 患者の治療において、疼痛改善を含む疾患活動性の改善は望まれる治療効果であり、副作用や感染症が望まれない効果であることに関するばらつきはおそらくないものと考える。

基準 6. 効果のバランス　望ましい効果と望ましくない効果のバランスは介入もしくは比較対照を支持するか？

判断	リサーチエビデンス	追加的考察
○ 比較対照が優れている ○ 比較対照がおそらく優れている ○ 介入も比較対照もいずれも支持しない ● おそらく介入が優れている ○ 介入が優れている ○ さまざま ○ 分からない	JAK 阻害薬の介入によって、望ましい効果の大きさは小で、望ましくない効果の大きさは中であった。ただし、重篤な感染症の絶対効果が重篤な副作用の絶対効果を大きく上回っており、これは他の臨床試験の頻度を引用して計算したためであり、推定値が不正確な可能性を考慮する必要がある。 本ガイドライン作成時点において、我が国の JIA に対する JAK 阻害薬の効果や長期使用における安全性のデータがないが、益と害のバランスから「おそらく介入が優れている」と判断した。	重大なアウトカムの NNT は、再燃阻止が 3.4、JIA/ACR pedi 30 達成が 3.9、ID 達成率が 11.4、NNH は重篤な副作用が 111、重篤感染症が 8 であった。

基準 7. 費用対効果　その介入の費用対効果は介入または比較対照のどちらを支持するか？

判断	リサーチエビデンス	追加的考察
○ 比較対照の費用対効果がよい ○ 比較対照の費用対効果がおそらくよい ○ 介入も比較対照もいずれも支持しない ○ 介入の費用対効果がおそらくよい ○ 介入の費用対効果がよい ○ さまざま ● 採用研究なし	費用対効果に関する日本のエビデンスはない。	BAR の薬価は 2mg/4mg: 2705.90 円/ 5274.90 円(2023 年 7 月現在) UPA に関しては小児において体重に応じた懸濁液が治験で用いられているが薬価などは不明。 関節型 JIA において中程度の経済的負担があったとしても、病勢をコントロールすることで障害を残さず成長する可能性が高まることから、介入による費用対効果は大きいことが予想される。

基準 8. 必要資源量　資源利用はどの程度大きいか？

判断	リサーチエビデンス	追加的考察
○ 大きな増加 ● 中等度の増加 ○ 無視できるほどの増加や減少 ○ 中等度の減少 ○ 大きな減少 ○ さまざま ○ 分からない	経口薬のため追加で必要な医療資源はない。	患者一人にかかる BAR のコストとしては 1 か月 30 日として、9 歳以上において 4mg/day で約 158,247.00 円/月、9 歳未満で 2mg/day の治療が想定されることから、81,177.00 円/月程度コストがかかる。 小児慢性特定疾病医療費助成制度または指定難病医療給付制度の対象となれば、一般所得家庭で上限 1～2 万円/月程度の負担増となる。 2 割負担(未就学児)では 16,235.40 円/月、3 割負担(小学生以上)では 24,353.10～47,474.10 円/月増加するが自治体による乳幼児医療費助成制度なども適用される。 UPA 懸濁液の必要資源量に関しては不明。

基準 9. 容認性　この選択肢は重要な利害関係者にとって妥当なものか？

判断	リサーチエビデンス	追加的考察
○ いいえ ○ おそらく，いいえ ● おそらく，はい ○ はい ○ さまざま ○ 分からない	なし	薬剤費は高額であるものの、効果のバランスから JAK 阻害薬の関節型 JIA 患者に対する使用は患者および臨床医にとってはおそらく妥当な選択肢になると考えられる。しかし、一部の臨床医や患者は長期安全性が確立されていないことから反対する可能性がある。競合する可能性がある生物学的製剤の製造販売者は反対する可能性がある。

基準 10. 実行可能性　その介入は実行可能か？

判断	リサーチエビデンス	追加的考察
● いいえ ○ おそらく，いいえ ○ おそらく，はい ○ はい	なし	JAK 阻害薬の TOF は 2020 年に米国 FDA において関節型 JIA に対して承認されている。BAR と UPA に関しては 2023 年 7 月現在おいても本邦を含めた国際治験が行われ

○ さまざま ○ 分からない		ている途中であり、今後保険適用となることが期待される。 しかし一部の小児においては、適用される剤型(錠剤)が服用できないために、介入が実行困難となる可能性がある。 懸濁液など他の剤型の保険適用も望まれる。

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