Data Supplement

Data S1 (Search strategy and terms)

De-escalating biologic DMARDS – combined searches – 2014-August 30, 2021
PubMed: 974; Embase: 2996; Cochrane: 1793 - 4429 Total after deduplication

Prisma Diagram

5763 references imported for screening as 5762 studies
- 1333 duplicates removed

4429 studies screened against title and abstract
- 3925 studies excluded

504 studies assessed for full-text eligibility
- 494 studies excluded
  - 350 Wrong study design
  - 65 duplicates
  - 62 reviews
  - 8 retrospectives
  - 8 editorials
  - 1 not in English
- 0 studies ongoing
- 0 studies awaiting classification

10 studies included

PubMed
TNF-inhibitor agents[tw] OR TNF inhibitors[tw] OR TNF agents[tw] OR TNF blocker[tw] OR "tumor necrosis factor inhibitors"[mesh] OR tumor necrosis factor inhibitors[tw] OR tumour necrosis factor inhibitors[tw] OR tumor necrosis factor agents[tw] OR tumour necrosis factor agents[tw] OR Tumor necrosis factor blocker[tw] OR Tumour necrosis factor blocker[tw] OR disease-modifying antirheumatic drugs[tw] OR DMARD[tw] OR Etanercept[tw] OR Methotrexate[Mesh] OR Methotrexate[tw] OR etanercept[mesh] OR etanercept[tw] OR infliximab[mesh] OR infliximab[tw] OR adalimumab[mesh] OR adalimumab[tw] OR golimumab[Supplementary Concept] OR golimumab[tw] OR Certolizumab Pegol[mesh] OR Certolizumab[tw] OR tocilizumab[tw] OR abatacept[mesh] OR abatacept[tw] OR "Sulfasalazine"[Mesh] OR Sulfasalazine[tw] OR "Hydroxychloroquine"[Mesh] OR Hydroxychloroquine[tw] OR "Leflunomide"[Mesh] OR Leflunomide[tw] OR Sarilumab[tw] OR "sarilumab" [Supplementary Concept] OR Tofacitinib[tw] OR "tofacitinib" [Supplementary Concept] OR upadacitinib [tw] OR Janus Kinase Inhibitors[Mesh] OR Janus Kinase Inhibitors[tw] OR Jak-inhibitors[tw] OR "Rituximab"[Mesh] OR Rituximab[tw]
AND
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NOT (animals[mesh] NOT humans[mesh])
NOT comment[pt] OR letter[pt] OR "historical article"[pt] OR news[pt] OR "newspaper article"[pt] OR "case report"[ti]
AND English[language]
AND 2014-2021

EMBASE
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adalimumab:ti,ab,de,tn,kw OR 'golimumab'/exp OR golimumab:ti,ab,de,tn,kw OR 'Certolizumab Pegol'/exp OR Certolizumab:ti,ab,de,tn,kw OR tocilizumab:ti,ab,de,tn,kw OR 'abatacept'/exp OR abatacept:ti,ab,de,tn,kw OR 'salazosulfapyridine'/exp OR Sulfasalazine:ti,ab,de,tn,kw OR 'hydroxychloroquine'/exp OR Hydroxychloroquine:ti,ab,de,tn,kw OR 'leflunomide'/exp OR Leflunomide:ti,ab,de,tn,kw OR Sarilumab:ti,ab,de,tn,kw OR 'sarilumab'/exp OR Tofacitinib:ti,ab,de,tn,kw OR 'tofacitinib'/exp OR Baricitinib:ti,ab,de,tn,kw OR 'baricitinib'/exp OR upadacitinib:ti,ab,de,tn,kw OR 'upadacitinib'/exp OR 'Janus Kinase Inhibitor'/exp OR Janus Kinase Inhibitors:ti,ab,de,tn,kw OR Jak-inhibitors:ti,ab,de,tn,kw OR 'Rituximab'/exp OR Rituximab:ti,ab,de,tn,kw
AND
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AND
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AND ('article'/it OR 'article in press'/it OR 'review'/it OR editorial/it)
AND [humans]/lim
AND [english]/lim
AND [2014-2021]/py

Cochrane
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AND
Stop:ti,ab,kw OR stopping:ti,ab,kw OR Withdrawal:ti,ab,kw OR Withdrawals:ti,ab,kw OR Withdraw:ti,ab,kw OR Withdraws:ti,ab,kw OR withdrawing:ti,ab,kw OR Tapering:ti,ab,kw OR Taper:ti,ab,kw OR tapered:ti,ab,kw OR reduction:ti,ab,kw OR de-escalation:ti,ab,kw OR "drug-free remission":ti,ab,kw
AND
"Rheumatoid arthritis":ti,ab,kw OR RA:ti,ab,kw OR [mh "arthritis, rheumatoid"]
NOT
[mh "Spondylitis, Ankylosing"] OR [mh Spondylarthropathies] OR [mh "Lupus Erythematosus, Systemic"] OR [mh "Scleroderma, Diffuse"] OR [mh "Arthritis, Psoriatic"] OR [mh Vasculitis]
NOT ([mh animals] NOT [mh humans])
NOT comment:pt OR letter:pt OR "historical article":pt OR news:pt OR "newspaper article":pt OR "case report":ti
with Cochrane Library publication date from Jan 2014 to present

Table S1: Risk of bias assessment of nonrandomized study included in analysis using ROBINS-I

Domains:

D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.

Criteria for determining overall risk-of-bias judgements using the ROBINS-I:

Low risk of bias: The study is judged to be at low risk of bias for all domains.
Moderate risk of bias: The study is judged to be at low or moderate risk of bias for all domains.
Serious risk of bias: The study is judged to be at serious risk of bias in at least one domain, but not at critical risk of bias in any domain.
Critical risk of bias: The study is judged to be at critical risk of bias in at least one domain.
No information denotes no information upon which to base a judgement about risk of bias. There is no clear indication that the study is at serious or critical risk of bias and there is a lack of information in one or more key domains of bias.

Meng et al. J Rheumatol 2022. doi:10.3899/jrheum.220152

Table S2: Patients, interventions, comparators, outcomes and design of included studies					
Trial/ Author	**Participants**	**Intervention**	**Comparison Group***	**Outcome Measure (for REM)**	**Design**
SEAM Curtis et al	Established RA patients (classification criteria not specified) on ETA+MTX n SDAI REM <3.3 by end of 24 wk run-period MTX≥ 8 weeks	1) ETA + placebo (MTX WD, n= 101)	2) continue ETA + MTX (n=51) 3) oral methotrexate + sq placebo (ETA WD, n=101)	prop of patients achieving SDAI REM <3.3 without disease worsening at wk 48 in ETA mono vs MTX mono group	International, multicenter study with 24 wk open-label run-in period 48 wk randomized, controlled double-blind Treatment WD period
AVERT 2 Emery et al	Early RA by ACL/EULAR 2010 criteria Disease duration < 6 mos anti-CCP positive Active disease SDAI > 11, CRP > 3 or ESR > 28 and > 3 TJC + 3 SJC DMARD-naive achieved sustained SDAI REM <3.3 at wks 40 and 52 in induction period	1) ABA mono + placebo (MTX WD, n= 47)	2) ABA+MTX (n=50) 3) MTX + placebo ABA (from induction period)* (ABA WD, n=37) 4) ABA every other wk + MTX for 24 wks then ABA placebo + MTX for 24 wks(ABA taper then WD, n=50)	exploratory endpoints at DE wk 48 (study wk 104) prop of patients with SDAI REM < 3.3 at wk 48 of DE period	Phase 3b, randomized, double-blind clinical trial with 56 wk induction treatment period: Randomized 3:2 to blinded induction treatment ABA+MTX or ABA placebo + MTX or taper ABA before stopping ABA+MTX 48 wk treatment de-escalation period (DE)
ORAL Shift Cohen et al	Established RA > 6 score on 2010 ACR/EULAR criteria moderate to severe disease CDAI>10 and DAS28ESR>3.2 and > 4 TJC and > 4 SJC inadequate response to methotrexate received oral MTX continuously > 4 mos at stable dose prior to screening achieved LDA (CDAI<10) on study treatment by end of treatment phase	TOFA + placebo (MTX WD, n=267)	TOFA + MTX (n=266)	prop achieving REM by ACR-EULAR Boolean REM, DAS28-4[ESR]<2.6, DAS28-4[CRP]<2.6, CDAI<2.8, or SDAI <3.3 at wks 36 and 48	Global, multi-center, 48-wk, phase 3b/4 WD study across 16 countries: 30 day screening phase 24-wk open-label run-in treatment phase: tofacitinib + MTX 24-wk randomized, double-blind, placebo-controlled non-inferiority MTX WD phase
COMET Emery et al	Early RA (classification criteria not specified), 3-24 mos duration MTX-naïve DAS28 > 3.2 ESR > 28 or CRP > 20 2019 post-hoc analysis of those who met REM DAS28 < 2.6 at wk 52 (Abstract)	1) ETA+MTX year 1 and ETA + placebo year 2 (EM/E) (n=111)	*2) ETA+MTX year 1 and 2 EM/EM (n=111)* 3) M/EM (n=90) - MTX + placebo/ETA+MTX 4) M/M (n=99)- MTX+placebo year 1 and 2	prop achieving DAS28 REM at wk 104 Odds ratios comparing the ETA+MTX and ETA arms for each wk 52 DAS28 status calculated and their interaction as predictors of achieving REM.	2 year, double-blind, randomized study 1) ETA+MTX year 1 and 2 (EM/EM) 2) ETA+MTX year 1 and ETA mono year 2 (EM/E) 3) MTX mono year 1 and ETA+MTX year 2 (M/EM) 4) MTX mono year 1 and 2 (M/M)
JUST-ACT Pablos et al	Established RA (classification criteria not specified) moderate to severe disease DAS28>3.2 receiving MTX for > 12 wks at stable dosage for > 6 wks before study treatment. Achieved LDA DAS28 < 3.2 in treatment phase	TCZ + placebo (MTX WD, n=82)	TCZ + MTX (n=83)	prop of clinical REM at wk 28 based on DAS28 >2.6	Phase 3, multicenter, randomized, double-blind, parallel group, placebo-controlled study. 16 wk treatment period with TCZ IV + MTX 12 wk WD MTX phase until wk 28
Pope et al	Established RA (classification criteria not specified) on csDMARD deemed to benefit from adding CZP per Canadian product monograph, met reimbursement criteria to obtain CZP achieved change in DAS28 ≥ 1.2 on treatment	1) Stop csDMARD (CZP MONO n=45)	2) continue csDMARD + CZP (COMBO n=43)	prop of DAS28 REM <2.6, CDAI REM < 2.8	Real-world, multicenter, open-label RCT comparing discontinuing csDMARD after CZP added versus continuing combination therapy with 1 year follow-up. No protocolized intervention besides randomization.

Meng et al. J Rheumatol 2022. doi:10.3899/jrheum.220152

COMP-ACT Kremer et al	Established RA by 1987 ACR criteria moderate to severe disease, DAS28>4.4 , inadequate response to MTX and weighing < 150 kg, who completed treatment period and who achieved LDA DAS28-ESR< 3.2 entered the WD period. Those who did not achieve LDA DAS28-ESR<3.2 were assigned to open-label nonrandomized arm and continued to receive TCZ+MTX through wk 52 (n=308)	TCZ+ placebo (TCZ monotherapy, n=147)	Continue TCZ + MTX (n-147)	prop of patients with DAS28-ESR < 2.6 at wk 40 and wk 52	Randomized, multi-center, double-blind, parallel group, 52-wk study plus 8 wks follow up 24 wk treatment period: TCZ sq plus oral MTX 28 wk MTX WD period
ACT-TAPER Edwards et al	Established RA by 2010 ACR/EULAR criteria inadequate response to two DMARDs including MTX and no previous bDMARD DAS28>5.1 on 2 occasions 1 mo apart achieved good/moderate EULAR response (see outcome measures) at wk 24 of treatment	Group A: double-blind MTX taper + TCZ Taper occurred every 8 wks until 0 mg at wk 48 or disease flare occurred (n=136) Placebo details not specified	Group B: double-blind stable MTX + TCZ (n=136)	prop of patients in DAS28 REM <2.6 at wks 60 and 72	Randomized, placebo-controlled, non-inferiority study with open label treatment phase followed by randomized WD phase 24 wk treatment phase: all DMARDs except MTX were discontinued and started open-label IV TCZ every 4 wks and open-label MTX 48 wk MTX WD double-blinded phase
CAMEO Keystone et al	Established RA by 1987 ARA criteria on stable MTX therapy > 4 wks before baseline with inadequate response, TNFi-naive moderate to severe disease (>3 swollen joints, DAS28>3.2) were treated during study as standard of care (no sponsor drug), with ability to access ETA via insurance. 2016 2 year update did pre-specified analysis stratified by response at time of randomization at mo 6 by DAS28-ESR LDA/REM < 3.2 vs moderate to high disease activity (MHDA; DAS28-ESR > 3.2)	ETA monotherapy (n=98)	ETA + MTX (n=107)	DAS28-ESR REM at mo 24	Phase 4, multicenter, open-label, unblinded randomized 24 mo trial across 27 centers in Canada 6 mo treatment phase: ETA+ MTX 18 mo MTX WD phase
Keystone et al (observational)	Early RA < 3 years by 1987 ACR criteria DMARD-naive + SJC $\geq$ 8 + TJC $\geq$ 10 + ESR $\geq$ 28 or CRP $\geq$ 1.5 RF+ or $\geq$ 1 joint erosion achieved DAS28-CRP<3.2 LDA on ADA+MTX during a 2 year double blind study could then receive ADA monotherapy for up to 8 years during LTE.	Observed discontinuation of MTX defined as MTX non-use	Those who restarted open-label MTX per investigator discretion, defined as MTX use	DAS28-CRP <2.6 REM	Post-hoc analysis of LTE study (up to 3 years) of early RA who attained LDA on ADA+MTX and withdrew MTX. Rates of retaining LDA and achieving REM between those who did not use MTX and those who restarted it were compared.

* in cases of multiple comparator groups, one selected for meta-analysis is italicized* ADA adalimumab, bDMARDs biologic DMARDs, CDAI Clinical disease activity index, CRP C-Reactive Protein, csDMARDS conventional synthetic DMARDs, CZP certolizumab, DAS28 Disease Activity Score 28, DAS28-ESR Disease Activity Score 28 (using ESR), both DAS28 which uses the ESR and DAS28-CRP REM defined as score < 2.6, DMARD Disease Modifying Anti-Rheumatic Drug, ESR erythrocyte sedimentation rate, ETA etanercept, LDA low disease activity, Mono monotherapy, MTX methotrexate, LTE long-term extension, RF rheumatoid factor, RCT randomized controlled trial, SDAI Simplified disease activity index, SJC swollen joint count, TJC tender joint count, TCZ tocilizumab, TNFi TNF-inhibitor, TOFA tofacitinib, targeted therapy bDMARDs and JAK-i, mo month, wk week, WD withdrawal.

Figure S1: Comparison of studies tapering methotrexate from targeted therapy by established or early RA

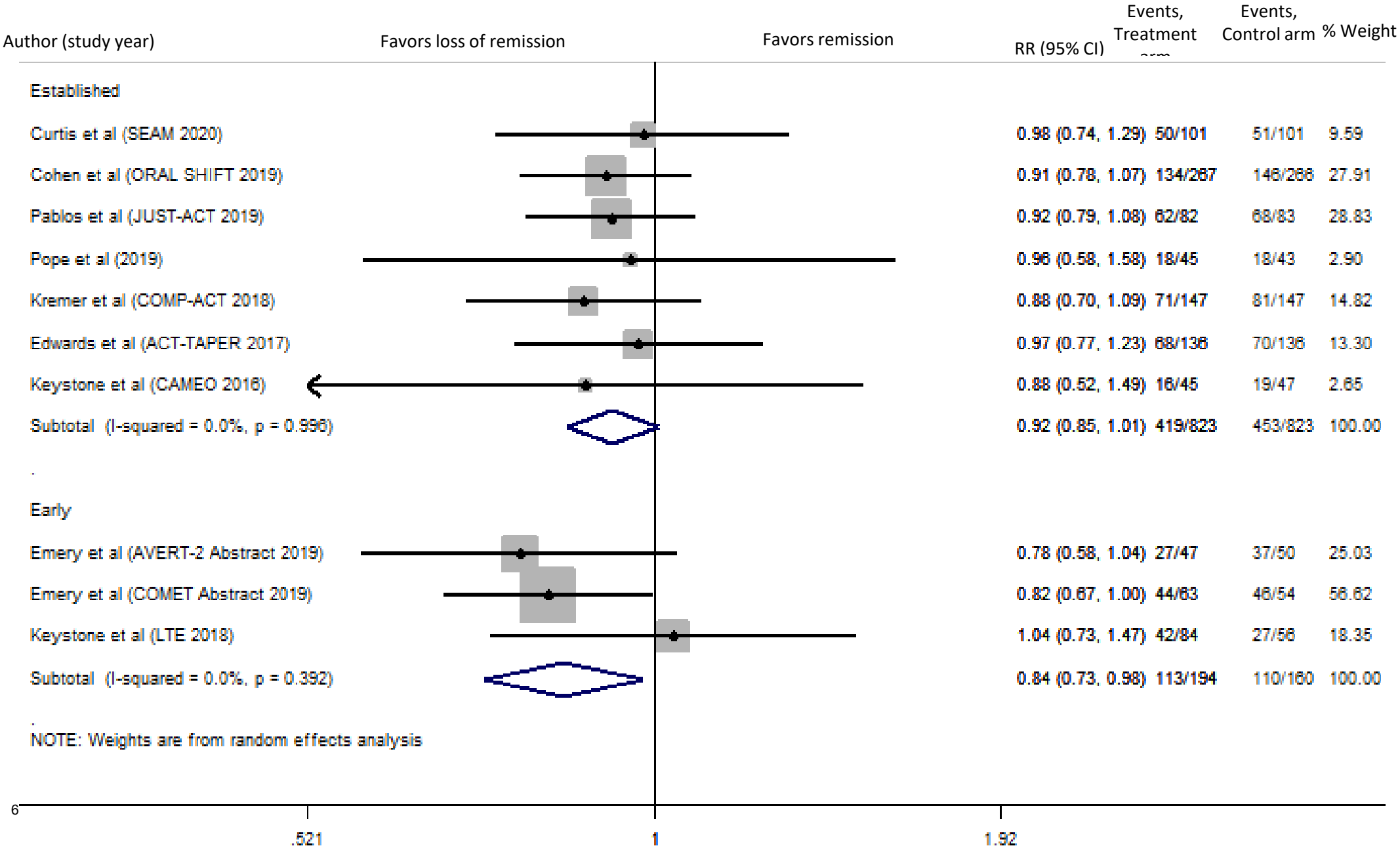

Figure S2: Studies tapering methotrexate from targeted therapy evaluating low disease activity (LDA) outcomes

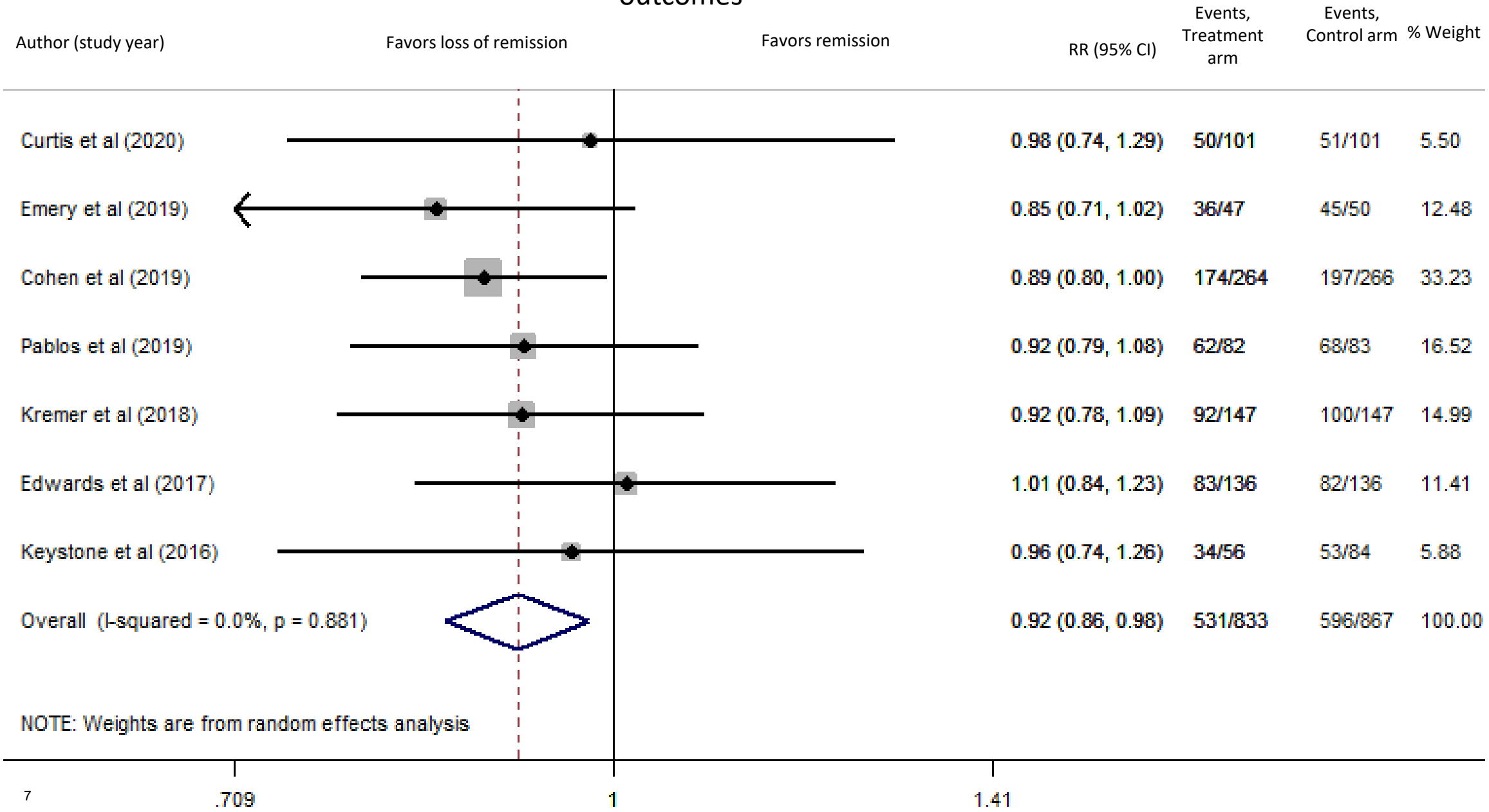

Figure S3: Sensitivity analysis with LTE 2018 omitted

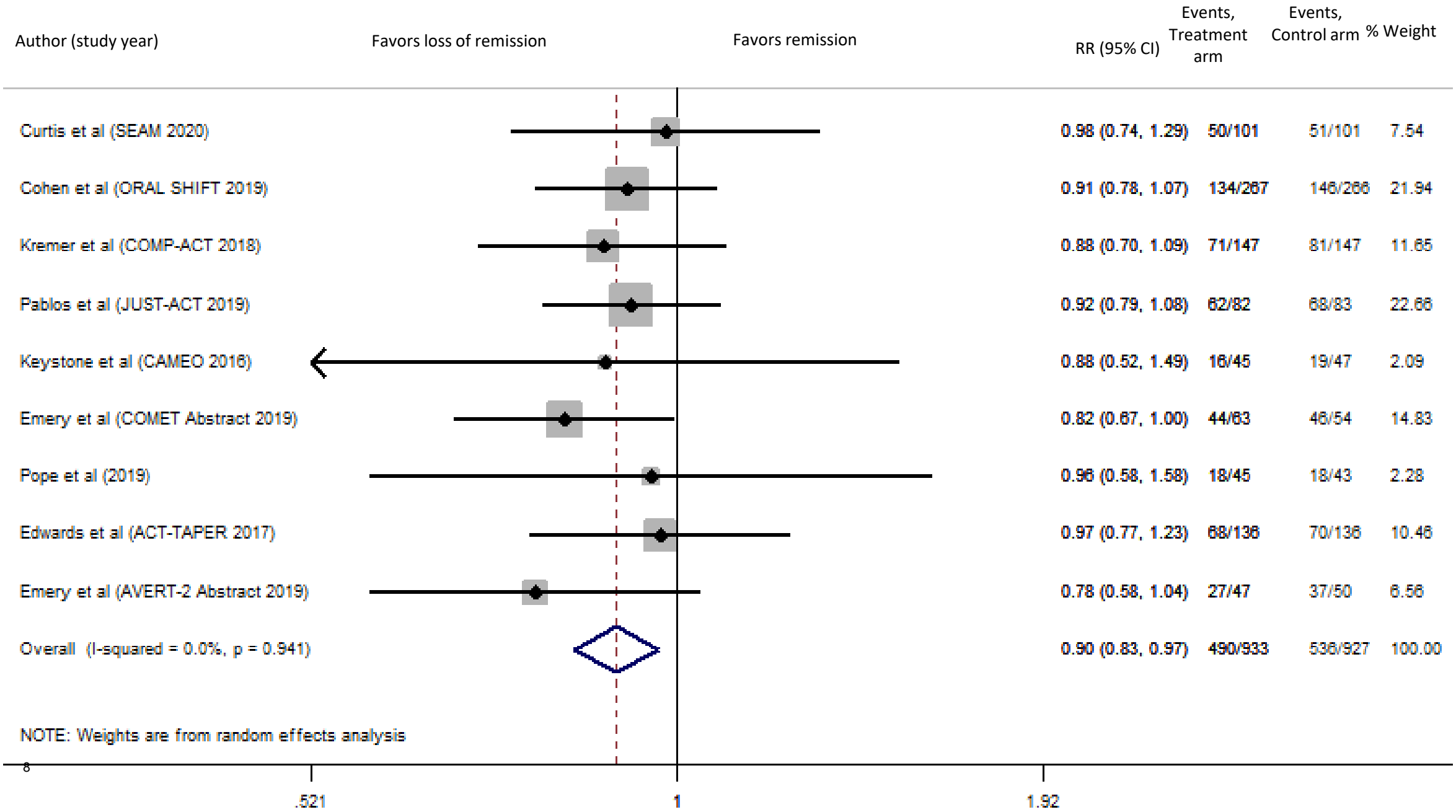

Figure S4: Risk differences of studies tapering methotrexate from targeted therapy