Methods

Study selection

1) Glucocorticoids in early RA

A systematic literature search was performed in PUBMED Medline, EMBASE and Cochrane library databases after January 2009 until January 2013, using the followings key-words for articles in English: rheumatoid arthritis, Glucocorticoids, Prednisone, Prednisolone. The trials were initially selected on the basis of their titles and abstract, then on the full texts. Two investigators selected the articles. The inclusion criteria were RCTs reporting the efficacy on signs and symptoms, disability and/or structure of csDMARDs to the same synthetic csDMARD but with different glucocorticoids dose regimen, in adults with early RA (<2 years of duration). Additional studies were identified by hand searching reference lists and abstracts presented at the American College of Rheumatology 2011-2012 and European League Against Rheumatism from 2011 to 2013.

2) csDMARD

Literature published after January 2009 on the following csDMARDs, given in monotherapy and in combination, was examined: methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, intramuscular gold, auranofin, azathioprine, cyclosporine, minocycline, D-penicillamin, cyclophosphamide, chlorambucil, mycophenolate, tacrolimus. Systematic literature search was performed in PUBMED Medline, EMBASE and Cochrane library databases after January 2009 until January 2013, using the following key-words for articles in English: rheumatoid arthritis, name of drug or combination. Additional studies were identified by hand searching reference lists and abstracts presented at the American College of Rheumatology 2011-2012 and European League Against Rheumatism from 2011 to 2013. Concerning the efficacy of MTX in monotherapy versus in combination, we included RCTs

comparing in adult RA, MTX monotherapy to MTX in combination with another csDMARD without glucocorticoid differences.

3) Tofacitinib

A systematic literature search was performed in PUBMED Medline, EMBASE and Cochrane library databases until March 2013 without limitation of year of publication or journal, using the followings key-words for articles in English: rheumatoid arthritis, tofacitinib, Jak inhibitor, CP-690,550. Additional studies were identified by hand searching reference lists and abstracts presented at the American College of Rheumatology 2011-2012 and European League Against Rheumatism from 2011 to 2013. The trials were initially selected on the basis of their titles and abstract, then on the full texts. Two investigators selected the articles. The inclusion criteria were all RCTs reporting the efficacy on signs and symptoms, disability and/or structure of tofacitinib in adult with RA.

Data Collection

Efficacy was assessed by the change in signs and symptoms or disability status between baseline and week 24, week 52 and week 104 when available, and by the change in radiographic joint damage between baseline and week 52 and week 104 when available in both groups.

Two investigators collected the data, using a predetermined form. The following methodological features were collected: blinding, intent-to-treat-analysis or not, number of participants who completed the follow-up. The evaluation of the validity of the included studies was done using the Cochrane Collaboration's tool for assessing risk of bias.

For each trial, demographic characteristics (sex, mean age), RA duration, background treatment, type of glucocorticoids (with doses), type of DMARD (with doses), type of comparator, and duration of follow-up were collected. Signs and symptoms were extracted

from the studies, as available, by swollen joint count (SJC), Disease Activity Score (DAS/DAS28), ACR 20, 50, 70 response rates, remission rates, pain, patient global assessment, physician global assessment, erythrocyte sedimentation rate (ESR), C reactive protein; disability was extracted, as available, by the health assessment questionnaire (HAQ or MHAQ); structure was assessed by different scores according to different studies (total Sharp score, Sharp modified by Van der Heijde, Larsen score...).

Statistical analysis

In each trial the ES or the SRM for continuous measures and Odds-Ratios (OR) for dichotomous measures were determined to assess the magnitude of treatment effect. The effect size (ES) is calculated as the ratio of the treatment effect (mean differences in treatment group minus differences in control group) to the pooled baseline standard deviation. This calculation entails the use of means, for both baseline and final data with a measure of variability such as SD. The standardized response mean (SRM) is also calculated as the ratio of the treatment effect (mean change in treatment group minus mean change in control group) divided by pooled SD of the change when available. Improvement, e.g. lower pain VAS was considered as a positive change. Every effort was made to calculate the ES or the SRM in all studies. However, if no measure of variability was given the ES or the SRM could not be extrapolated. By convention, an ES <0.2 is usually considered as trivial; 0.2-0.5 as small; 0.5-0.8 as moderate; 0.8-1.2 as important and >1.2 as very important. A SRM >0.8 is considered as large. Pooled ES, pooled SRM and pooled OR were calculated by meta-analysis, using the inverse of variance method. RevMan version 5.2 (Review Manager, Copenhagen, The Nordic Cochrane centre, The Cochrane Collaboration, 2012) statistical software was used. Statistical heterogeneity was tested by Q test and I^2 test. All meta-analyses were carried out with use of random-effects model in case of significant heterogeneity.

Figure A: <u>Literature search strategy for all RCTs reporting the efficacy of glucocorticoids in EA</u>

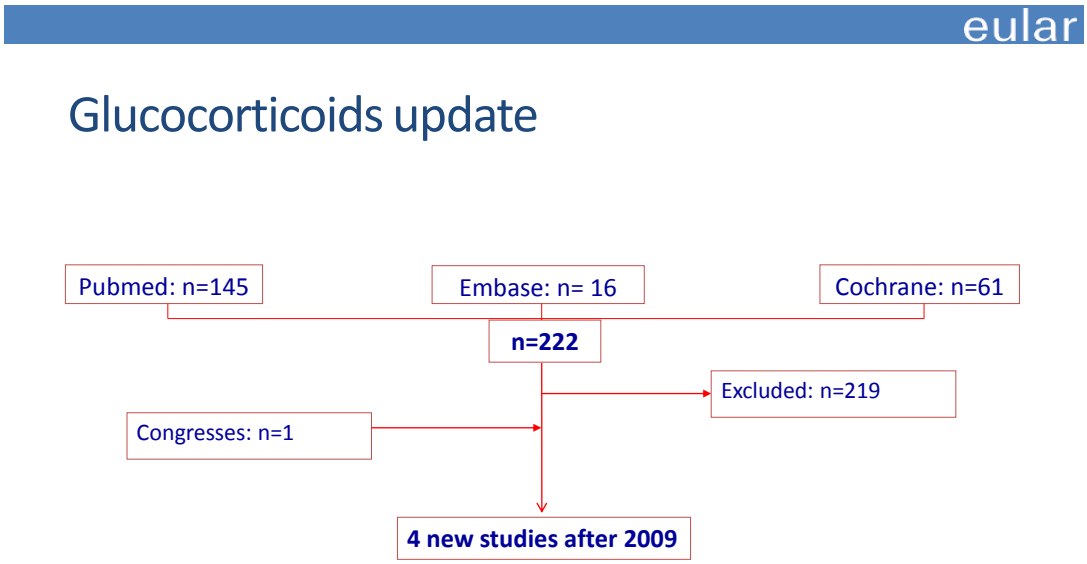


Figure B: <u>Literature search strategy for all RCTs reporting the efficacy of MTX monotherapy versus MTX in combination with other csDMARD</u>

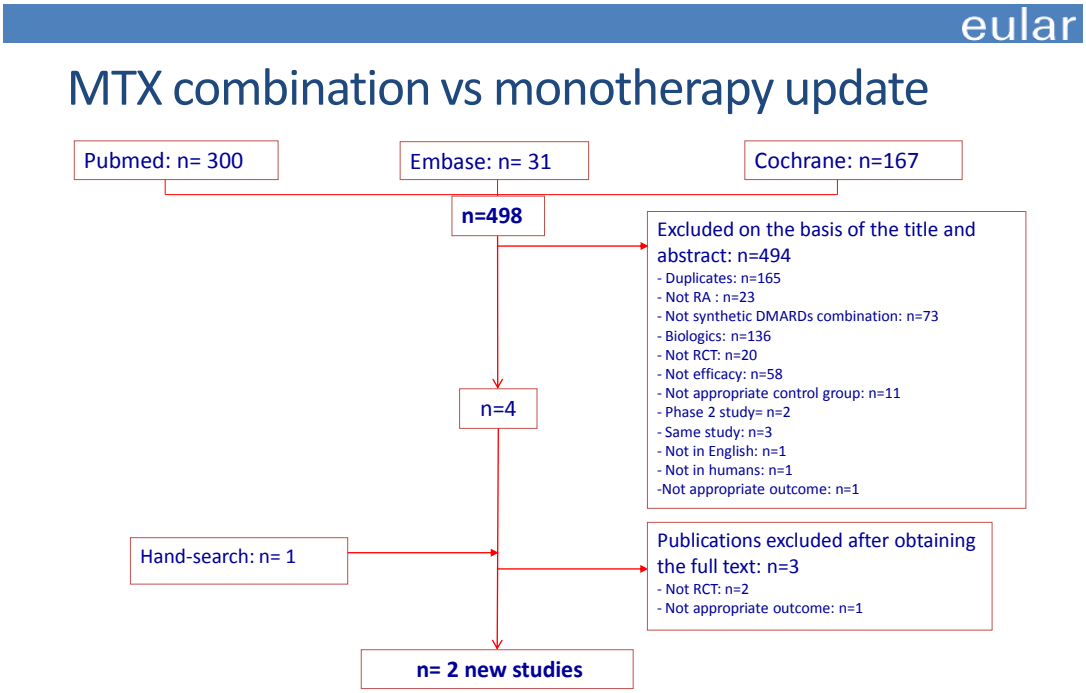
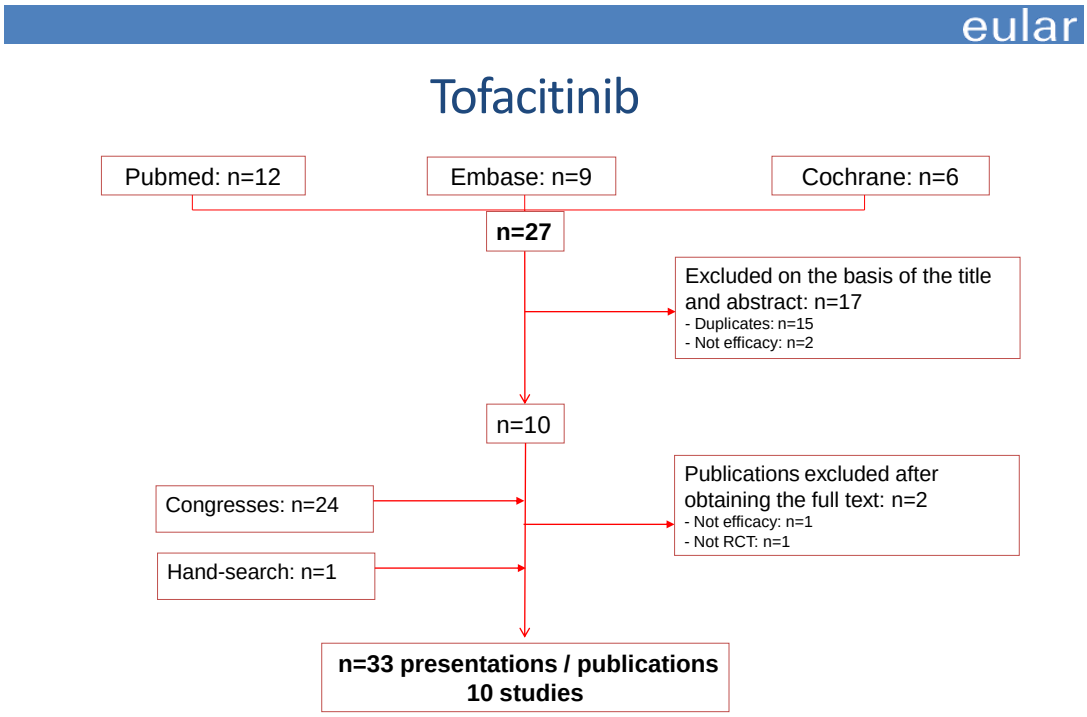


Figure C: <u>Literature search strategy for all RCTs reporting the efficacy of tofacitinib</u>



The efficacy of tofacitinib 5 mg BID versus placebo at 24 weeks

Outcome	N Studies	N Patients	Statistical Method	Effect Estimate
Pain SRM	2	355	Std. Mean Difference (IV, Fixed, 95% CI)	0.45 [0.21, 0.69]
SJC SRM	2	355	Std. Mean Difference (IV, Random, 95% CI)	0.28 [-0.23, 0.78]
TJC SRM	2	355	Std. Mean Difference (IV, Fixed, 95% CI)	0.28 [0.04, 0.51]
Patient Global assessment SRM	2	355	Std. Mean Difference (IV, Random, 95% CI)	0.44 [0.03, 0.84]
Physician Global assessment SRM	2	354	Std. Mean Difference (IV, Fixed, 95% CI)	0.53 [0.29, 0.77]
HAQ SRM	3	573	Std. Mean Difference (IV, Fixed, 95% CI)	0.55 [0.36, 0.75]
DAS28-ESR SRM	2	484	Std. Mean Difference (IV, Fixed, 95% CI)	0.30 [0.06, 0.53]
ACR 20	5	1628	Odds Ratio (M-H, Fixed, 95% CI)	2.44 [1.97, 3.02]
ACR 70	3	845	Odds Ratio (M-H, Fixed, 95% CI)	2.87 [1.72, 4.80]
CRP SRM	2	354	Std. Mean Difference (IV, Fixed, 95% CI)	0.63 [0.39, 0.87]

SJC: swollen joint count SRM: standardised response mean IV: inverse of variance MH: Mantel- Haenszel

The efficacy of tofacitinib 10 mg BID versus placebo at 24 weeks

Outcome	N Studies	N Patients	Statistical Method	Effect Estimate
Pain SRM	2	394	Std. Mean Difference (IV, Random, 95% CI)	0.49 [0.06, 0.92]
SJC SRM	2	395	Std. Mean Difference (IV, Random, 95% CI)	0.34 [-0.23, 0.91]
TJC SRM	2	395	Std. Mean Difference (IV, Fixed, 95% CI)	0.42 [0.19, 0.65]
Patient Global assessment SRM	2	394	Std. Mean Difference (IV, Fixed, 95% CI)	0.60 [0.37, 0.84]
Physician Global assessment SRM	2	394	Std. MeanDifference (IV, Random, 95% CI)	0.58 [-0.02, 1.18]
HAQ SRM	3	621	Std. Mean Difference (IV, Random, 95% CI)	0.59 [0.12, 1.06]
DAS28-ESR SRM	2	486	Std. Mean Difference (IV, Fixed, 95% CI)	0.52 [0.28, 0.75]
ACR20	5	1639	Odds Ratio (M-H, Random, 95% CI)	3.17 [2.11, 4.76]
ACR 70	2	742	Odds Ratio (M-H, Random, 95% CI)	3.08 [0.86, 11.03]
CRP SRM	2	395	Std. Mean Difference (IV, Random, 95% CI)	0.68 [-0.00, 1.36]

SJC: swollen joint count SRM: standardised response mean IV: inverse of variance MH: Mantel- Haenszel