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# **Ability of disease-modifying antirheumatic drugs to prevent or delay rheumatoid arthritis onset: a systematic literature review and meta-analysis**

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\*The 2 first authors contributed equally to the manuscript and are first co-authors.

**Key words:** rheumatoid arthritis, very early arthritis, pre-RA, treatment, glucocorticoids, disease-modifying antirheumatic drugs.

*Competing interests:* there are no competing interests for any author.

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## **Abstract** (250)

**Background:** Recent advances in knowledge of the pathogenesis of rheumatoid arthritis (RA) has led to promoting very early intervention.

**Objectives:** To assess the efficacy of therapeutic interventions in preventing or delaying RA onset with a systematic literature review (SLR) and meta-analysis (MA).

**Methods:** The SLR aimed to include all reports of randomized controlled trials of disease-modifying antirheumatic drugs or glucocorticoids used in patients presenting genetic and/or environmental risk factors for RA and/or systemic autoimmunity associated with RA, and/or symptoms without clinical arthritis and/or unclassified arthritis and in RA patients. We searched PubMed, EMBASE and Cochrane databases for English articles published from 2006 to 2016 using the keywords “undifferentiated arthritis” or “very early rheumatoid arthritis” with “therapy” or “treatment”. Main outcome was RA occurrence, defined as fulfillment of the 1987 ACR criteria. The MA was performed with RevMan with the Mantel-Haenszel method.

**Results:** Among 595 abstracts screened, 10 reports of trials were selected. The studies included 1,156 patients, with mean symptom duration  $16.2 \pm 12.6$  weeks. The occurrence of RA was available for 9 studies, assessing methylprednisolone, methotrexate, a TNF blocker, abatacept or rituximab. In the group arthralgia without arthritis (people at risk of RA), the MA of the 2 available studies did not show significant reduction in RA occurrence at week 52 or more (pooled OR 0.74, 95% CI [0.37; 1.49]). For people with undifferentiated arthritis, the MA of the 7 available studies revealed significant risk reduction with OR 0.73 [95% CI: 0.56 – 0.97].

**Conclusions:** This MA demonstrates that early therapeutic intervention may significantly reduce the risk of RA onset in this very first phase of the disease.

## INTRODUCTION

During the last decades, substantial knowledge has accumulated on the very early stages of rheumatoid arthritis (RA), notably the very early immunological pathogenic mechanisms leading to RA [1–4]. This knowledge has deeply altered the nosologic RA concept and its diagnosis.

For a long time, RA diagnosis required a quite complete and comprehensive clinical presentation, including bilateral symmetrical polyarthritis, involving the hands, eventually associated with serum rheumatoid factor (RF), nodules or radiographic joint erosions, as included in the 1987 American College of Rheumatology (ACR) classification criteria [5]. This “full presentation” does not fit with RA early stages, and the 1987 ACR criteria were found to adequately classify patients as having RA only 2 years after disease onset [6]. In 2010, the joint effort of the ACR and European League Against Rheumatism (EULAR) widened the spectrum of early RA by reducing the minimal synovitis number to 1 and including serum anticitrullinated peptide antibody (ACPA) positivity in addition to RF as immunologic biomarkers [7]. The new classification showed higher sensitivity to detect patients with early RA [8] and affected the diagnostic concept of unclassified arthritis (UA) as well as very early RA (VeRA) [9,10].

The combination of advances in RA pathogenesis and progress in RA diagnosis has contributed to redefining the RA early stages as a continuum spreading over several years [4,11] starting from (1) a first autoimmune phenomenon related to a host–environment interaction (e.g., interaction between smoking and the presence of the shared epitope leading to ACPA production); (2) preclinical RA (pre-RA), in which levels of autoimmunity biomarkers increase and mature, potentially associated with mild inflammatory features (e.g., arthralgia without arthritis/synovitis); (3) UA with at least 1 synovitis present, without satisfaction of the 1987 ACR criteria (but potentially satisfying the 2010 ACR/EULAR criteria); and finally (4) defined RA, with “full-picture” RA and satisfaction of 1987 ACR classification criteria [10,11]. These concepts have been retained in recent EULAR recommendations for research of individuals at risk of RA [12].

Besides diagnosis, the therapeutic issue is also important. Early therapeutic interventions, within the first months after RA onset, were clearly found associated with better RA outcomes [13–15], thereby validating the concept of a “window of opportunity”. In addition, the PROMPT trial demonstrated the ability of early methotrexate initiation to prevent onset of RA in patients with unclassified arthritis [16,17]. This situation raised the question of delaying or preventing RA if RA treatments are started at preclinical or in the very early clinical stages of the disease [11].

Although international clinical practice guidelines focus on methotrexate or other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) in early RA [18], numerous other therapeutic options are available, and several, including glucocorticoids or biologic DMARDs (bDMARDs), have been tested in individuals at risk of RA. A recent meta-analysis (MA) of studies of experimental animal models suggested that DMARDs are not equally efficacious in the prevention or treatment of the early arthritis animal model [19].

Thus, we conducted a systematic literature review (SLR) and MA of randomized controlled trials (RCTs) of patients at risk of RA to assess the efficacy of glucocorticoids, csDMARDs or bDMARDs for preventing or delaying RA development and/or blocking structural damage. The notion of prevention of RA refers to the ability of a treatment to block the pathogenic process and prevent more established forms of RA. Thus, the target population for such an action is people at risk of RA (family history and presence of (high titer) autoantibodies, or with arthralgia and autoantibodies, or people with unclassified arthritis).

## **METHODS**

### *Search strategy*

We performed a systematic literature search of PubMed, Medline, EMBASE and the Cochrane Controlled Trials Register up to June 2017 for articles published from 2006 to 2016 and EULAR and ACR scientific meeting abstracts from the last 2 years (2015 and 2016). We used the following key words: “Arthritis, Rheumatoid”[MeSH] AND "very early" AND "treatments"[all fields] OR “therapy”[all field], or “undifferentiated arthritis”[All Fields] AND "therapy"[all fields] or “treatments”[all fields]. We limited our search to English-language reports of RCTs of adults  $\geq 18$  years old. In addition, we hand-searched reference lists of papers initially detected to identify additional relevant reports. The reports of clinical trials were initially selected on the basis of the title and abstract, then the full text. Duplicate references were removed.

### *Study selection criteria*

To be selected, reports had to satisfy the following:

- (1) The study design should be an RCT.
- (2) The enrolled patient diagnosis should be one of (A) patients presenting genetic and/or environmental risk factors for RA and/or systemic autoimmunity associated with RA, and/or symptoms without clinical arthritis and/or unclassified arthritis [7,12,20]; (B) patients with clinical arthritis evolving for  $< 16$  weeks and fulfilling the 2010 ACR/EULAR criteria but not the 1987 ACR criteria.
- (3) Study treatment should be glucocorticoids or any other DMARD, either a csDMARD (methotrexate) or bDMARD (tumor necrosis factor [TNF] blocker or other mode of action).
- (4) Study outcomes should be measured at week 52 or closest time point.

### ***Data extraction***

Two independent readers (SH, BH) extracted the following data by using a standardized form: patient characteristics at baseline (i.e., demographics and disease characteristics, including classification criteria fulfilment); therapeutic intervention; occurrence of RA at week 52 or closest time point, defined as fulfillment of the 1987 ACR classification criteria [17,21–25] or ACR EULAR 2010 or according to the rheumatologist's opinion [21,26]; clinical remission rates at week 52, defined by validated composite criteria (i.e., Disease Activity Score in 28 joints [DAS28] [17,21–25,27], Simple DAI [SDAI], Clinical DAI [CDAI] or boolean [25], with adequate threshold); structural damage progression seen on X-rays at week 52 (Table 2) based on the van der Heijde-modified Sharp score or any other validated score [17,21,23–25,27]; and safety based on a descriptive analysis.

To define specific phases of RA, patients were classified into groups according to the EULAR recommendations for terminology [12] as follows : (a) : genetic risk factors for RA ; (b) environmental risk factors for RA ; (c) : systemic auto-immunity associated with RA ; (d) : symptoms without clinical arthritis ; (e) unclassified arthritis ; (f) RA.

Study quality was assessed by the Jadad scale [28] with 2 questions (answer Yes/No) for randomization, 2 for masking, and 1 (answer Yes/No) evaluating the reporting of withdrawals and dropouts. A total of 5 points could be awarded, with higher scores indicating higher quality.

### ***Statistical analysis and MA***

The MA was performed accordingly to the Cochrane Collaboration guidelines [29] for RA occurrence, defined as a *definite* RA, which is mostly according to the 1987 ACR classification criteria in the literature (or ACR EULAR 2010) at week 52 or closest time point, radiographic progression and clinical remission. Concerning RA occurrence, data at week 52 and beyond this time were pooled to strengthen the results. A sensitivity analysis was conducted to isolate the impact of TNF-blocker treatment. Statistical heterogeneity was tested by the chi-square Q test, [30];

with significant heterogeneity, a random-effects model was used. The MA was performed with RevMan v5.3 (The Nordic Cochrane Centre, Copenhagen, 2014) with the Mantel-Haenszel method, estimating odds ratios (ORs) and 95% confidence intervals (CIs). A descriptive analysis was performed for other measures such as the DAS28, Health Assessment Questionnaire (HAQ), and side effects (infectious, intolerance).



## RESULTS

### Selected studies

The search identified 595 abstracts, with reports of 10 RCTs selected (including 2 congress abstracts) and 10 exploited for analysis (Figure 1). The main reasons for exclusion were disease duration at baseline (many studies included patients with RA evolving for more than 16 weeks); study design (i.e., non-RCTs); study endpoints different from the outcomes of interest; and incomplete results (i.e., missing data for means and/or SD). The mean Jadad score was 5, which indicates high methodological quality of studies.

Seven were related to (e) criteria, two to (d) and one to (f) [12]. The therapeutic strategies tested were methylprednisolone at a single dose of 80 mg [21] or 120 mg [22], intramuscularly in 2 studies; dexamethasone at the dose of 100 mg IM at week 0 and week 6 [31] oral methotrexate up to 30 mg/week for X weeks or months in 1 study [17]; TNF blockers — infliximab (3 mg/kg at weeks 0-2-4-6-14 +/-22) [23,32] or etanercept (50 mg/kg/wk) [25,27] at labelled doses — in 4 studies, used alone or with methotrexate (up to 30 mg/wk); intravenous abatacept (100 mg/kg every 2 weeks for 1 month, then monthly) [24] at a labelled dose in 1 study; and finally intravenous rituximab at 1 g once only in 1 study (Table 1).

The SLR and MA included 1,239 patients (mean percentage of females 66.0 % with weighted mean age  $45.8 \pm 15.2$  years and mean symptom duration  $16.2 \pm 12.6$  weeks).

### Data synthesis

#### *Preventing or delaying RA occurrence*

RA occurrence, defined as satisfaction of the 1987 ACR classification criteria, was found in 9 of 10 papers assessing methylprednisolone (80 to 120 mg intramuscularly), dexamethasone, methotrexate, TNF blocker (infliximab in the Saleem and Durez trial; etanercept in EMPIRE), abatacept or rituximab.

2 studies are related to arthralgia without arthritis (d) [26,31] evaluating dexamethasone and rituximab. 7 are related to unclassified arthritis (e) [21–25,32,33].

In the group arthralgia without arthritis (d), the MA of the 2 available studies did not show significant reduction in RA occurrence at week 52 or more (pooled OR 0.74, 95% CI [0.37; 1.49] (figure 2a).

For people with undifferentiated arthritis (e), the MA of the 7 available studies revealed significant risk reduction with OR 0.73 [95% CI: 0.56 – 0.97]. All drugs tended to reduce the risk of RA occurrence, except TNF blockers (Figure 2a).

As a sensitivity analysis, the MA was performed without the 2 TNF-blocker studies, which resulted in a more significant pooled OR: 0.68, 95% CI [0.50; 0.92] (Figure 2b).

### ***Clinical remission***

Clinical remission at week 52, according to the DAS28, SDAI, CDAI or boolean definitions, was available for 5 studies of glucocorticoids and TNF blockers (etanercept or infliximab) or abatacept. The Saleem and Durez study used another criteria (no swollen joint and C-reactive protein level < 10 mg/L). Only the COMET trial [27] demonstrated a significant effect of etanercept on remission. The MA revealed that early intervention increased the odds of achieving remission (pooled OR 1.84, 95% CI [1.08; 3.16]) (Figure 3).

### ***Radiographic progression***

Data on radiographic progression were available for 5 studies, evaluating methylprednisone, methotrexate, or a TNF blocker (etanercept and infliximab). The outcomes were the Sharp score (modified or not) and Larsen score. No significant risk reduction was revealed for radiographic progression (Figure 4). The MA yielded a pooled OR of 1.36 (95% CI [0.82; 2.27]). We found no

difference between treatments for radiographic progression. The analysis without TNF blockers did not alter the results.

### ***Other outcomes and side effects***

With the descriptive analysis, similar side effects were observed between placebo and methylprednisone without notable difference [21,22]. The observed side effects were the expected ones: hypertension, lower-limb oedema [22], anaphylactic reaction and mood swings [21]. The PROMPT study found no significant safety difference for methotrexate versus placebo (26/55 with methotrexate and 18/55 with placebo,  $p = 0.17$ ). Side effects described were benign gastrointestinal events, elevated serum liver enzyme levels and dermal/mucosal events with methotrexate. bDMARDs were associated with respiratory and urinary tract infections, with 2 severe cases [25]. No malignancy was identified. There were 10 safety events with abatacept versus 11 with placebo [24]. The most frequently reported events were nasopharyngitis, urinary-tract infection and gastroenteritis. The abstract for the PRAIRI study (rituximab) did not specify side effects [26].

## DISCUSSION

The present SLR and MA provides information that a very early therapeutic intervention may significantly reduce the risk of RA onset with patients at risk of RA and significantly increase the rate of clinical remission. Although the notion of a window of opportunity is well accepted in people with already diagnosed RA [15,34], our work reveals that an even earlier therapeutic intervention could prevent RA or delayed its onset. This conclusion seems to be available in patients with arthritis. In symptomatic patients without arthritis, no significant reduction was observed, potentially partly due to a lack of power with the only 2 available studies.

This work also suggests that the beneficial effect of very early treatment in RA could differ between csDMARDs or bDMARDs. Although a reduced risk of RA occurrence was observed with glucocorticoids, methotrexate, abatacept or rituximab, the trend seemed not confirmed for TNF blockers [23,25]. This finding is likely to be a class effect rather than a single molecule effect because it was observed with 2 different agents, one soluble receptor (etanercept) and one monoclonal antibody (infliximab). They may be not as important in the very early steps of the disease in which autoimmune phenomenon are present but not joint or systemic inflammation [35]. TNF blockers have been mainly tested, and are currently recommended, in established active RA and eventually in early RA with pejorative prognostic factors such as high swollen joint count, increased acute-phase reactant levels or joint erosions; this is in line with the association between TNF and detectable inflammation [36–40]. Pharmacologic agents such as glucocorticoids, methotrexate, rituximab or abatacept may have a broader effect and act higher in the pathogenic cascade, including antigen presentation and early steps of the autoimmune reaction; they could thus prevent the immune system activation, whereas TNF blockers could only reduce already existing inflammation. We have no data available for interleukin 6 (IL-6) blocking agents, although IL-6 seems to be involved in the very early steps of RA pathogenesis [41].

Several strengths of the study must be underlined. The study applied the methodological standards recommended by the Cochrane collaboration for an SLR and MA, including double data extraction

and entry [29]. Although people in very early phases of the disease constitute a challenging population for clinical research, 9 reports of RCTs were identified and the data could be integrated in the MA. These trials cover almost all possible modes of action for RA, except IL-6 blockers and JAK inhibitors.

However, our work has some limitations. Although data about RA diagnosis according to 1987 ACR classification criteria were available in most of the studies (7 of 9), only a few reported data on clinical remission (5 of 9). Structural damage information was assessable in 5 studies ; however, the progression was small in RA, and we could not identify any significant benefit of early therapeutic intervention for this outcome. In addition, we found substantial heterogeneity in the outcome measures used in the selected trials: DAS28, SDAI, CDAI or Boolean definitions for remission and Larsen or van der Heijde-modified Sharp score for radiographic progression. For feasibility reasons, we pooled the remission rates or percentages for patients without structural damage progression, regardless of the tool used. This move could have biased our results in part.

An important concern comes with the distinction of the very early steps of RA [12,35]. We chose the cutoff of 4 months of disease duration to select the studies for our MA, which was based on data from a few studies [25,27] using the cutoff of 3 to 4 months to define the very early RA phase. This choice is of course partly arbitrary and reveals the complexity to define the initial RA phases, which constitute a continuum [1] rather than a succession of clearly different health states [35,42]. The 2010 ACR/EULAR criteria [7] allowed for identifying RA patients at an earlier stage than did the 1987 criteria [8]. However, the criteria are operational only for patients with significant RA symptoms and do not cover the whole spectrum of people with less specific symptoms such as those with arthralgia or limited arthritis, with or without family history of RA, and/or with or without serum ACPA positivity. The development of clinical practice guidelines for people at risk of RA was an important step forward [12] but did not completely fix the overlap of the existing definitions of the RA early phases [35,42].

Despite these difficulties, our results reinforce the view of “the sooner the better” in terms of therapeutic decision making within the pathogenic RA continuum. This paradigm raises an important additional question related to the duration of such a very early therapeutic intervention aiming to prevent RA onset or completely abate the disease. Whatever the RA stage, the risk of relapse seems substantial when treatments are not maintained (17,21–26). However, there is potential for “immunologic remission” in some RA patients [i.e., resolution of any sign of joint or systemic inflammation with disappearance of serum autoantibodies (RF or ACPA)] [43]. Early or very early intervention may favor such immunologic remission and could correspond to some kind of resetting of the immune system with complete resolution of any autoimmune phenomenon. The optimal strategy for such patients could then be an induction therapeutic sequence to prevent RA or achieve immunologic remission, then a drug tapering or discontinuation sequence to reach sustained and stable drug- and disease-free states [44–47]. This move would probably require as an intermediary step a better assessment and quantification of the risk of developing RA for a given patient to facilitate the implementation of more personalized therapeutic schemes. A risk stratification score, based on family history as well as patient clinical and biologic features, has been proposed in the context of the Leiden Early Arthritis Clinic [47]. Finally, this notion of prevention in patients at risk of developing RA needs to be handled with caution for 2 reasons. Firstly, in all the trial, the treatment of patients with arthralgia and autoantibodies or with unclassified arthritis have mainly shown their capacity to delay or postpone RA onset, but only a minority of them will durably remain asymptomatic if the tested DMARD is discontinued [16,17,26]. Secondly, it must be kept in mind that these patients may correspond to patients achieving spontaneous remission with no or only little role for the DMARD. In a recent work conducted in the ESPOIR and the Leiden early arthritis cohorts, such an evolution – i.e., DMARD-free sustained remission – could be observed in 5.4% (29/533 in ESPOIR) to 11.5% (85/738 in LEAC) [15]. It is important to note that delay is not prevention. It remains to date unknown whether a minority will remain asymptomatic after DMARD is discontinued.

This question deserves to be further studied, why not by creating a two arms study with early intervention in case of arthralgia and auto-immunity comparing intervention only when clinical arthritis develops.

In conclusion, this SLR and MA clearly demonstrates the potential benefits of very early therapeutic intervention for people who start RA and specifically its ability to prevent established RA. Our results fit perfectly with the 2017 EULAR campaign on early actions in rheumatic disorders: “Don’t delay, Connect today”

([https://www.eular.org/what\\_we\\_do\\_dont\\_delay\\_connect\\_today.cfm](https://www.eular.org/what_we_do_dont_delay_connect_today.cfm)).

**Table 1: Study characteristics**

Trial name (reference)	Inclusion	Terminology (REF)	N	Intervention	Outcome	Evaluation Time of Outcome
<b>Bos 2009 (31)</b>	Arthralgia without synovitis	(d)	83	Dexamethasone 100mg IM, W0 and W6	- RA occurrence	- W52 and more (mean duration of follow up: 52,5 months)
<b>Gerlag 2016 (PRAIRI) (26)</b>	Arthralgia without synovitis	(d)	81	RTX 1000 mg J0	- RA occurrence	- 29 months
<b>Verstappen2009 (STIVEA) (21)</b>	UA ACPA/RF+ naive of treatment	(e)	224	80 mg MP W0-1-2	- DAS - HAQ - Radiographic score - RA occurrence*	- Baseline, W24, 52 - Baseline, W52 - W52 - W52
<b>Machold 2009 (SAVE) (22)</b>	UA ACPA/RF + Naive	(e)	303	120 mg MP J0	- DAS - RA occurrence	- Baseline, W12, W52 - 12 months
<b>Van Dongen 2007 (PROMPT) (17)</b>	UA ACPA/RF + GC allowed	(e)	55	MTX until 30 mg/wk	- DAS - Radiographic score - RA occurrence	- Baseline, W12, W52 - Baseline, M18 - 30 months, 60 months
<b>Saleem 2008 (23)</b>	UA ACPA/RF + GC allowed	(e)	17	INF 3 mg/kg W0-2-4-6-14	- DAS - HAQ - Radiographic score - RA occurrence	- Baseline, W12, 24 - Baseline, W12, 24, - W52 - W52
<b>Durez 2011 (48)</b>	UA ACPA +	(e)	30	INF 3 mg/kg W0, 2, 6, 14, 22	- RA occurrence - DAS28 - ACR 20 -50-70	- 12 months - W52 - W14
<b>Nam 2013 (EMPIRE) (25)</b>	UA ACPA/RF + GC allowed	(e)	82	ETN50 mg/wk + MTX	- DAS - HAQ - Radiographic score - RA occurrence	- Baseline, W12, W52, M18 - Baseline, W52, M18 - Baseline, W52, M18 - 12 Months
<b>Emery 2009 (ADJUST) (24)</b>	UA ACPA/RF + or VERA GC allowed (<10mg/day)	(e) or (f)	11	ABA 100 mg/kg Day: 1-15-29-57-85-113-141-169	- DAS - Radiographic score - HAQ - RA occurrence	- Baseline, W24, 52 - Baseline, W52 - Baseline - 6 Months
<b>Emery 2011 (COMET) post-hoc [48]</b>	VERA	(f)	112	MTX vs. MTX + ETN 50 mg/wk	- DAS28 - Radiographic score	- W52 - Baseline, W52



UA: unclassified arthritis (i.e., patients presenting arthritis and ultrasound-detected synovitis, without ACPA or RF positivity); VeRA (i.e., patients with clinical arthritis evolving for < 16 weeks and fulfilling the 2010 ACR/EULAR criteria but not the 1987 ACR criteria).

ACPA: anticitrullinated protein antibody. RF: rheumatoid factor. DAS: disease activity score. HAQ: health assessment questionnaire.

RA occurrence : according to ACR 1987 for all studies except for PRAIRI and STIVEA which correspond to the rheumatologist's opinion.

(a) : genetic risk factor of RA ; (b) environmental risk factor of RA ; (c) : systemic auto-immunity associated with RA ; (d) : symptoms without clinical arthritis ; (e) unclassified arthritis ; (f) RA (according EULAR 2012 recommendations for terminology[12])

GC: glucocorticoids. MTX: methotrexate. INF: infliximab. RA: rheumatoid arthritis. ABA: abatacept. ETN: etanercept. RTX: rituximab. MP: methylprednisolone. W: week.

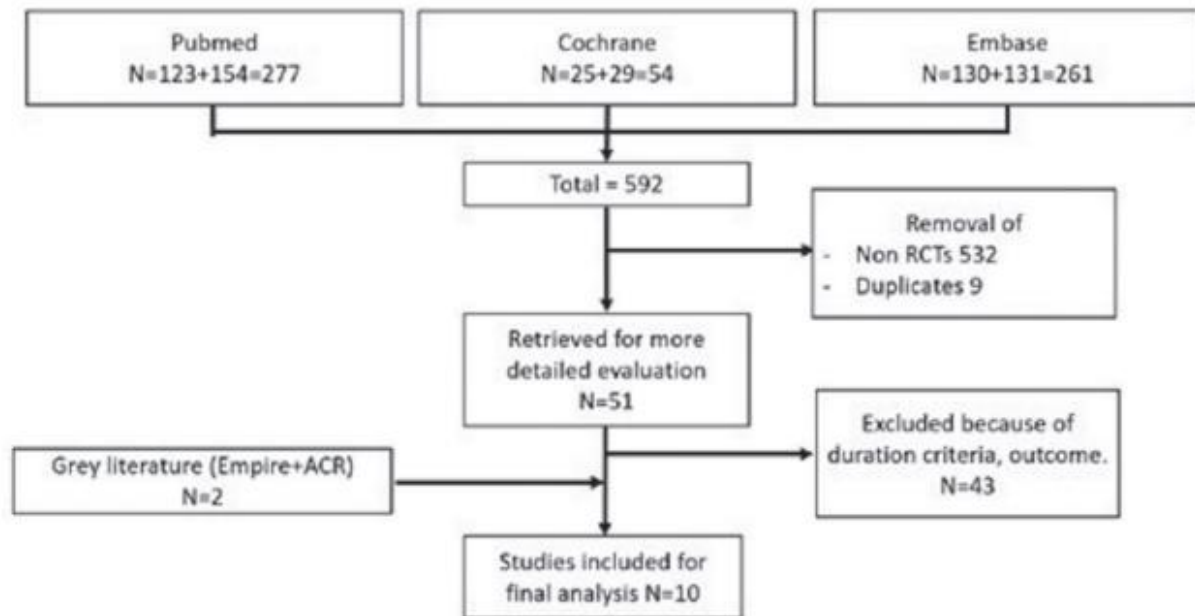
**Table 2: Main outcome results**

Trial name (reference)	Group	RA occurrence		% Clinical remission		% No radiographic progression	
		W52 or more		W52		W52 or more	
Bos 2009 (31)	DXM IM	16,7	7/42	n.a.	n.a.	n.a.	n.a.
	Pcb	22,5	9/40				
Gerlag 2016 (PRAIRI)(26) ‡	RTX+CS	34	14/41	n.a.	n.a.	n.a.	n.a.
	Pcb	40	16/40				
Verstappen 2009 (STIVEA) (21)‡	MP IM	48.6	54/111	20.7	23/111	12.7	9/71
	Pcb	60.4	67/111	11.7	13/111	14.8	9/61
Machold 2009 (SAVE) (22)	MP	47.6	69/145	16.2	32/198 ***	n.a.	n.a.
	Pcb	52.4	76/145	17.8	33/185		
Van Dongen 2007 (PROMPT) (17)	MTX	40	22/55	n.a.	n.a.	88	48/55
	Pcb	53	29/55			73	40/55
Saleem 2008 (23)	IFN	100	10/10	20	2/10	80.0	8/10
	Pcb	71.4	5/7	14.3	1/7	71.4	5/7
Durez 2011 (48)	INF	73.3	11/15	50.0	7,5/15 **	n.a.	n.a.
	Pcb	66.7	10/15	21.4	3,2/15		
Nam 2013 (EMPIRE) (25)	MTX+ETN	61,5	33/52	68.8	38/55 **	93.1	51,2/55
		63,5	35/53	47.5	26/55 ****	(87.1=M18)	
	MTX+Pcb			62.5	34/55 **	95.5	52,5/55
				37.0	20/55 ****	(80.0=M18)	
Emery 2009 (ADJUST) (24)	ABA	46.2	12/26	47.4	9/19 **	n.a.	n.a.
	Pcb	66.7	16/24	38.5	5/13		
Emery 2011 (COMET) post-hoc [48]	ETN+MTX	n.a.	n.a.	69.8	44/63 **	80.6	50,8/63
				24.1	15,2/63*****		
	MTX			34.7	17/49 **	73.9	36,2/49
				13.6	6,7/49 ****		

‡diagnosis of RA relied on the rheumatologist's opinion.

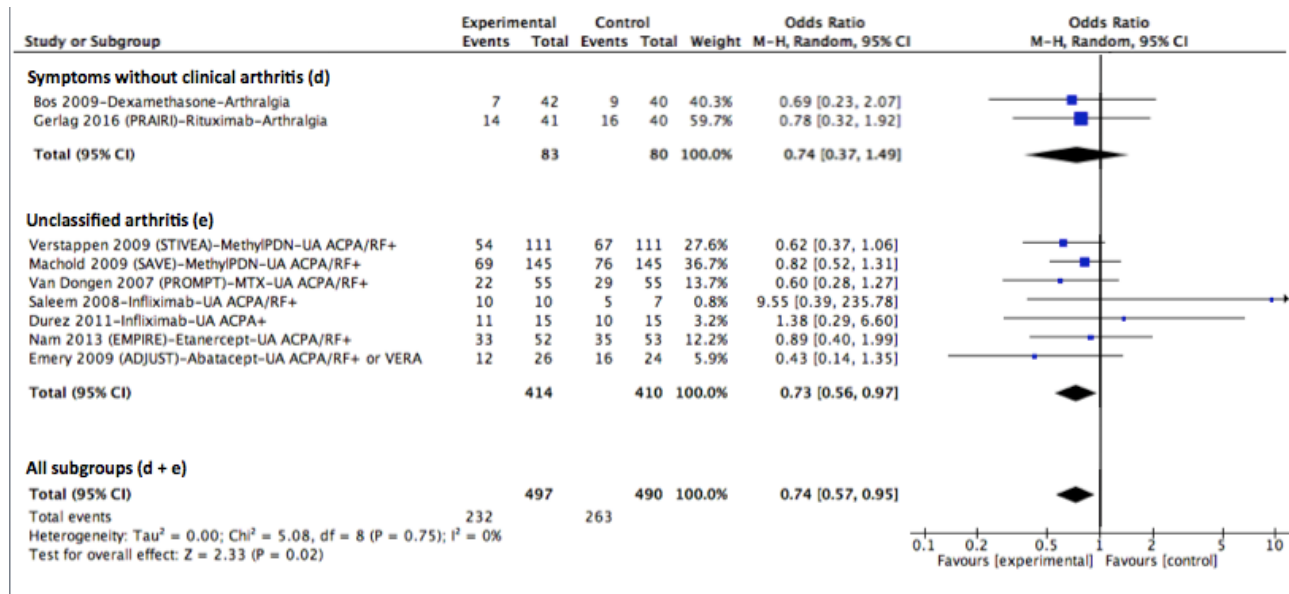
\*\* DAS28 < 2.6 ; \*\*\* No SJ and  $\leq 2$  tender joint (TJ) + 2/3 of following: normal CRP level, visual analog scale score for pain or activity < 10/100 + no past or current treatment with disease-modifying antirheumatic drugs (DMARDs) or glucocorticoids except study drug; \*\*\*\* Simple DAI  $\leq 3.3$   
DXM : Dexamethasone. GC: glucocorticoids. MP: methylprednisolone. Pcb: Placebo. MTX: methotrexate. INF: infliximab. ABA: abatacept. ETN: etanercept. RTX: rituximab.  
n.a.: not available

**Figure 1:** *Flow of studies in the review*

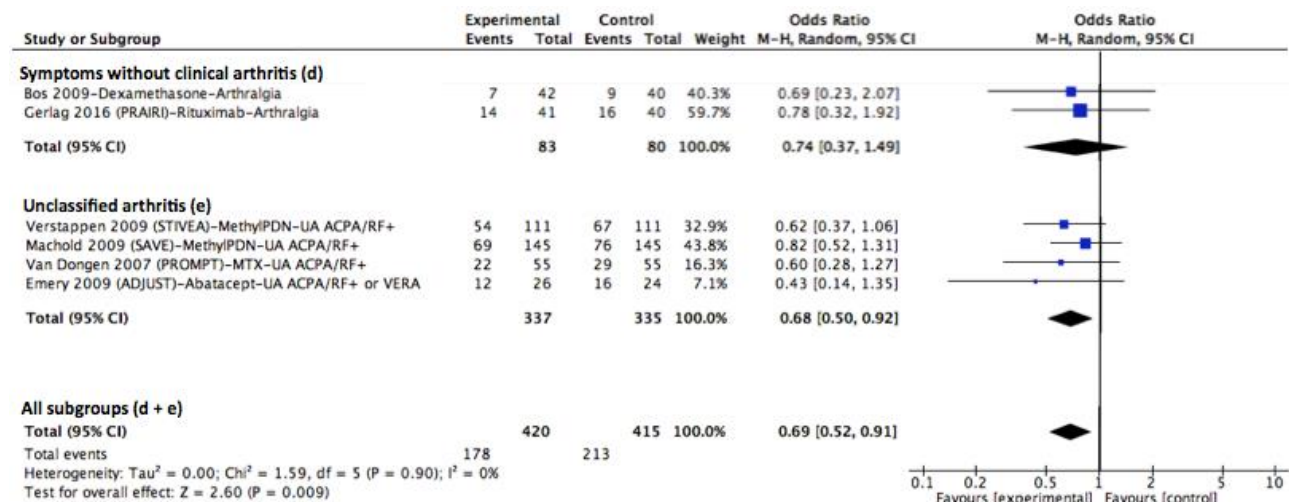


**Figure 2**

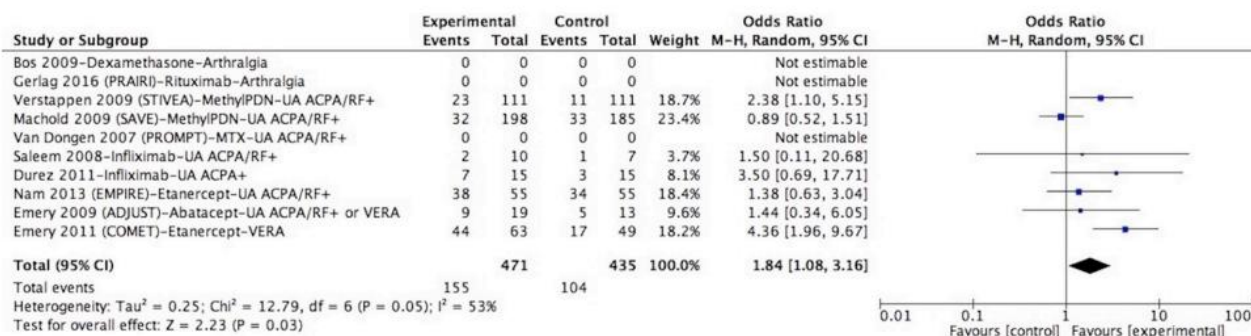
**a. RA diagnosis at week 52 or more including tumor necrosis factor (TNF) blockers.**



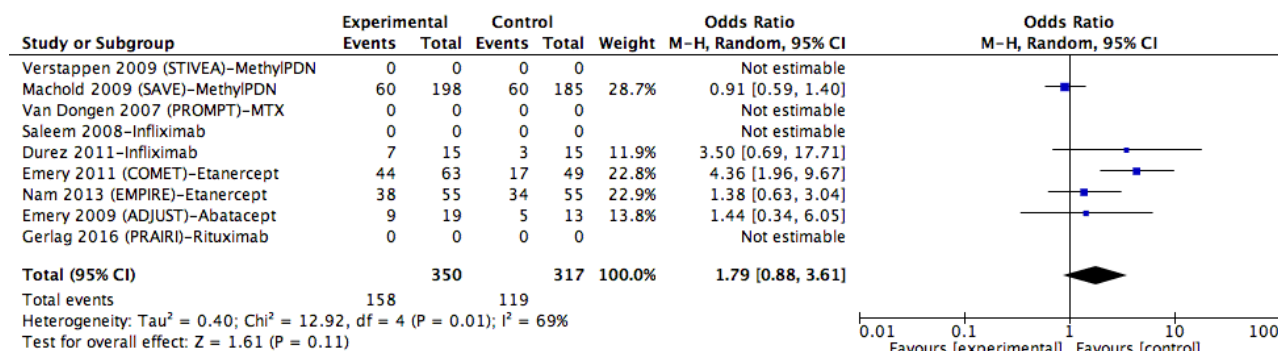
**b. RA diagnosis at week 52 or more not including TNF blockers.**



**Figure 3: Clinical remission at week 52**



**Figure 4: Absence of radiographic progression at week 52**



UA: unclassified arthritis (i.e., patients presenting arthritis and ultrasound-detected synovitis, without ACPA or RF positivity); VeRA (i.e., patients with clinical arthritis evolving for < 16 weeks and fulfilling the 2010 ACR/EULAR criteria but not the 1987 ACR criteria).

ACPA: anticitrullinated protein antibody. RF: rheumatoid factor. DAS: disease activity score. HAQ: health assessment questionnaire.

RA occurrence : according to ACR 1987 for all studies except for PRAIRI and STIVEA which correspond to the rheumatologist's opinion.

(a) : genetic risk factor of RA ; (b) environmental risk factor of RA ; (c) : systemic auto-immunity associated with RA ; (d) : symptoms without clinical arthritis ; (e) unclassified arthritis ; (f) RA (according EULAR 2012 recommendations for terminology[12])

MethylPDN : methylprednisolone. MTX: methotrexate. INF: infliximab. RA: rheumatoid arthritis. ABA: abatacept. ETN: etanercept. RTX: rituximab. MP: methylprednisolone. W: week

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