Review

Comparison of Biological Agent Monotherapy and Associations Including Disease-Modifying Antirheumatic Drugs for Rheumatoid Arthritis: Literature Review and Meta-Analysis of Randomized Trials

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Abstract: Objective: Update the available evidence comparing biologic disease-modifying antirheumatic drugs (bDMARDs) in combination with conventional synthetic disease-modifying antirheumatic drugs (CsDMARDs) to bDMARDs in monotherapy in patients with rheumatoid arthritis. Methods: Research was limited to randomized controlled trials. Major outcome: ACR 20 response criteria at 24 weeks. Secondary outcomes: clinical and radiographic criteria at week 24, 52 and 104. Results: 23 trials (6358 patients), including seven bDMARDs and one other molecule: Anbainuo (anti-TNF-R). No study satisfied our search criteria for anakinra, certolizumab and infliximab. Compared to bDMARD monotherapy, combination therapy gives a better ACR 20 at 24 weeks (RR: 0.88 (0.84–0.94)) in fixed and random effect models, and this result is sustained at 52 and 104 weeks. The results were mostly similar for all other outcomes without increasing the risk of adverse effects. Conclusion: This meta-analysis confirms the superiority of combination therapy over monotherapy in rheumatoid arthritis, in accordance to the usual guidelines.

Keywords: rheumatoid arthritis; DMARDs (synthetic); biologic agents; systematic reviews; meta-analysis

1. Introduction

Rheumatoid arthritis (RA) is the most common inflammatory rheumatism in adults [1]. The EULAR and French recommendations stipulate that methotrexate (MTX) should be started as soon as possible after the diagnosis of established RA [1,2]. If remission or low disease activity is not achieved after six months of conventional synthetic DMARDs (CsDMARDs) in patients without factors associated with a poor prognosis, treatment with another CsDMARD may be considered. By contrast, in the presence of a poor prognosis factor, biological treatment should be considered in association with the CsDMARD previously used [3]. In total, ten biological agents (bDMARDs) have been approved for RA treatment. Among them, adalimumab, certolizumab and etanercept have also been approved for use in monotherapy, as have abatacept, anakinra, tocilizumab and sarilumab. New strategies for RA treatment based on the inhibition of Janus kinase (JAK) pathways have been developed, but are not reviewed here. Many RA patients find it difficult to adhere to their CsDMARD prescription because of intolerance or contraindications [4–10]. It is, therefore, important to evaluate the benefits and harm associated with the use of biological agents in monotherapy. We conducted a systematic review of the literature and a meta-analysis, to update the available evidence already established [11] comparing the use of bDMARD and CsDMARD combination therapy with the use of biotherapy in monotherapy in patients with rheumatoid arthritis.

2. Materials and Methods

A PICOS design (Participants, Interventions, Comparisons and Outcomes) was used for the search strategy. The study selection, assessment of eligibility criteria, data extraction and statistical analyses were performed with a predefined protocol [12]. The reporting of the systematic review and meta- analysis conforms to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) statement [13].

2.1. Literature Search

CENTRAL, EMBASE and MEDLINE were used to identify published reports. Additional randomized controlled trials (RCTs) identified in relevant systematic reviews not retrieved through the electronic databases were then collated.

2.2. Trial Selection

Articles were screened independently by two authors of the review (C.D. and L.F.X.) for inclusion on the basis of their title, abstract and full text if necessary. Disagreements were resolved by consensus or through discussion with a third author (P.H.). Search results were limited to randomized controlled trials (RCTs) with two arms. We included open-label trials in our qualitative and quantitative analysis and performed a meta-regression analysis to determine whether the inclusion of these studies with a lower grade of recommendation modified our findings. We did not include trials for which a full text in English was not available and trials not reporting American College of Rheumatology (ACR) responses. We chose to stop studying inclusion after 104 weeks of follow-up.

2.3. Participants

Adults (>18 years) with RA, according to the 1987 or 2010 classification criteria.

2.4. Types of Interventions

Biologics used alone compared to biologics used in combination with a conventional synthetic DMARD.

2.5. Outcome Measures

We used all the available data published in the selected studies for the meta-analysis. We decided a priori to use the outcome assessment at 24 weeks, 52 and 104 weeks, to determine whether early outcomes were sustained over time. Our major outcome was the ACR 20 response criteria at 24 weeks. The secondary outcomes were: the ACR 20 criteria at 52 and 104 weeks, the ACR 50, 70, 90 response criteria, the DAS 28 remission score (including C-reactive protein (CRP) concentration or erythrocyte sedimentation rate (ESR)), the proportion of Van der Heide-modified Sharp's scores (mTSS) non-progressor (≤ 0.5), the proportion of patients withdrawing from the study due to adverse events and for lack of efficacy, improvement in the Health Assessment Questionnaire (HAQ) score > 0.22 and remission according to the Clinical Disease Activity Index (CDAI) and Simple Disease Activity Index (SDAI) scores. Concerning tolerance, we assessed adverse events, serious adverse events, infections, serious infections, cancers and tuberculosis.

2.6. Data Collection and Handling of Missing Data

Data from the trials were independently extracted by two abstractors (C.D. and F.X.L.). We obtained additional information from the online Supplementary Materials of the original RCTs when necessary. For graphic data, we used WebPlotDigitizer-**4.2 copyright 2010–2019 Ankit Rohatgi** for digital data extraction. Several studies [14–17] have shown the tool's reliability and validity to extract data from single-case graphs.

2.7. Risk of Bias

We assessed the risk of bias for each trial included, using the Cochrane 'Risk of bias' tool and the following criteria: selection bias, performance bias, detection bias, attrition

bias and reporting bias [18]. The risk of bias has been classified as: 'low', 'high' or 'unclear' (due to either a lack of information or uncertainty over the potential for bias). The GRADE score reflects the extent to which we are convinced that the actual effect is close to that estimated in the meta-analysis (Figure 1).
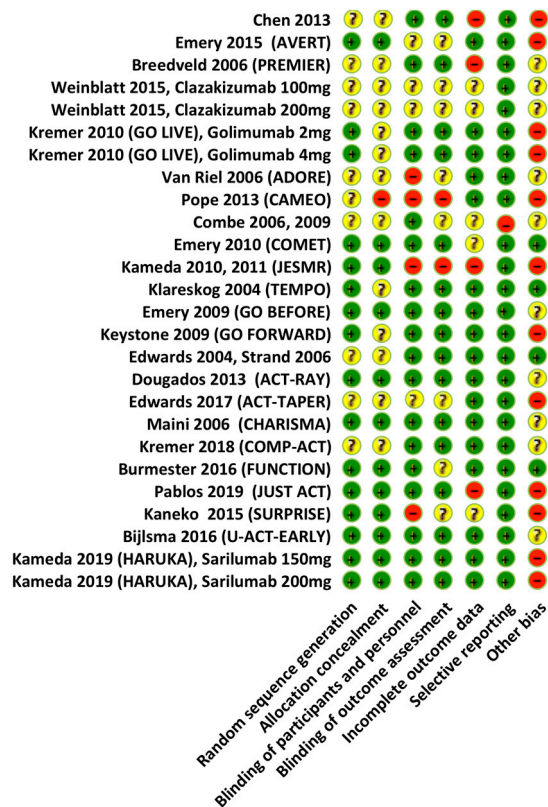

Figure 1. Assessment of the risk of bias. The Cochrane Collaboration tool used for randomized trials.

2.8. Statistical Analysis

We performed meta-analyses with fixed and random effects models in R version 3.6.1 (5 July 2019) Copyright © 2022 The R Foundation for Statistical Computing. The relative risk (RR) was the metric of choice for binary outcomes, and the mean difference (MD) or the standardized mean difference (SMD) was used for quantitative variables. Inverse variance weighting was used for the pooling of studies [19]. We used the DerSimonian–Laird method to estimate the variance between studies [20]. Between-study heterogeneity was assessed with the Q-test, considering a p-value < 0.05 to be statistically significant. The I^2 statistic was calculated to quantify the residual heterogeneity, ranging from 0 to 100% [21]. A leave-one-out method was used to identify outlying studies responsible for heterogeneity. Sensitivity analyses were conducted by meta-regression. The criteria included in the meta-regression analysis included: dose titration allowed in the study protocol, mean duration of disease, history of CsDMARD and bDMARD use before inclusion, presence or absence of a disease stabilization phase before randomization, positivity for RF and/or ACPA, severity on the DAS at inclusion, authorization of corticosteroid therapy use during the study and blinding throughout the study. Publication bias was evaluated by a graphical method, with a rank correlation test for funnel plot asymmetry [22].

3. Results

3.1. Study Selection Process

We identified 2566 publications: 1281 from PUBMED, 1015 from EMBASE, 232 from the Cochrane Library and 38 Cochrane reviews (Figure 2). We retained 23 articles, corresponding to 6358 patients. Of these studies, one focused on abatacept [23], one on adalimumab [24], six on etanercept [25–32], one on a similar molecule of etanercept, abainuo [33],

three on golimumab [34–38], one on rituximab [39,40], eight on tocilizumab [41–50], one on sarilumab [51] and one on clazakizumab [52]. Of these studies, four had open-label designs [29,30,32,50]. In the COMET [28], COMP-ACT [48] and JUST-ACT [47] studies, the participants were randomized into the two arms of interest after an initial period of 52 weeks, 24 weeks and 16 weeks, respectively, during which all patients received a combination of bDMARDs + CsDMARDs. In the ACT-TAPER [4] study, patients achieving a good/moderate EULAR response were randomized to a double-blind MTX taper arm, in which the MTX dose was tapered to 5 mg at 16 weeks, with complete withdrawal of MTX at 24 weeks, or to a stable MTX dose arm. We defined the day of inclusion, D0, for this study as the day on which methotrexate was completely withdrawn. We have not identified any studies satisfying our search criteria for anakinra, certolizumab or infliximab.
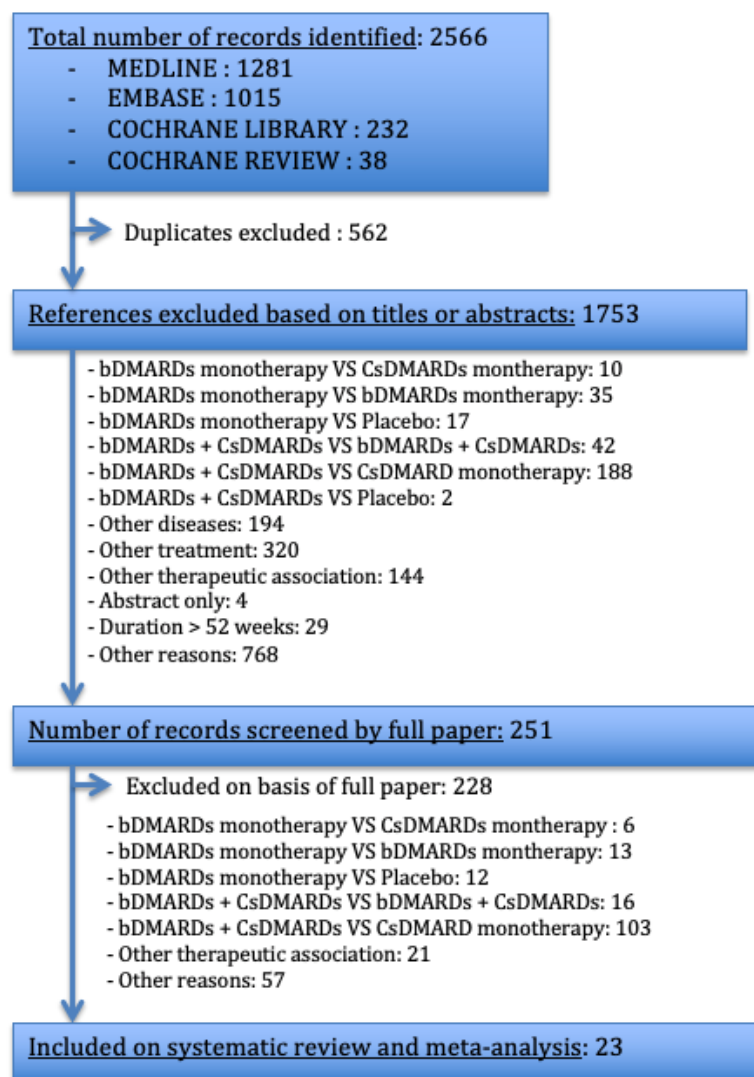
Total number of records identified: 2566
- MEDLINE : 1281
- EMBASE : 1015
- COCHRANE LIBRARY : 232
- COCHRANE REVIEW : 38

Duplicates excluded : 562

References excluded based on titles or abstracts: 1753

- bDMARDs monotherapy VS CsDMARDs montherapy: 10
- bDMARDs monotherapy VS bDMARDs montherapy: 35
- bDMARDs monotherapy VS Placebo: 17
- bDMARDs + CsDMARDs VS bDMARDs + CsDMARDs: 42
- bDMARDs + CsDMARDs VS CsDMARD monotherapy: 188
- bDMARDs + CsDMARDs VS Placebo: 2
- Other diseases: 194
- Other treatment: 320
- Other therapeutic association: 144
- Abstract only: 4
- Duration > 52 weeks: 29
- Other reasons: 768

Number of records screened by full paper: 251

Excluded on basis of full paper: 228

- bDMARDs monotherapy VS CsDMARDs montherapy : 6
- bDMARDs monotherapy VS bDMARDs montherapy: 13
- bDMARDs monotherapy VS Placebo: 12
- bDMARDs + CsDMARDs VS bDMARDs + CsDMARDs: 16
- bDMARDs + CsDMARDs VS CsDMARD monotherapy: 103
- Other therapeutic association: 21
- Other reasons: 57

Included on systematic review and meta-analysis: 23

Figure 2. Flow diagram for study inclusion/exclusion. CsDMARDs: Conventional synthetic disease-modifying anti-rheumatic drugs; bDMARDs: Biological disease-modifying anti-rheumatic drugs; VS: versus.

3.2. Study Characteristics

The characteristics of the studies included in the meta-analysis are displayed in Table 1. Regarding the history of CsDMARD use, three studies included only patients who had never used CsDMARDs (13%), 16 included patients not naïve for CsDMARD use (69.6%) and four were not selective on the basis of these criteria (17.4%). All but two of the studies used MTX as the CsDMARD. For the history of bDMARD use, nine studies included only

patients who had never used bDMARDs (39.1%), eight included patients with a possible history of use before inclusion (34.8%) and five included patients not naïve for bDMARD treatment (21.7%). Of the studies, eight included (26.1%) planned treatment adjustment during the trial a priori, with a rescue treatment administered if the main endpoint was not reached within the time allowed.

Table 1. Study characteristics.

Studies	Follow-Up	CsDMARD History	WO Period	bDMARD History	WO Period	RA Duration	Treatment	Doses (mg)	Dose Adjustment Defined a Priori	N
Anbainuo, Chen, 2013 [33]	24 weeks	Naive	/	Naive	/	ND	Abainuo + MTX	Abainuo: 25 mg SC 2x/Week	No	N = 132
							Abainuo	MTX: 10–15 mg/Week PO		N = 132
Abatacept (AVERT), Emery, 2015 [23]	48 weeks	Naive: MTX-naive or received MTX (≤10 mg/week) for ≤4 weeks	MTX 1 month	Naive	/	<2 years	ABA + MTX	ABA: 125 mg SC/Week	No	N = 119
							ABA	MTX: 7.5–20 mg/Week PO		N = 116
Adalimumab (PREMIER), Breedveld, 2006 [24]	48/104 weeks	Naive or not: MTX, cyclophosphamid, CYC, AZA, or 2 other CsDMARDs were excluded	4 weeks	Naive	/	<3 years	ADA + MTX	ADA: 40 mg SC/2 weeks	Increased dosing with ADA/placebo to weekly if ACR 20 not achieved in 2 consecutive visits after week 16.	N = 268
							ADA	MTX: 7.5–20 mg/Week PO		N = 274
Clazakizumab, Weinblatt, 2015 [53]	24 weeks	Non naive: MTX failure (>3 months treatment)	/	Naive	/	>16 weeks	CLZ + MTX	CLZ: 100 mg SC/4 wks	If <20% reduction SJC/TJC: receive open-label CLZ 200 mg SC/4 wk + MTX	N = 60
							CLZ	MTX: 10–22 mg/Week PO		N = 60
Etanercept, (ADORE), van Riel, 2006 [32]	16 weeks	Non naive: MTX >12.5 mg/week for >3 months	12 weeks	Naive	/	ND	ETN + MTX	ETN: 25 mg SC 2x/Week	No	N = 155
							ETN	MTX: >12.5 mg/week PO or SC		N = 159
Etanercept, (CAMEO), Pope, 2013 [29]	24/104 weeks	Non naive: MTX therapy for >12 weeks	/	Non naive: ETN + MTX for 6 months	/	> 6 months	ETN + MTX	ETN: 50 mg SC/Week	No	N = 107
							ETN	MTX: ≥15 mg/week		N = 98

Table 1. *Cont.*

Studies	Follow-Up	CsDMARD History	WO Period	bDMARD History	WO Period	RA Duration	Treatment	Doses (mg)	Dose Adjustment Defined a Priori	N
Etanercept, Combe, 2006 [25]	24/48/104 weeks	Non naive: SSZ for >4 months	Other than SSZ: 3 month	Naive or not: ineligible if they had received ETN or other TNF antagonists	bDMARDs or CTX: 6 months	<20 years	ETN + SSZ	ETN: 25 mg SC 2x/Week	No	N = 101
							ETN	SSZ: 2–2.5–3 g/day PO		N = 103
Etanercept (COMET), Emery, 2010 [28]	52 weeks	Non naive: ETN + MTX for 52 weeks before new randomization.	No	Non naive: ETN + MTX during 52 weeks before new randomization.	No	4 months until 2 years	ETN + MTX	ETN: 25 mg SC 2x/week	No	N = 111
							ETN	MTX 7.5–20 mg/Week PO		N = 111
Etanercept, (JESMR), Kameda, 2010 and 2011 [30,31]	24/52 weeks	Non naive: MTX 6 mg/week for >3 months	/	Naive	/	ND	ETN + MTX	ETN: 25 mg SC 2x/Week	No	N = 76
							ETN	MTX: 6–8 mg/week		N = 71
Etanercept (TEMPO), Klareskog, 2004 [27]	24/52/104 weeks	CsDMARD non naive, but MTX naive or not	MTX 6 month	Naive or not: Ineligible if previously received ETN or other TNF antagonists.	ISD: 6 months bDMARD: 3 months	6 months until 20 years.	ETN + MTX	ETN: 25 mg SC 2x/week	No	N = 231
							ETN	MTX: 7.5–20 mg/Week PO		N = 223
Golimumab (GO BEFORE), Emery, 2009 [35]	24/52/104 weeks	Naive or not: had not received more than 3 weekly doses of oral MTX	/	Naive or not: IFX, ETN, ADA, RTX, NTZ, or cytotoxic agents, and alkylating agents, were excluded	ANK: 4 weeks alefacept/efalizumab: 3 months, other: 5 half-lives	3 months until 3 years	GOL + MTX	GOL: 100 mg SC/4 weeks	If <20% improvement from baseline SJC/TJC entered early escape any time after week 24.	N = 159
							GOL	MTX: 10–20 mg/Week PO		N = 159
Golimumab (GO FORWARD), Keystone, 2009 [38]	24/52/104 weeks	Non naive: had been receiving a stable dose of MTX 15–25 mg/week for at least 4 weeks	Other than MTX 4 weeks	Naive or not: excluded if used anti- TNF agent, RTX, NTZ or cytotoxic agents	ANK: 4 weeks alefacept efalizumab: 3 months	NR	GOL + MTX	GOL: 100 mg SC/4 weeks	If <20% improvement from baseline TJC/SJC escape any time after week 24.	N = 89
							GOL	MTX: 15–20 mg/week PO		N = 133

Table 1. *Cont.*

Studies	Follow-Up	CsDMARD History	WO Period	bDMARD History	WO Period	RA Duration	Treatment	Doses (mg)	Dose Adjustment Defined a Priori	N
Golimumab (GO LIVE), Kremer, 2010 [37]	24/48 weeks	Non naive: MTX for >3 months	/	Naive or not: limited to 20% of the study population. (Excluded if RTX, ABA, or NTZ).	IFX, alefa-Cept/ efalizumab: 3 months, ETN/ADA 2 month-sANK/ ABA/NTZ. 4 weeks	<8 years	GOL 2 mg/kg + MTX / GOL 4 mg/kg + MTX / GOL 2 mg/kg / GOL 4 mg/kg	GOL: 2 mg/kg OR 4 mg/kg IV/12 weeks / MTX: 15 mg/Week PO	At weeks 16 and 24, patients with <20% improvement from baseline in both the SJC and TJC entered early escape and dose regimen	N = 128 / N = 129 / N = 129 / N = 128
Rituximab, Edwards, 2004, Strand, 2006 [40,41]	24/48/104 weeks	Non naive: had failed 1–5 CsDMARDs and MTX with treatment for >16 weeks	/	ND	/	ND	RTX + MTX / RTX	RTX: 1000 mg IV on days 1 and 15 all 6 months / MTX: 12.5–15 mg/ Week PO	No	N = 40 / N = 40
Sarilumab, (HARUKA) Kameda, 2019 [52]	24/52 weeks	Naive or not: - monotherapy: CsDMARDs naive -combination: CsDMARDs non naive	/	Naive or not	CYC, MF-MAZA, CTX, bD-MARD: 4–12 weeks	ND	SLM 150 mg + non-MTX CsD-MARDs / SLM 200 mg + non-MTX CsD-MARDs / SLM 150 mg / SLM 200 mg	SLM 150 or 200 mg/2 Weeks SC	No	N = 15 / N = 15 / N = 30 / N = 31
Tocilizumab (ACT RAY), Douga-dos, 2013 [42]	24/52/104 weeks	Non naive: MTX for at least 12 weeks	LEF: 3 month Other 1 month	Naive or not	bDMARD 1 month	ND	TCZ + MTX / TCZ	TCZ: 8 mg/kg IV/4 weeks / MTX: 15–20 mg/ Week PO	At week 24, if DAS28 > 3.2; an open-label CsDMARD was added. At week 36, if DAS28 > 3.2, an additional CsDMARD added.	N = 277 / N = 276
Tocilizumab (ACT-TAPER), Edwards, 2017 [50]	24 weeks	Non naive: had inadequately responded to 2 CsDMARDs, including MTX.	/	Non naive	Had have TCZ 8 mg/kg/ 4 weeks for 24 weeks	ND	TCZ + MTX stable dose / TCZ + MTX Tapering dose	TCZ: 8 mg/kg IV/4 weeks / MTX stable dose: 10–15 mg/ Week MTX tapering dose S24 to S40: 5 mg /week; S40 to S48: 0 mg.	No	N = 136 / N = 136

Table 1. *Cont.*

Studies	Follow-Up	CsDMARD History	WO Period	bDMARD History	WO Period	RA Duration	Treatment	Doses (mg)	Dose Adjustment Defined a Priori	N
Tocilizumab (CHARISMA), Maini, 2006 [54]	16/20 weeks	Non naive: MTX failure >6 months of treatment	LEF: 6 months Other 4 weeks	Naive or not	anti-TNF agents: 12 weeks	ND	TCZ + MTX	TCZ: 8 mg/kg IV/4 weeks	No	N = 50
							TCZ	MTX: 10–25 mg/ Week PO		N = 52
Tocilizumab (COMP-ACT), Kremer, 2018 [49]	24 weeks	Non naive: TCZ + MTX during 24 weeks before new randomization.	/	Non naive: TCZ + MTX for 24 weeks before new randomization.	/	ND	TCZ + MTX	TCZ: 162 mg/ week (≥100 kg) or /2 weeks (<100 kg)	No	N = 147
							TCZ	MTX: >15 mg/ week PO		N = 147
Tocilizumab (FUNC-TION), Burmester, 2016 [45]	24/52/104 weeks	CsDMARD-naive or not but MTX-naive	/	Naive	/	<2 years	TCZ + MTX	TCZ:8 mg/ kg IV /4 wks	No	N = 291
							TCZ	MTX: 7.5–20 mg/ Week PO		N = 292
Tocilizumab (JUST ACT), Pablos, 2019 [48]	12 weeks	Non naive: TCZ + MTX 16 weeks before randomization.	/	Non naive: TCZ + MTX 16 weeks before randomization.	/	NR	TCZ + MTX	TCZ: 8 mg/ kg IV/4 wks	No	N = 83
							TCZ	MTX: >15 mg/ Week PO		N = 82
Tocilizumab, (SUR-PRISE), Kaneko, 2015 [51]	24/52/104 weeks	Non naive: MTX ≥6 mg/ week for at least 8 weeks	LEF: 12 weeks, other: 8 weeks	Naive	Tacrolimus: 4 weeks	<10 years	TCZ + MTX	TCZ: 8 mg/ kg IV/4 wks	No	N = 118
							TCZ	MTX: >6 mg/ Week PO		N = 115
Tocilizumab (U-ACT-EARLY), Bijlsma, 2016 [46]	24/52/104 weeks	Naive	/	Naive	/	<1 year	TCZ + MTX	TCZ:8 mg/ kg IV/ 4 wks	No	N = 106
							TCZ	MTX: 10–30 mg/ Week PO		N = 103

ND: not disclosed; N: number; IV: intravenous; IM: intramuscular; PO: per os; SC: subcutaneous; wks: weeks; mths: months; WO: wash out; min: minimum; ACR 20: American college of Rheumatology 20; SJC: swollen joint count; TJC: tender joint count; sDMARDs: conventional disease-modifying antirheumatic drugs; bDMARDs: biologic disease-modifying antirheumatic drugs; ABA: abatacept; ADA: adalimumab; ANK: anakinra; AZA: azathioprine; CLZ: clazakizumab; CTX: cyclophosphamide; CYC: ciclosporine; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; HCQ: hydroxychloroquine; IFX: infliximab; ISD: immunosuppressive drug; LEF: leflunomide; MMF: mycophenolate; MTX: methotrexate; NTZ: natalizumab; RTX: rituximab; SLM: sarilumab; SSZ: sulfasalazine; TCZ: tocilizumab.

3.3. Principal Characteristics of the Patients

More than 75% of the patients were women, and the mean age was 55 years (range: 45.4 ± 11.9 to 63.3 ± 10.6 years). Disease duration ranged from 26 days to 12 years, and most of the patients for whom the information was available had tested positive for

autoantibodies (RF and/or ACPA). The DAS 28 score at baseline ranged from 2.6 to 6.8, and the mTSS score ranged from 0 ± 0 to 39.6 ± 56.1.

3.4. Primary Efficacy Endpoint: ACR 20 at 24 Weeks

The ACR 20 results at 24 weeks were reported for 16 studies. Using a random effects model, we found that the therapeutic combination performed significantly better for this endpoint, RR = 0.88 (0.83; 0.93), despite significant heterogeneity between studies (I^2 = 46%, τ^2 = 0.0068, p = 0.02) (Figure 3). We made the results more consistent by performing a sensitivity analysis and a funnel plot asymmetry test. The remaining 14 studies showed that significantly better results for this endpoint were obtained with the combination treatment (RR = 0.91 (0.88; 0.95); I_2 = 0%, τ^2 = 0, p = 0.53). We decided a priori to include open-label studies in the quantitative analysis and to use the qualitative analysis to check whether this decision had any effect on the results. Consistent with the τ^2 test results, we can conclude that the inclusion of SUPRISE, ADORE and JESMR with an open-label design, despite their lower grade of recommendation, had no effect on the results of the analysis.
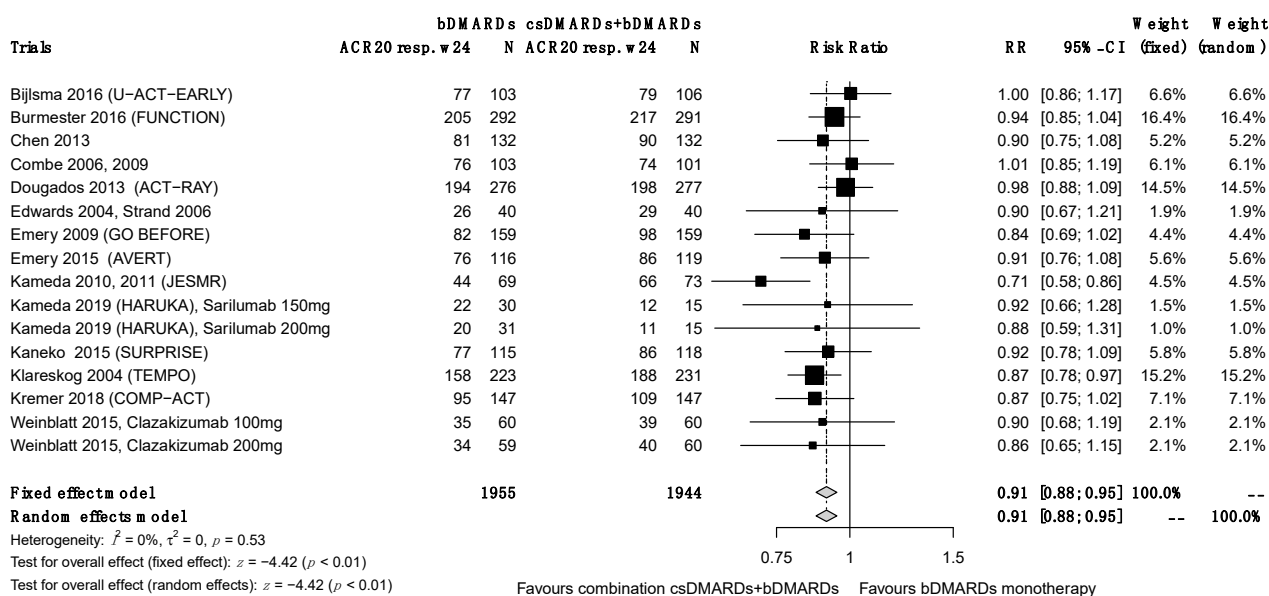
Trials	bDMARDs ACR20 resp. w 24	N	csDMARDs+bDMARDs ACR20 resp. w 24	N	Risk Ratio	RR	95% -CI	Weight (fixed)	Weight (random)
Bijlsma 2016 (U-ACT-EARLY)	77	103	79	106		1.00	[0.86; 1.17]	6.6%	6.6%
Burmester 2016 (FUNCTION)	205	292	217	291		0.94	[0.85; 1.04]	16.4%	16.4%
Chen 2013	81	132	90	132		0.90	[0.75; 1.08]	5.2%	5.2%
Combe 2006, 2009	76	103	74	101		1.01	[0.85; 1.19]	6.1%	6.1%
Dougados 2013 (ACT-RAY)	194	276	198	277		0.98	[0.88; 1.09]	14.5%	14.5%
Edwards 2004, Strand 2006	26	40	29	40		0.90	[0.67; 1.21]	1.9%	1.9%
Emery 2009 (GO BEFORE)	82	159	98	159		0.84	[0.69; 1.02]	4.4%	4.4%
Emery 2015 (AVERT)	76	116	86	119		0.91	[0.76; 1.08]	5.6%	5.6%
Kameda 2010, 2011 (JESMR)	44	69	66	73		0.71	[0.58; 0.86]	4.5%	4.5%
Kameda 2019 (HARUKA), Sarilumab 150mg	22	30	12	15		0.92	[0.66; 1.28]	1.5%	1.5%
Kameda 2019 (HARUKA), Sarilumab 200mg	20	31	11	15		0.88	[0.59; 1.31]	1.0%	1.0%
Kaneko 2015 (SURPRISE)	77	115	86	118		0.92	[0.78; 1.09]	5.8%	5.8%
Klareskog 2004 (TEMPO)	158	223	188	231		0.87	[0.78; 0.97]	15.2%	15.2%
Kremer 2018 (COMP-ACT)	95	147	109	147		0.87	[0.75; 1.02]	7.1%	7.1%
Weinblatt 2015, Clazakizumab 100mg	35	60	39	60		0.90	[0.68; 1.19]	2.1%	2.1%
Weinblatt 2015, Clazakizumab 200mg	34	59	40	60		0.86	[0.65; 1.15]	2.1%	2.1%
Fixed effect model		1955		1944		0.91	[0.88; 0.95]	100.0%	--
Random effects model						0.91	[0.88; 0.95]	--	100.0%

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.53
Test for overall effect (fixed effect): z = −4.42 (p < 0.01)
Test for overall effect (random effects): z = −4.42 (p < 0.01)

0.75 1 1.5
Favours combination csDMARDs+bDMARDs   Favours bDMARDs monotherapy

Figure 3. ACR 20 responses at week 24.

3.5. Other Endpoints

3.5.1. ACR Reponses

With fourteen studies providing ACR 20 results at 52 weeks, the overall result obtained with the random effects model was significantly in favor of the therapeutic combination (RR= 0.90 (0.84; 0.97)). However, it was not possible to have confidence in the results, due to the degree of heterogeneity (I^2 = 64%, τ^2 = 0.0116, p < 0.01). After controlling for heterogeneity, we selected 11 studies. The results were also in favor of the combination treatment (RR = 0.94 (0.90; 0.98), I^2 = 7%, τ^2 = 0.0004, p = 0.38). The ACR 20 results at 104 weeks were available for eight studies. The results were significantly in favor of the combination treatment both before (RR = 0.89 (0.84; 0.94), I^2 = 66%, τ^2 = 0.0129, p < 0.01) and after the sensitivity analysis (RR = 0.92 (0.87; 0.98)) (I^2 = 0%, τ^2 = 0, p = 0.42). The ACR 50 scores were significantly in favor of the combination treatment and were not affected by sensitivity testing (RR = 0.81 (0.76; 0.87), I^2 = 0%, τ^2 = 0, p = 0.77) at 24 weeks, (RR = 0.89 (0.82; 0.97), I^2 = 10%, τ^2 = 0.0019, p = 0.35) at 52 weeks and (RR = 0.84 (0.77; 0.93), I^2 = 14%, τ^2 = 0.0022, p = 0.32) at 104 weeks. The same was true for the ACR 70 score at weeks 24 and 52 (RR = 0.76 (0.68; 0.85), I^2 = 10%, τ^2 = 0.0055, p = 0.33) at 24 weeks, (RR = 0.81 (0.73; 0.90), I^2 = 16%, τ^2 = 0.0063, p = 0.28) at 52 weeks. At 104 weeks, the ACR 70 data were significantly in favor of the combination treatment in the analysis (RR = 0.77

(0.64; 0.93), I^2 = 61%, τ^2 = 0.00393, *p* = 0.01), but were not significant after sensitivity analysis (RR = 0.89 (0.78; 1.01), I^2 = 0%, τ^2 = 0, *p* = 0.84). Overall, five studies reported ACR 90 scores at 24 weeks, showing these results to be significantly in favor of the combination treatment (RR = 0.64 (0.44; 0.93), heterogeneity: I^2 = 0%, τ^2 = 0, *p* = 0.70). At 52 weeks, the ACR 90 data were not significantly in favor of either therapeutic strategy, even after sensitivity analysis (RR = 0.88 (0.65; 1.19), I^2 = 0%, τ^2 = 0, *p* = 0.84). Only two studies reported ACR 90 scores at 104 weeks; the lack of data did not allow for reliable analyses.

3.5.2. Remission According to DAS 28 (Using ESR or CRP)

At 24 weeks, remission according to DAS 28 (<2.6) was reported, based on CRP in six RCTs and ESR in eight RCTs. For the DAS 28–CRP remission scores, the objective was achieved significantly more frequently for the combined treatment group at weeks 24 and 52 (RR = 0.66 (0.56–0.77), I^2 = 0%, τ^2 = 0.00, *p* = 0.70) at 24 weeks and (RR = 0.73 (0.63–0.85), I^2 = 0%, τ^2 = 0.00, *p* = 0.92) at 52 weeks. Only two studies provided results at 104 weeks. For the DAS 28–ESR remission scores, the initial data at 24 weeks showed an I^2 value of 0% for heterogeneity, but the funnel plot asymmetry test revealed a publication bias for the GO-FORWARD study, so we excluded this study from the final analysis. The objective was significantly more frequently achieved in the association group at weeks 24 and 52 (at 24 weeks, RR = 0.87 (0.80–0.95), I^2 = 0%, τ^2 = 0, *p* = 0.90 (Figure 4); at 52 weeks, RR = 0.86 (0.76–0.97), I^2 = 22%, τ^2 = 0.0026, *p* = 0.28), but the results ceased to be significant at 104 weeks (RR = 0.83 (0.83–1.05), I^2 = 0%, τ^2 = 0.00, *p* = 0.89). Note that the results at 52 weeks were initially non-significant but became so after sensitivity analysis.

Trials	bDMARDs DAS28VS resp. w 52	N	csDMARDs+bDMARDs DAS28VS resp. w 52	N	Risk Ratio	RR	95% −CI	Weight (fixed)	Weight (random)
Burmester 2016 (FUNCTION)	115	292	142	291		0.81	[0.67; 0.97]	33.4%	33.5%
Dougados 2013 (ACT−RAY)	101	276	126	277		0.80	[0.66; 0.98]	28.0%	29.1%
Kaneko 2015 (SURPRISE)	78	115	83	118		0.96	[0.81; 1.15]	38.6%	37.4%
Fixed effect model		683		686		0.86	[0.78; 0.96]	100.0%	--
Random effects model						0.86	[0.76; 0.97]	--	100.0%

Heterogeneity: I^2 = 22%, τ^2 = 0.0026, *p* = 0.28
Test for overall effect (fixed effect): *z* = −2.69 (*p* < 0.01)
Test for overall effect (random effects): *z* = −2.40 (*p* = 0.02)

0.75   1   1.5
Favours combination csDMARDs+bDMARDs   Favours bDMARDs monotherapy

Figure 4. DAS 28–ESR remission at 52 weeks.

3.5.3. HAQ, CDAI and SDAI Scores

In total, nine RCTs reported an improvement in HAQ $\geq$ 0.22 and showed an absence of significance for either arm of the study at 24 weeks (RR = 0.90 (0.80; 1.01), I^2 = 0%, τ^2 = 0.00, *p* = 0.49), but a significant difference emerged from 52 weeks onwards in favor of the combination therapy (RR= 0.83 (0.75; 0.92), I^2 = 4%, τ^2 = 0.0005, *p* = 0.37 at 52 weeks; RR= 0.89 (0.83; 0.96), I^2 = 17%, τ^2 = 0.0012, *p* = 0.31 at 104 weeks). Similar results were obtained for CDAI remission (<2.8) at 24, 52 and 104 weeks and SDAI remission (<3.3) at 24 and 52 weeks after sensitivity analysis (no results available at 104 weeks).

3.5.4. Subgroup Meta-Analysis

All our results show an RR close to 1, meaning that the combination therapy was not much more effective than the biological agent used as a monotherapy. We decided to perform a subgroup analysis by successively removing etanercept, tocilizumab and then both molecules from the analysis to try to explain these results. We found that removing tocilizumab resulted in a decrease in RR, whereas removing etanercept did not appear to change the results. This sub-analysis suggests that tocilizumab appears to be more effective as a single agent than other available biotherapies.

3.5.5. Structural Progression

A total of eleven RCTs reported X-ray progression based on mTSS <0 or <0.5 at weeks 24, 52 and/or 104. A significantly lower progression was observed for the combination

treatment from 52 weeks (Figure 5) and remained at 104 weeks before and after sensitivity analysis; the results at 24 weeks were not significant (RR = 0.98 (0.91; 1.04), $I^2 = 6\%$, $\tau^2 = 0.0003$, $p = 0.35$ at 24 weeks; RR = 0.94 (0.89; 0.99), $I^2 = 16\%$, $\tau^2 = 0.0008$, $p = 0.31$ at 52 weeks; RR = 0.92 (0.87; 0.98), $I^2 = 12\%$, $\tau^2 = 0.0008$, $p = 0.34$).
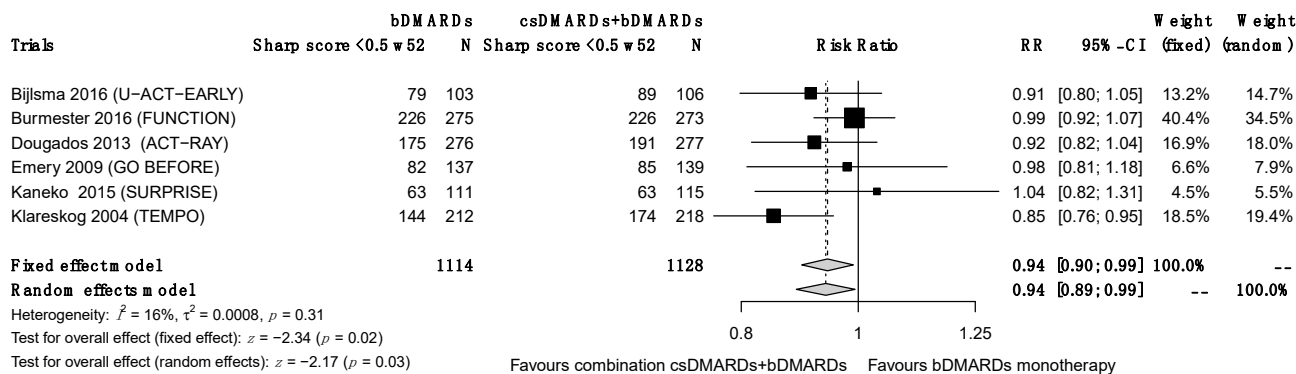
Figure 5. Sharp remission at 52 weeks.

3.5.6. Discontinuation Due to a Lack of Efficacy

The rate of discontinuation due to lack of efficacy did not differ between groups up to 52 weeks (RR = 1.74 (0.92; 3.29) with $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.59$ at 24 weeks; RR = 1.39 (0.88; 2.18) with $I^2 = 6\%$, $\tau^2 = 0.0241$, $p = 0.39$ at 52 weeks). However, an increase in the number of discontinuations due to a lack of efficacy was reported at 104 weeks for the biotherapy monotherapy group (RR= 2.83 (1.82; 4.41) with $I^2 = 19\%$, $\tau^2 = 0.0398$, $p = 0.30$ at 104 weeks).

3.5.7. Toxicity

The heterogeneity of the toxicity data made it impossible to perform a reliable statistical analysis. Nevertheless, we were able to compare study outputs for discontinuation due to adverse events. We found no advantage for either group in terms of the number of discontinuations: RR = 0.73 (0.53; 1.01) with $I^2 = 0\%$ and $\tau^2 = 0$, $p = 0.70$ at 24 weeks; RR= 0.95 (0.70; 1.31) with $I^2 = 40\%$, $\tau^2 = 0.1151$, $p = 0.07$ at 52 weeks; and RR = 0.84 (0.67; 1.05) with $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.53$ at 104 weeks. The I^2 value for heterogeneity obtained at 52 weeks was >30%. We decided to retain this result because significance did not differ before and after sensitivity analysis, and a cutoff of 40% has been reported to be acceptable [54].

4. Discussion

Through this systematic review and meta-analysis, we aimed to compare the use of biological agents in monotherapy and in association with a CsDMARD. Many meta-analyses have compared studies of different therapeutic combinations (for example, biotherapies in monotherapy versus CsDMARDs or placebo), making it difficult to extrapolate results to our arms of interest [55–59].

This is the second systematic review comparing the value of adding MTX to bDMARD treatment with bDMARD monotherapy. Our work confirms the work of Tarp and al. [11], with the difference that our study is more recent, which allowed us to include a larger number of randomized trials and, therefore, patients.

We found that the combination treatment was more effective than monotherapy, as shown by the main endpoint, ACR 20 at 24 weeks. The results are similar for the other endpoints, with, for some, a loss of efficacy at 104 weeks, possibly with a loss of power of the study. The modified Sharp's score was significantly in favor of the combined treatment from 52 weeks onwards. At 24 weeks, the duration of exposure may not have been sufficiently long to distinguish between the two study arms considered. It is interesting to note that the PREMIER study [24] was a source of great heterogeneity for several of the variables studied with no obvious cause found. Our results are comparable with French and international recommendations [1,2].

The purpose of this meta-analysis was not to compare the different bDMARDs between each other. Nevertheless, we could observe that all our results showed an RR close to 1, showing little difference in clinical efficacy between groups. The subgroup analysis showed that excluding tocilizumab from the analysis decreased this RR, suggesting that tocilizumab is probably the most effective single-agent biologic. These results are consistent with the literature. Tarp et al. [60] have shown that most biological agents are effective in monotherapy, with an advantage for etanercept and tocilizumab supported by other network meta-analyses [57,59,61]. Some studies about IL-6 receptor blockers in monotherapy have shown that tocilizumab monotherapy yields response rates close to those obtained in combination with MTX in randomized studies and cohorts [62,63]. The ADACTA and MONARCH studies have shown tocilizumab and sarilumab to be superior to adalimumab in monotherapy [64,65]. In the TOCERRA registry [63], the therapeutic efficacy and maintenance of tocilizumab monotherapy are similar to those of the anti-TNF agents associated with MTX.

Finally, structural damage was not studied for all the biological treatments included in our meta-analysis. Tarp et al. [11] obtained identical results to those reported here and, after a subgroup analysis, no structural differences were found.

We found no difference in terms of safety between the two treatment arms, essentially due to the heterogeneity of the data collection. However, we were able to show that there was no difference between the study arms in terms of the rate of treatment discontinuation due to adverse events. With regard to the risk of infection, Singh et al. [66] showed that, in patients treated with CsDMARDs, the median annual absolute risk of infection was 2%, or 20 per 1000 treated patients per year, whereas there was an increase to 6 per 1000 patients treated with bDMARDs in combination with a CsDMARD, with a significant difference. Ramiro et al. [67] confirmed that patients on bDMARDs (both anti-TNF and no anti-TNF agents) had a higher risk of serious infections than patients on CsDMARDs, and that there was generally no difference between bDMARDs. They also investigated the occurrence of different cancers after exposure to biologics. Relative to both the general population and patients on CsDMARDs, patients on bDMARDs had no higher risk of individual solid cancers or of lymphoma. By contrast, non-melanoma skin cancer may occur more frequently in patients on bDMARDs than in the general population (HR 1.7), but the risk in these patients is no higher than that in patients treated with CsDMARDs. One study with a low risk of bias showed that patients on bDMARDs may have a higher risk of melanoma than patients on CsDMARDs (HR 1.5, 95% CI 1.0 to 2.2) [68].

Nevertheless, our study has several limitations. First, as with all systematic literature reviews, this study is subject to certain publication and selection biases. Second, there was some heterogeneity between these studies. The variables tested with the sensitivity analysis did not significantly influence the results of the meta-analysis. In addition, few studies have used CsDMARDs other than methotrexate, limiting the extrapolation of results for leflunomide or sulfasalazine. We also chose to consult the data collected at weeks 24, 52 and 104; when data for these time points were not available, other time points were used. Comparisons at different time points may limit the interpretation of our results, as may not having been able to contact the authors to recover missing data.

5. Conclusions

Our meta-analysis confirms the results of a previous one, but with updated research and a larger number of studies included. The results indicate that the combination therapy of a biological agent with CsDMARDs is more effective than monotherapy and should be preferred in uncontrolled RA, in accordance with the usual guidelines. MTX should be switched to another CsDMARD in the case of contraindication or intolerance.

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