Analysis of efficacy and safety of abatacept for rheumatoid arthritis: systematic review and meta-analysis

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Abstract

Objective

Abatacept (Orencia) is a drug used to treat patients with rheumatoid arthritis. The agent improves patients' pain and joint inflammation through modulation of a co-stimulatory signal necessary for T cell activation. We aimed to analyse the efficacy and safety of abatacept in the management of rheumatoid arthritis using the Cochrane systematic review.

Methods

We conducted a systematic search among PubMed, Cochrane central register of controlled trials, Web of Science, and Embase databases from the establishment of these databases to April 2022. The effectiveness and safety of abatacept in treating rheumatoid arthritis were assessed in terms of American College of Rheumatology (ACR) 20/50/70/90 responses, Disease Activity Score-28 for Rheumatoid Arthritis with C-reactive protein (DAS-28-CRP), and adverse events. The Relative Risks (RRs) of relative safety and efficacy and their corresponding 95 confidence intervals (CIs) were used to compute the pooled assessments of the outcomes. We used the review manager software version 5.4 to analyse our data, and the PRISMA checklist 2020 was used to ensure that our work conforms with the specification of meta-analysis.

Results

Our study included 13 randomised control trials with a total of 5978 adult patients from different geographic regions and races. Following the combined analysis of these enrolled studies, the RRs for ACR 20/50/70/90 responses were 1.57 [95%CI 1.27, 1.93], 1.84 [95%CI 1.38, 2.44], 2.36 [95%CI 1.60, 3.47], and 2.95 [95%CI 1.88, 4.63], respectively. Such findings suggest that abatacept-treated patients were 1.57, 1.84, 2.36, and 2.95 times more likely to achieve ACR 20/50/70/90 responses, respectively, than those treated with placebo, conventional synthetic disease-modifying anti-rheumatic drugs, and or other biologic disease-modifying anti-rheumatic drugs. An exclusive comparison of abatacept and other biologic/targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs) indicated that participants who were treated with abatacept could achieve better ACR responses than those treated with other b/tsDMARDs. Adverse events were less seen in abatacept-treated patients than in those who were given other b/tsDMARDs.

Conclusion

This meta-analysis concludes that in adult with rheumatoid arthritis, abatacept can achieve better health outcomes than other biologic drugs.

Key words

adults, rheumatoid arthritis, treatment, abatacept, safety, efficacy, Orencia, CTLA-4

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Introduction

Rheumatoid arthritis (RA) is one of the most prevalent autoimmune diseases affecting the joints. The disease is characterised by chronic joint inflammation but can also have extra articular manifestations such as vasculitis, pulmonary involvement, rheumatoid nodules, and systemic comorbidities (1). Uncontrolled Inflammation from this systemic disorder can lead to disability, social dysfunction, and even early death (2). Over the past decade, the management of RA has known a therapeutic revolution which has improved the disease outcome (3, 4). Treatment options such as pharmacological interventions, balneotherapy and physical therapy can manage the symptoms, normalise joint functions, and prevent long-term deterioration (5). Pharmacotherapy is usually achieved by conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) in combination with corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) or biologic DMARDs (bDMARDs) (5, 6). Despite progress in treating RA, no drug has been developed to effectively cure this condition and side effects from current medications cannot be tolerated by every patient (7). Abatacept, brand name Orencia, is a biological agent that decreases T-cell stimulation resulting in the downregulation of B-cell and macrophage activation (8). Given the key role of T cells in the development of RA (9), the drug has been used to treat people with rheumatoid arthritis, especially those who do not respond well to csDMARDs and tumour necrosis factor (TNF) inhibitors (10-12). Although the literature offers some information about this compound, there is a lack of updated study that quantifies and analyses its benefit and potential harm. Therefore, this article aims to systematically review the safety and effectiveness of abatacept in RA using data from randomised control trials (RCTs).

Materials and methods

Search method

PubMed, Cochrane, Web of Science, and Embase electronic databases were searched for randomised clinical trials. The search was from the establishment of the databases to April 2022 and was not limited by language. The terms "rheumatoid arthritis" and "abatacept" OR "Orencia" OR "CTLA-4" were used as key words.

Inclusion and exclusion criteria

- Inclusion criteria:

To be eligible for inclusion, a study must be an RCT of abatacept treatment for rheumatoid arthritis. The participants must be adults who have been diagnosed with rheumatoid arthritis. The experimental group includes abatacept alone or in combination with csDMARDs. The control group includes placebo or other bDMARDs or csDMARDs. No restriction was established in terms of duration of intervention or dosage.

Type of outcomes:

- ACR 20/50/70/90 responses as defined by the American College of Rheumatology (13).
- DAS-28-CRP
- Adverse events

- Exclusion criteria:

Non randomised controlled trials were excluded from this study.

Data collection and analysis

- Selection of studies

The results from different electronic databases (PubMed, Cochrane, Web of Science, and Embase) were independently reviewed by two authors. Titles, abstracts and sometimes the full text were assessed to evaluate whether the trial met the inclusion criteria.

- Data extraction

After the removal of duplicates using the EndNote library, two independent authors extracted and tabulated the following data from the selected studies:

- Authors, publication year, eligibility criteria and Sample size,
- Baseline characteristics of treated patients (control and intervention),
- Treatment comparators, dosage, method of administration and course of treatment,
- Outcomes (ACR 20/50/70/90 responses, DAS 28-CRP, and adverse events).

Quality assessment

The risk of bias was assessed by two independent reviewers using the Cochrane collaboration tool for assessing risk bias. This includes sequence generation, allocation concealment, blinding methods, incomplete outcome data, selective result reporting, and other biases such as co-interventions. The quality of literature was assessed using the PRISMA quality evaluation system.

Statistical analysis

The Revman 5.4.1 software was used to analyse the results of the enrolled studies. Clinical and statistical heterogeneity was assessed using χ^2 test (statistical heterogeneity) and I^2 test (heterogeneity size). According to the origin of heterogeneity, we did a subgroup analysis. A fixed effect model was used if no statistical heterogeneity existed between the studies (p>0.1 or I2 <50%). We used a randomised effect model (p<0.1 or I2>50%) if statistical heterogeneity could be identified among the studies, followed by a subgroup analysis to assess the origin of the heterogeneity. Data were categorical and were expressed in Relative Risk 95% CI.

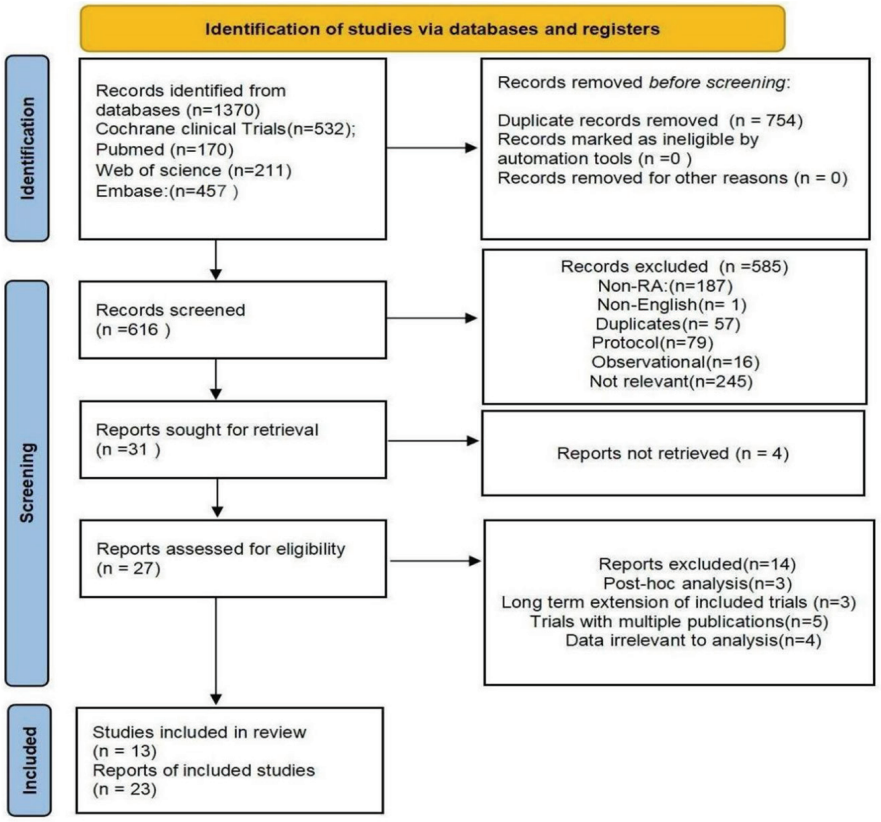


Fig. 1. Process of screening the literature (PRISMA 2020 flow diagram for new systematic reviews).

Results

Results search

1370 studies were retrieved from the electronic database search in April 2022. A total of 616 studies were enrolled after excluding duplicates. Based on the title or abstract, we removed 585 studies (the reasons for exclusion are detailed in Figure 1) and remained with 31 studies, of which 4 could not be retrieved. After reviewing the full text of the remaining 27 articles, we excluded 14 reports (14-28) (either because they were *post-hoc* analysis, long term extension of included studies or data were irrelevant to analysis). Finally, 13 studies (29-41) were selected for this meta-analysis. Table I shows the essential characteristics of the enrolled studies.

Quality of the studies

The assessment of bias risk was performed using the Cochrane collaboration risk bias assessment tool and is shown in Figure 2. Table II shows the PRISMA literature quality evaluation of related studies.

Demographic characteristics of the participants

Our work included a combined study population of 5978 patients. This population originated from North America, South America, Central America, Europe, Asia, Saudi Arabia, and Other. The population race included White, Caucasian, Black, and Other, with White being the dominant race. The participants were all adult and the mean age varied between 45.9 and 56.62 years old. In each individual study the majority of the patients were female. The female gender percentage was between 64.5% and 82.65%. Table I summarises these characteristics.

Efficacy and safety of abatacept

Combined analysis of abatacept and other interventions (efficacy and safety of abatacept/abatacept + csDMARDs *vs*. placebo, csDMARDs or other b-DMARDs).

The efficacy of abatacept was analysed in terms of ACR20/50/70/90 responses, DAS28-CRP, and adverse events (Fig. 3-8).

8/13 studies (30-33, 35, 37, 39, 40) with a total of 3382 patients have reported a comparison of ACR 20 response between abatacept and csDMARDs *vs*. placebo and csDMARDs or other bDMARDs (Fig. 3). The RR was 1.57 [95%CI 1.27, 1.93] in favour of abatacept.

As for the ACR 50 response, 9 studies (30-33, 35, 37, 39-41) with a total of 3891 patients have reported an RR of 1.84 [95%CI 1.38, 2.44] in favour of abatacept (Fig. 4). The RR was 2.50 [95%CI 0.52, 11.96] in favour of abatacept during a period of 3 months (35). Similarly, at 6, and 12 months, the RRs were 2.40 [95%CI 1.75, 3.28], and 1.44 [95%CI 1.04, 1.99], respectively in favour of abatacept.

Likewise, the ACR 70 response was evaluated by 9 studies (30-33, 35, 37, 39-41) and the RR was 2.36 [95%CI 1.60, 3.47] in favour of abatacept (Fig. 5).

The ACR 90 response was reported by 2 studies (30, 41) with a total of 744 patients during a period of 12 months. The RR was found to be 2.95 [95%CI 1.88, 4.63] in favour of abatacept (Fig. 6).

Table I. Description of the enrolled studies.

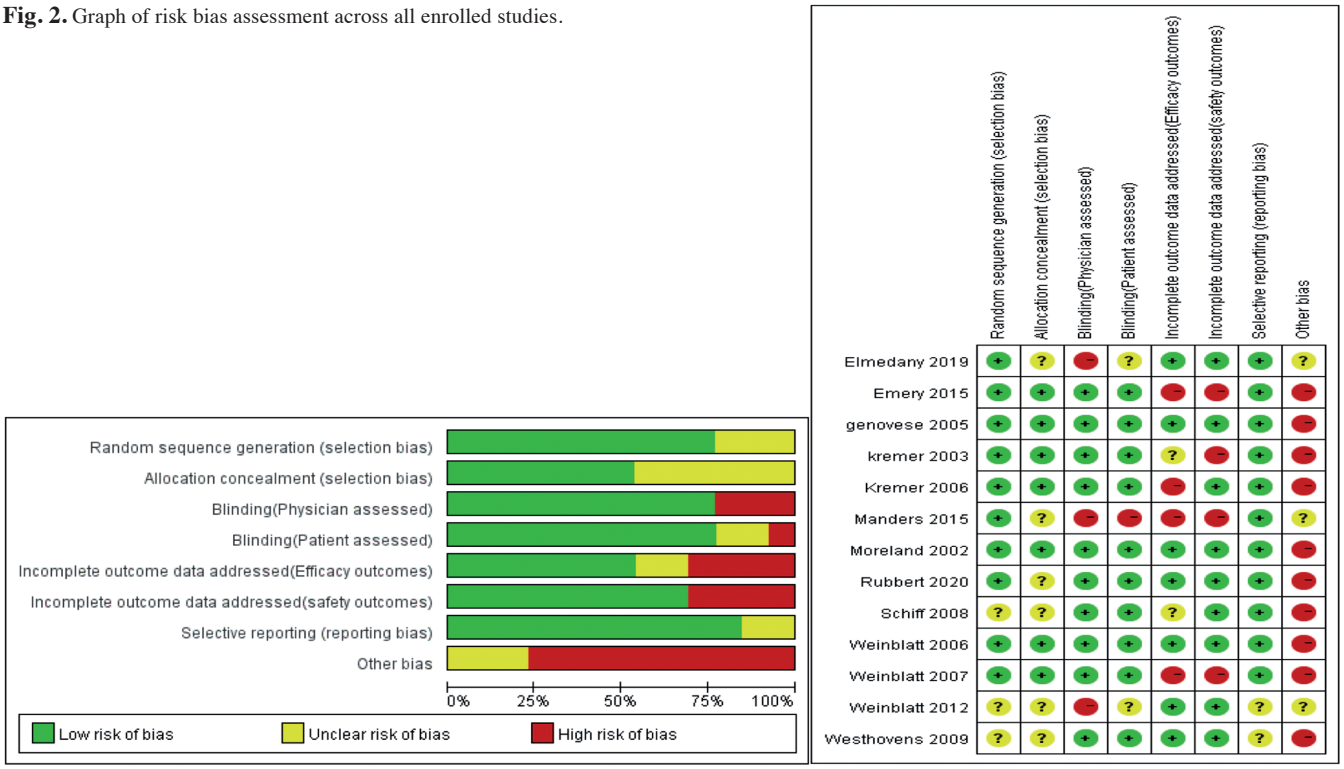
Study author (year)	Participants (sample size, age, gender, anti-seropositivity, ethnicity/geographic region, Previous bDMARD eligibility criteria)			Intervention treatment	control	Other drugs	Course of treatment	Outcome
	Abatacept group	Control group	Eligibility criteria					
1.Elmedany 2019	Abatacept n=64, Age (mean, SD) = 47.91y±15.12, % female=100%, disease duration in years (mean, SD) = 8.00(6.16), Saudi Arabian; ACCP: 71.87%, RF:75%; previous bDMARDs 1.3±0.36	Tocilizumab n=68, Age (mean, SD)= 51.12y±16.11 disease duration in years (mean, SD) =6.9(6.33), % female=100%, Saudi Arabian ACCP 73.52%, RF: 76.47%; previous bDMARDs 1.4±0.35	Adult females diagnosed with active RA according to the current criteria set by ACR/EULAR and who failed to respond to anti-TNF drugs, in multiple tertiary care institutes, Holly Makkah, Saudi Arabia	IV ABA infusion (500 mg for patients <60 kg body weight, 750 mg for 60–100 kg, and 1000 mg for > 00 kg) on days 1, 15, and 29 and then every 4 weeks	IV TCZ infusion (8 mg/kg every 4 weeks)	Oral MTX (15 mg once weekly)	6 months	Adverse events
2. Emery 2015	Abatacept monotherapy n=116, age in years (mean, SD) 45.4±11.9(45), % female=76.7, disease duration in year (mean, SD) 0.59±0.52 North America 18.1%, South America 20.7%, Europe 36.2%, ROW 25%; White race: 81.9% Anti-CCP2: 95%; RF: 95.7%; biologic naive	Abatacept+ MTX = 119, age in years (mean, SD) 46.4±13.2(45), % female =79.8, disease duration in year (mean, SD) 0.58±0.5 MTX n=116, age in years (mean, SD) 49.1±12.4(49), %female=76.7, disease duration in year (mean, SD) 0.50±0.49, North. America 14.3%, South America 21.8%, Europe 39.5%, ROW 24.4%; white race:84% Anti-CCP2: 95%; RF:95%: biologic naïve	Adults (≥18 years old) with active clinical synovitis of ≥2 joints for ≥8 weeks, persistent symptoms for ≤2 years, Disease Activity Score (DAS)28 (C-reactive protein (CRP)) ≥3.2 and anticitrullinated peptide (CCP)-2 antibody positivity	SC abatacept (125 mg/week).	Abatacept+ MTX, initiated at 7.5 mg/week and titrated to 15–20 mg/week within 6–8 weeks (≤10 mg/week per mitted in patients with intolerance	All patients received concomitant folic acid therapy.	12 months	ACR 20 ACR 50 ACR 70 ACR 90 DAS-defined remission -safety and tolerability.
3. Genovese 2005	Abatacept, n=258 age year (mean, SD)53.4/12.4, % female 77.1, disease duration in years (mean, SD) 12.2/8.5; White 96.1%; black 3.5%; another 0.4%/ North America 73.3%; Europe 26.7%; RF: 73.3% Previous bDMARDs 62%	Placebo, n=133, age year (mean, SD)55.7/11.3, % female 79.7, disease duration in years (mean SD), 11.4/8.9; White 93.2%; black 3.8 %; other: 3.0%/ North America 74.4 %; Europe 25.6%; RF:72.9% Previous b DMARDs58.6%;	patients met the American College of Rheumatology (ACR) criteria for rheumatoid arthritis, were at least 18 years of age, had had rheumatoid arthritis for at least one year, and had an inadequate response to anti–TNF-α therapy with etanercept, infliximab, or both at the approved dose after at least three months of treatment.	Abatacept (10 mg/kg) +DMARDs.in a 30-minute intravenous infusion on days 1, 15, and 29 and every 28 days there after, up to and including day 141.	Placebo+ DMARDS	DMARDS	6 months	-ACR 20 -ACR 50 - ACR 70 at 6 months -DAS28 -Adverse events
4. Kremer, J 2003	Abatacept n= 220 (115 for 10 mg and 105 for 2mg), age per year (mean SD) 54.4 range 23-80, 55.8 range 17-83, % female 63 range 23-80,75 range 17-83, duration of disease in year (mean, SD) =9.7/8.1 range 23-80, 9.7/9.8 range 17-83.; White race 87%; RF: 90%; previous bDMARDs 5.7%	Placebo n=119 Age per year (mean SD) 54.7 % female 66, duration of disease in year (mean, SD) =8.9/8.3; White race 87%; RF:90%; previous bDMARDS 2.6%	patients with active rheumatoid arthritis despite methotrexate therapy. ACR criteria for rheumatoid arthritis and were in functional class I, II, or III Nursing and pregnant women were excluded	Abatacept 2 mg/kg,10mg/kg a 30-minute period on days 1, 15, and 30 and monthly thereafter for a total of six months.	placebo	MTX	6 months	-ACR 20 -ACR 50 -ACR 70 -Adverse events
5.Kremer 2006	Abatacept n=433 age in years (mean, SD) 51.5(12.9), %female 77.8, disease duration 8.5(7.3); White race 87.5%; North America 21.5%, South America 40%, Europe 33%, Other: 5.5%; RF:81.8%; previous bDMARDs 0.2%	Placebo n=219 age in years (mean, SD) 50.4(12.4), %female 81.7, disease duration 8.9(7.1); White race 88.1%; North America 21%, South America 42.5%, Europe 30.6%, Other: 5.9%; RF: 78.5%; previous bDMARDS 0 %	At least 18 years of age, with rheumatoid arthritis for at least 1 year, and met the ARA criteria for RA. Rheumatoid arthritis was persistent and active despite methotrexate treatment. We excluded patients with a positive tuberculin skin test result unless they had completed treatment for latent tuberculosis before enrolment.	Abatacept (10 mg/kg) by 30-minute IV infusion on days 1, 15, and 29 and then every 28 days up to and including day 337.	Placebo	All patients were to receive MTX 15 mg or more per week, 10 mg per week was acceptable if the patient had a history of toxicity	1 year	-ACR 20 at 6 months. - ACR 50 and ACR 70 responses at 6 months and all ACR responses at 1 year. -DAS28 -Adverse events
6. Menders, 2015	Abatacept, n=43, age in years (mean, SD) =56.15(9.95), %female=88.4, mean disease duration= 6.56(2.56to11.96), RF:56.4%; previous bDMARDs 100%	Rituximab n=46, age in years (mean, SD) =57.09 (11.08), % female=63.0, mean disease duration= 7.7 (3.22 to 16.25), TNFi n=50, age in years (mean, SD) =55.81(12.53), % female=74.0, mean disease duration=5.64(1.79 to 12), RF:80%; previous bDMARDS 100%	Patients with previous treatment failure with their first TNFi, moderate to high disease activity and no previous treatment with abatacept or rituximab. Patients were excluded if they had a contraindication for treatment (for example, pregnancy, the presence of a serious infection) based on the rheumatologist' s judgment of if they had a strong preference or dislike for one of the treatment agents or did not want to be randomised. Patients were included between 2009 and 2012.	The dose of abatacept was based on the patient's body weight as follows: patients who weighed <60 kg received 500 mg, patients weighing 60 to 100 kg received 750 mg and patients who weighed >100 kg received 1,000 mg. The doses were delivered by infusion over 1 hour every 4 weeks.	Rituximab by in fusion (1,000 mg) at weeks 0 and 2. A second course could be administered after 6 months in patients who responded to the first course,	infliximab was administered at 3 mg/kg every 8 weeks after a loading dose given at weeks 0, 2 and 6; etanercept (50 mg per week or 25 mg twice per week); Golimumab (50 mg every 4 weeks); certolizumab (400 mg) in weeks 0, 2 and 4, followed by a 200-mg dose given every 2 weeks.	1 year	-Adverse events
7. Moreland, 2002	Abatacept n=32 (10 mg dosage) age (mean, SD) = 51.5±11.5, % female 69(for 10mg/kg) =, disease duration (mean, SD) =3.4/2.1; White race 94%, Black race 3%, other 3%;	Placebo n=32, Age (mean, SD) = 48.3±11.7, %female=81, disease duration (mean, SD) = 3.2/2.0; White race 94%, black 6%, other 0%;	18–65 years patients with a disease duration of <7years. who have been treated unsuccessfully with at least 1 DMARD. TB -positive patients, pregnant, and nursing women were excluded.	CTLA-4Ig at 0.5 mg/kg, 2 mg/kg, or 10 mg/kg; Patients received 4 infusions of study medication, on days 1, 15, 29, and 57.	LEA29Y at 0.5 mg/kg, 2 mg/kg, or 10 mg/kg; or placebo		3 months	-ACR 20 -ACR 50 -ACR 70 -Adverse events

Study author (year)	Participants (sample size, age, gender, anti-seropositivity, ethnicity/geographic region, Previous bDMARD eligibility criteria)			Intervention treatment	control	Other drugs	Course of treatment	Outcome
	Abatacept group	Control group	Eligibility criteria					
8. Rubbert-Roth 2020	Abatacept n=309, age in years (mean, SD) =55.8±11.9, % female (253(81.9), disease duration 11.8±8.3; White race 92.2%, black 4.5%, American Indian or Alaska native 0.6%; Asian 1.9%, Multiple: 0.6%; North America 23.6%, South America and Central America 32%, Western Europe 14.6%, Eastern Europe 24.9%, Asia 1.3%, Other 3.6%, RF and ACCP: 65%; previous bDMARDS: 0.6% (0), 65.4% (1), 22.7% (2), 11.3% (3)	Upadacitinib n=303, age in years (mean, SD) = 55.3±11.4, %female249 (82.2), disease duration 12.4±9.5; White race 95%; Black race 2.3%, American Indian or Alaska native 0.3%; Asian 1.7%, Multiple: 0.7%; North America 23.8%, South America and Central America 32.3%,Western Europe 14.2%, Eastern Europe 25.4%, Asia 1.3%, Other 3%, RF and ACCP: 62.4%; previous bDMARDS1.3% (0), 68.0% (1), 21.1% (2),9.6% (3)	18 years of age or older patients with a diagnosis of rheumatoid arthritis for at least 3 months who also met the 2010 American College of Rheumatology (ACR)–European League against Rheumatism classification criteria for rheumatoid arthritis. Exclusion: previous exposure to a JAK inhibitor or abatacept or had a history of inflammatory joint disease other than rheumatoid arthritis	Intravenous abatacept (at day 1 and weeks 2, 4, 8, 12, 16, and 20 [500 mg in patients with a body weight of <60 kg, 750 mg in those with a weight of 60 to 100 kg, and 1000 mg in those with a weight of >100 kg]). + oral placebo.	extended-release oral upadacitinib (15 mg once daily) + placebo intravenous infusions	DMARDS	24 weeks/6 months	-DAS28-CRP at week 12, -DAS28-CRP -Adverse events
9. Schiff, M. 2008	Abatacept n=156, age in years (mean, SD) =49(12.5), % female =83.3, disease duration in years (mean, SD) =7.9(8.5); Caucasian 80.8%, North America 10.3, South America 59.6%, Europe 25%, ROW 5.1%; RF: 87.2%;	Infliximab n=165, age in years (mean, SD) =49.1 (12.0), %female=82.4, disease duration in years (mean, SD) = 7.3(6.2) placebo n=110, age in years (mean, SD) =49.1(11.5), %female=87.3, disease duration in year (mean, SD) = (8.4(8.6); Caucasian80.6%: North America 9.1%, South America 58.2%, Europe 23.6%, ROW 9.1%; RF: 84.8%;	Eligible patients met the (ACR) criteria for RA, were at least 18 years of age, had RA for at least 1 year, and had an inadequate response to MTX. All patients were screened for tuberculosis.	Abatacept (approximating 10 mg/kg) by intravenous (IV) infusion, on a background of MTX.	Placebo+ MTX	Infliximab (3 mg/kg),	6 months	-ACR20,50,70 -Adverse events
10.Weinblatt 2006	Abatacept n=959, **Non-biologic backgroun**d: age in years (mean, SD) = 52.2±11.8% female= 83.1 disease duration in years (mean, SD)= 9.5±8.7: White race: 83.9% **Biologic background:** Age in years (mean, SD) =54.6±11.2 % female =75.7%, disease duration in years (mean, SD)= 11.3±8.9; White race 97.1% ;	Placebo n=482; **Non-biologic background**: age in years (mean, SD) = 52+/-12.1; %female= 83.7, disease duration in years (mean, SD)= 9.5±9.1; White race: 83.7%: **Biologic background**: Age in years (mean, SD) = 52.8±11.4; % female =75, disease duration in years (mean, SD)= 11.3±9.6; White race 92.2% ;	Men and women at least 18 years of age who met the 1987 American College of Rheumatology and the 1991 ACR criteria for RA functional classes I, II, III, or IV. Exclusion: unstable or uncontrolled renal, endocrine, hepatic, haematologic, gastrointestinal, pulmonary, cardiac, or neurologic diseases, or any autoimmune disorder other than RA as the main diagnosis. Active or chronic recurrent bacterial infections unless treated and resolved, active herpes zoster infection within the previous 2 months, hepatitis B or hepatitis C virus infection, and active or latent tuberculosis. Pregnant or nursing women	abatacept 10 mg/kg was administered via a 30-minute intravenous infusion on days 1, 15, and 29, and every 4 weeks thereafter, for a total of 14 doses.	placebo		1 year	-Adverse events
11. Weinblatt 2 007	Abatacept n=85, age in years (mean, SD) =49.8(23-73), % female =78, disease duration in years (mean, SD) =13(10.1). Caucasian 94%; previous bDMARDS 100%	Placebo n=36, age in years (mean, SD) =54.3(28-71), % female =72, disease duration in years (mean, SD) =12.8(8.6); Caucasian 100%; previous bDMARDS 100%	patients>18 years of age and met the criteria of the American College of Rheumatology (ACR) for rheumatoid arthritis, Important exclusion criteria included active or latent infection, recent opportunist infection, tuberculosis requiring treatment within the previous 3 years, history of cancer within the previous 5 years or history of drug or alcohol misuse. Pregnant and nursing women were excluded.	Abatacept 2 mg/kg and etanercept, was administered intravenously on days 1, 15 and 30, and every 4 weeks thereafter.	placebo and etanercept. Etanercept (25 mg, twice weekly) was continued in all patients for the duration of the study.		6M	-ACR 20 -ACR 50. ACR 70 -Adverse events
12. Weinblatt 2012	Abatacept+ MTX n=318, age in years (mean, SD) = 51.4±12.6, % female 81.4, disease duration in years (mean SD)= 1.9±1.4; White race 80.8%; North America: 72.3%, South America:27.7% RF: 75.5%; previous bDMARDs: biologic naive	Adalimumab n=328, age in years (mean, SD) = 51.0±12.8, %female82.3, disease duration in years (mean SD) = 1.7±1.4; White race 78%; North America: 71.6%, South America: 28.4%; RF: 77.4%; previous bDMARDS: biologic naive	Met the American College of Rheumatology (ACR) 1987 classification criteria for RA (16), were at least 18 years of age, had a confirmed diagnosis of RA for 5 years, had an inadequate response to MTX, and had not received previous bDMARD therapy	125 mg abatacept, administered SC once per week (without an intravenous loading dose),	40 mg adalimumab, administered SC every other week, both given in combination with MTX.		1 year	-ACR20 - ACR50 - ACR70 -DAS28-CRP -Adverse events
13.Westhovens 009	Abatacept n=256 Age in years, mean (SD) 50.1(12.4), % female =76.6, disease duration mean months (SD) 6.2(7.5); White race 78.9%; North America 18%, South America 40.2, Europe, 34.4%, ROW 7.4% RF:96.1% RF and ACCP 88.7%;	Placebo n=253 Age in years, mean (SD) 49.7 (13.0), % female =78.7, disease duration mean months (SD) 6.7(7.1); White race 86.6%; North America 15.8%, South America 40.3%, Europe 37.5%, ROW 6.3%; RF: 96.8, RF and ACCP: 83.4%;	18 years of age or older, with RA for 2 years or less, at least 12 tender and 10 swollen joints, C-reactive protein (CRP) 0.45 mg/ dl or greater, RF and/or anti-CCP2 seropositivity and radiographic evidence of bone erosion of the hands/wrists/feet.	Abatacept (10 mg/kg according to weight range) +MTX by intravenous infusion on days 1, 15 and 29, and every 4 weeks thereafter.	Placebo+ methotrexate	MTX	1 year	-DAS28-CRP -ACR 50 -ACR70 -ACR90 -adverse event

Table II. Quality evaluation of included studies using PRISMA.

Section and topic	Item no.	Checklist item	Yes (%)	No (%)
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	12 (90)	1 (10)
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	12 (90)	1 (10)
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4 (30)	9(70)
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	13 (100)	0 (0)
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	7 (60)	6 (40)
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	13 (100)	0 (0)
Support:				
Sources	5a	Indicate sources of financial or other support for the review	12 (90)	1 (10)
Sponsor	5b	Provide name for the review funder and/or sponsor	12 (90)	1 (10)
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	12 (90)	1 (10)
Introduction				
Rationale	6	Describe the rationale for the review in the context of what is already known	13 (100)	0 (0)
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	13 (100)	0 (0)
Methods				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	13 (100)	0 (0)
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	13 (100)	0 (0)
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	13 (100)	0 (0)
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	13 (100)	0 (0)
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	13 (100)	0 (0)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	13 (100)	0 (0)
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10 (70)	3 (30)
Outcomes and prioritisation	13	List and define all outcomes for which data will be sought, including prioritisation of main and additional outcomes, with rationale	13 (100)	0 (0)
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	13 (100)	0 (0)
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	0 (0)	13 (100)
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	0 (0)	13 (100)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	0 (0)	13 (100)

Fig. 2. Graph of risk bias assessment across all enrolled studies.



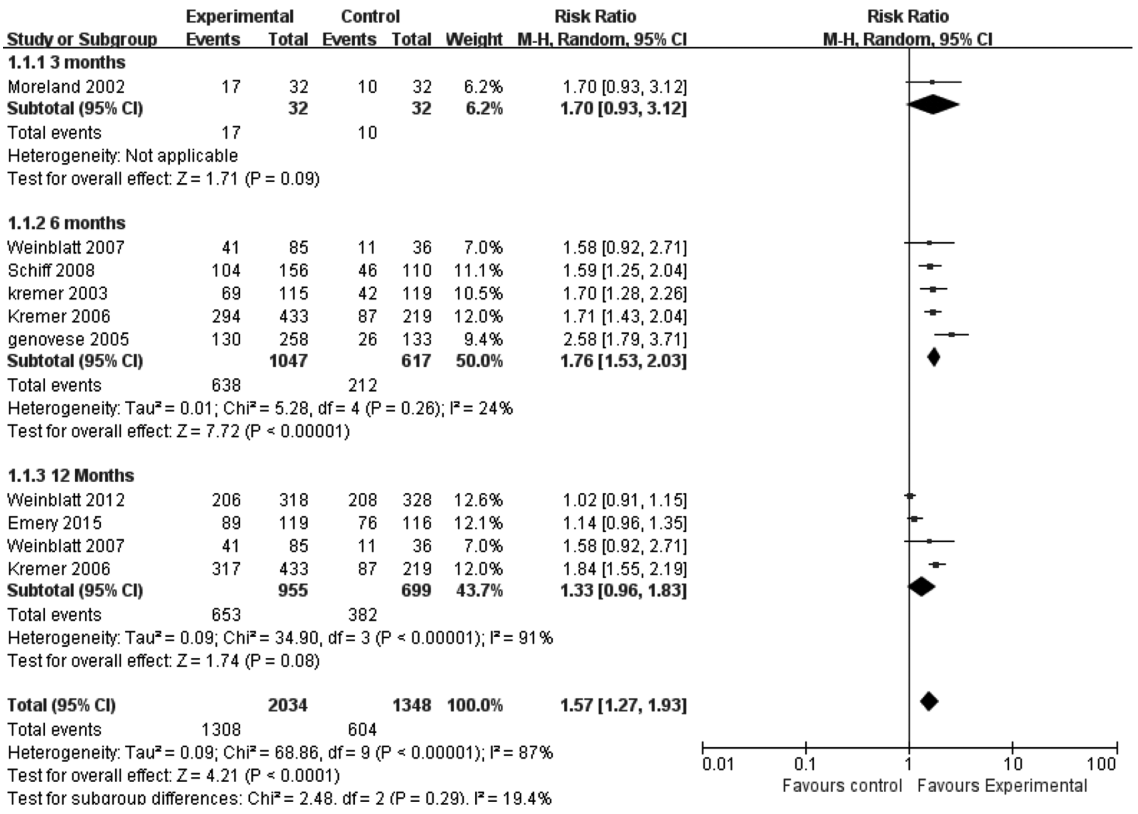


Fig. 3. Forest plot of comparison: Abatacept (2 mg/kg and 10 mg/kg) +csDMARDs or other biologics *vs*. placebo+/csDMARDs or other biologics; Outcome 1: ACR20 improvement.

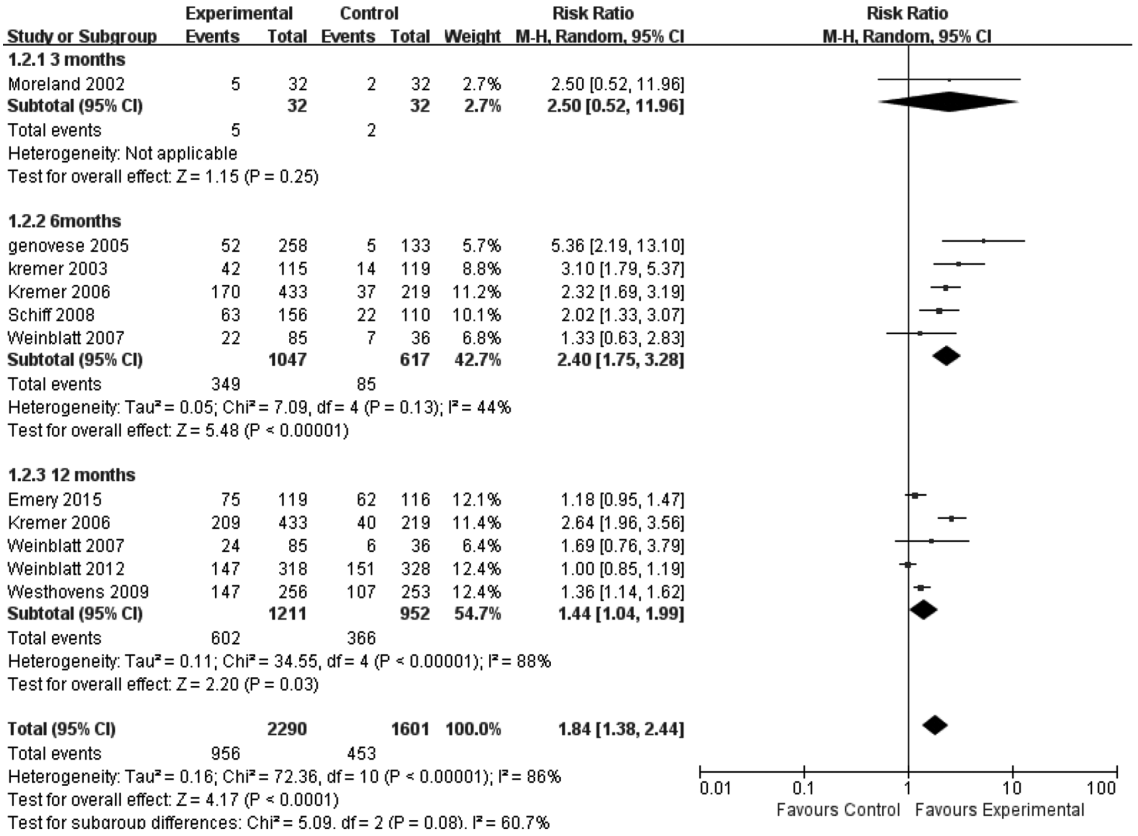


Fig. 4. Forest plot of comparison: Abatacept (2 mg/kg and 10 mg/kg) +DMARDs or other biologics *vs*. placebo+/DMARDs or other biologics; Outcome 2: ACR 50 improvement.

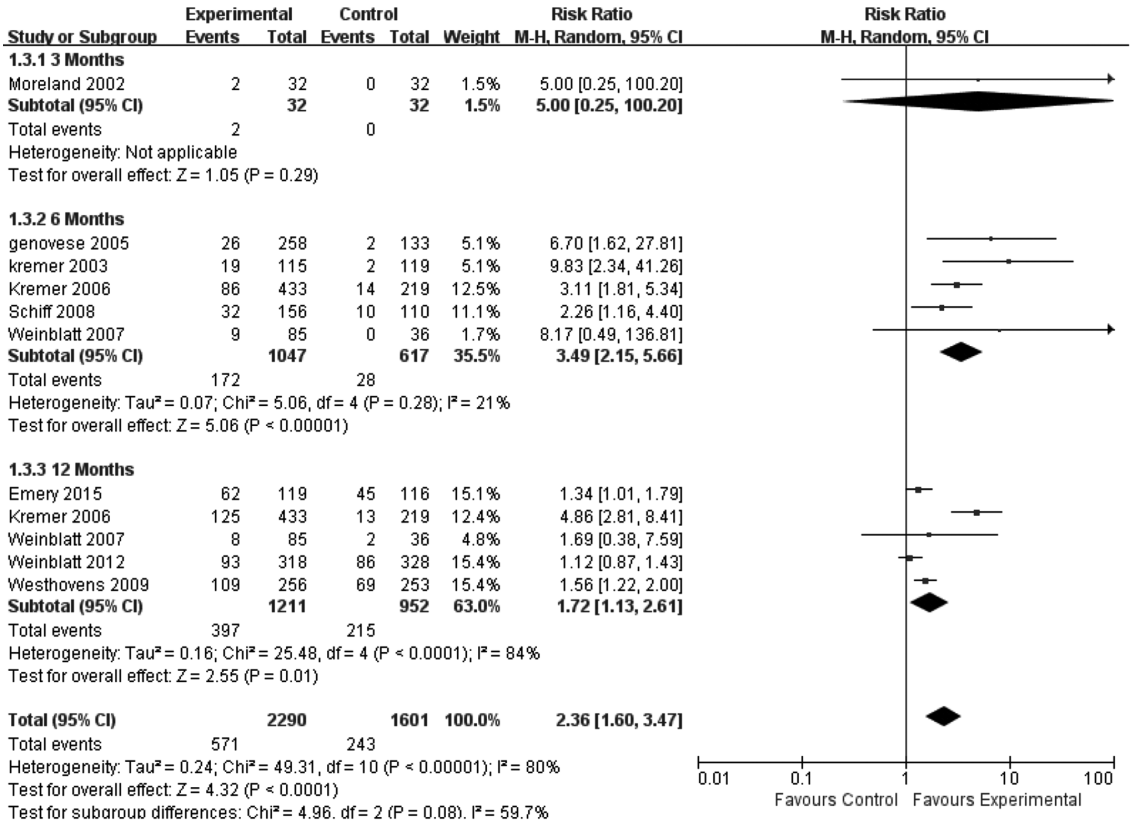


Fig. 5. Forest plot of comparison: Abatacept (2 mg/kg and 10 mg/kg) +DMARDs or other biologics *vs*. placebo+/DMARDs or other biologics; Outcome 3: ACR 70 improvement.

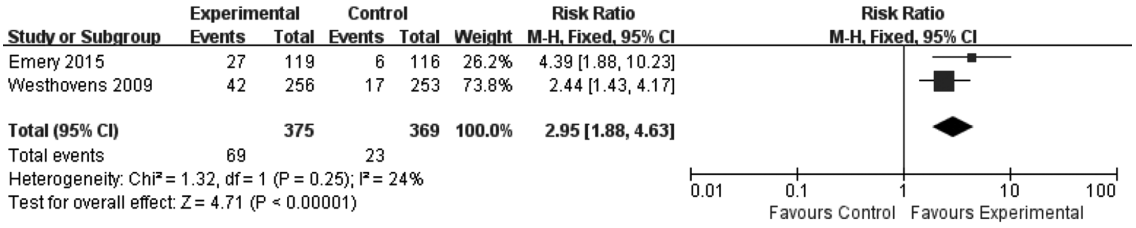


Fig. 6. Forest plot of comparison: Abatacept (2 mg/kg and 10 mg/kg) +DMARDs or other biologics *vs*. placebo+/DMARDs or other biologics; Outcome 4: ACR 90 improvement.

The DAS28-CRP outcome was assessed by 6 studies (30, 31, 33, 36, 40, 41) with a total of 3697 patients, and the RR was 1.92 [95%CI 1.12, 3.29] in favour of abatacept (Fig. 7).

As for the safety of abatacept, it was assessed by all the 13 enrolled studies in terms of adverse events. The RR was 0.93 [95%CI 0.84, 1.03], suggesting that patients in the abatacept group were less likely to have adverse events than those in the control group (Fig. 8).

Analysis of efficacy and safety of abatacept based on the type of intervention in the control group

In order to offer more pertinent data for clinical practice, we further performed an analysis based on the type of intervention in the control group.

Efficacy and safety of abatacept vs. placebo

5/13 articles (31-33, 38, 41) have assessed the efficacy and safety of abatacept *vs*. placebo (Fig. 9-14). Of these investigations, 3 studies with a total of 1277 participants have reported the ACR 20 response during a period of 6 months (Fig. 9). The RR was 1.88 [95%CI 1.50, 2.36] in favour of abatacept.

The ACR 50 and ACR 70 responses were evaluated by 4 studies with 2438 participants and the RRs were 2.45 [95%CI 1.58, 3.80], and 3.71 [95%CI 1.80, 7.64], respectively (Fig. 10-11). At 6 months, the RRs were 2.91 [95%CI 1.95, 4.36] for the ACR 50 improvement, and 4.53 [95%CI 2.22, 9.24] for the ACR 70 response in favour of abatacept. At 12 months the RRs were 1.88 [95%CI 0.94, 3.72] and 2.69 [95%CI 0.82, 8.83], respectively.

As for the ACR 90 response, it was reported by only one study during a period of 12 months. The RR was 2.44 [95%CI 1.43, 4.17] in favour of abatacept (Fig. 12).

The DAS28-CRP outcome was reported by 3 studies with 2204 participants and the RR was 5.70 [95%CI 1.57, 20.67]

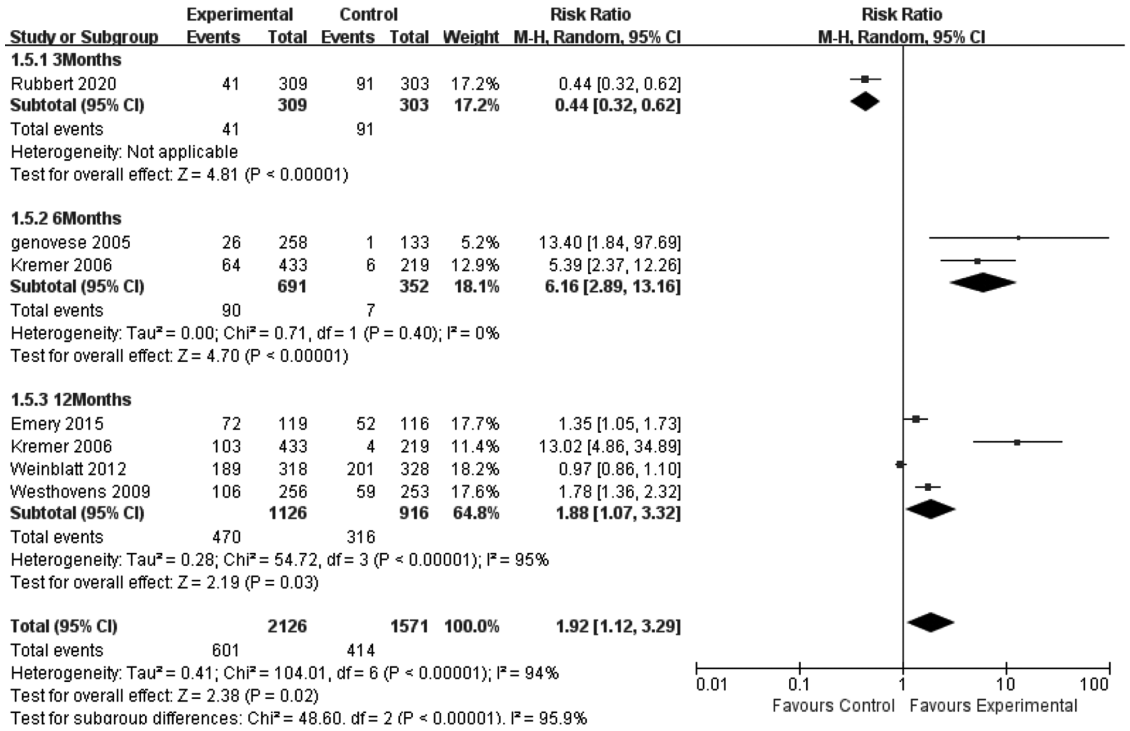


Fig. 7. Forest plot of comparison: Abatacept (2 mg/kg and 10 mg/kg) +DMARDs or other biologics *vs*. placebo+/DMARDs or other biologics; Outcome 5: DAS28-CRP.

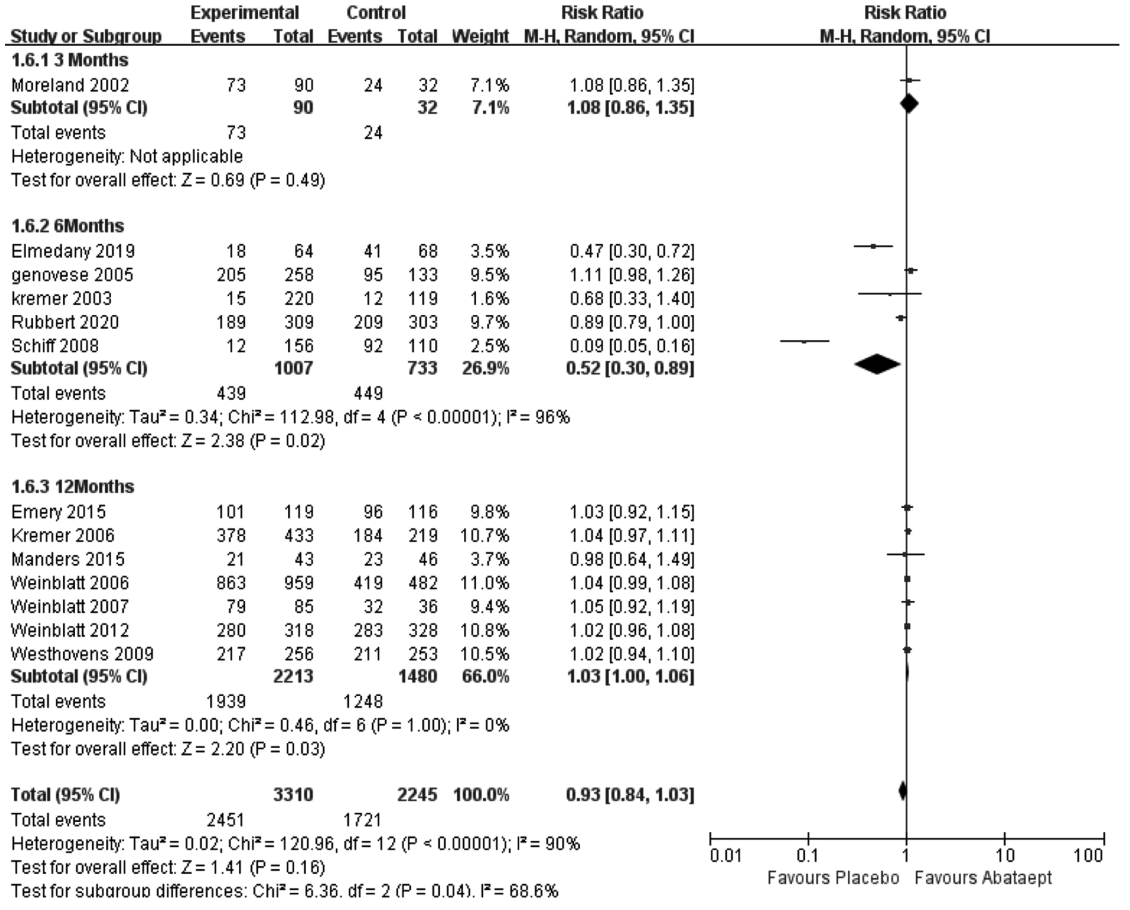


Fig. 8. Forest plot of comparison: Abatacept (2 mg/kg and 10 mg/kg) +DMARDs or other biologics *vs*. placebo+/DMARDs or other biologics; Outcome 6: adverse events.

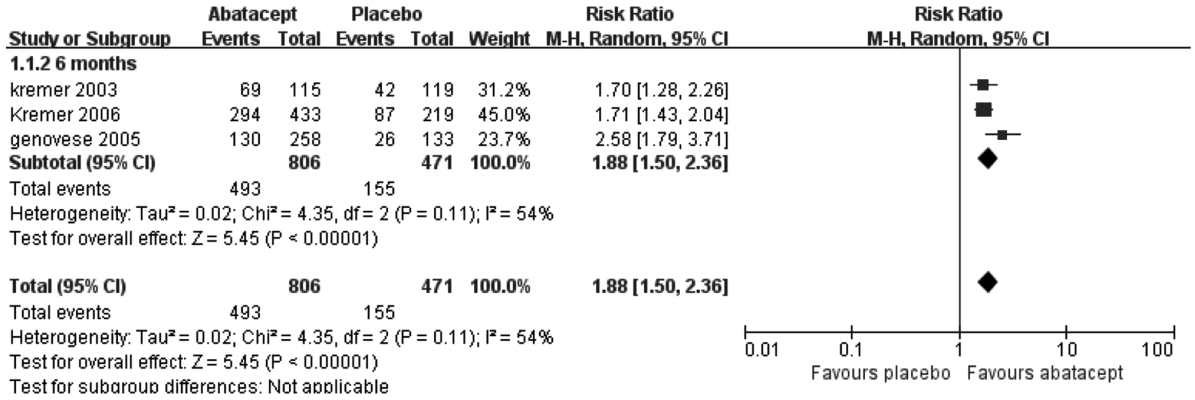


Fig. 9. Forest plot of comparison: Efficacy of Abatacept *vs*. placebo; Outcome 1: ACR20 improvement.

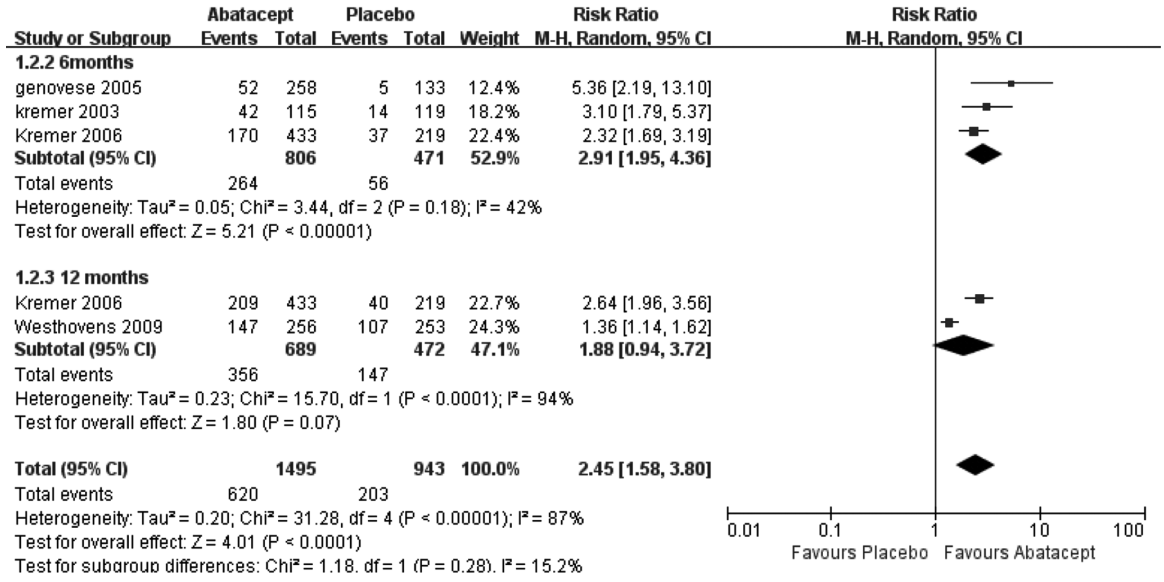


Fig. 10. Forest plot of comparison: Efficacy of Abatacept *vs*. placebo; Outcome 2: ACR 50 improvement.

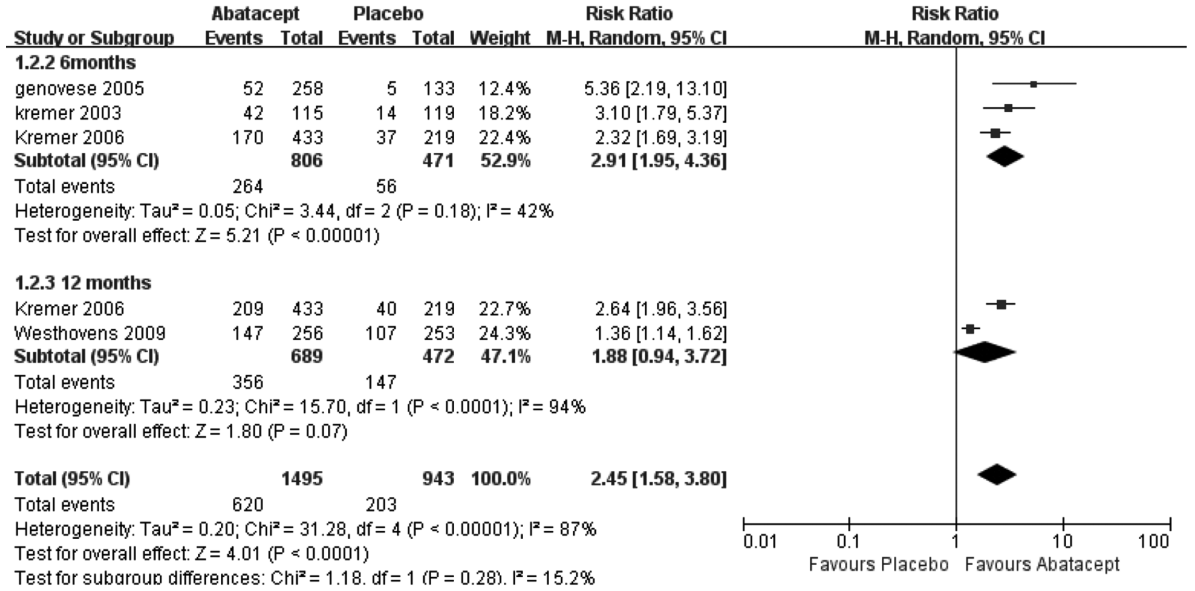


Fig. 11. Forest plot of comparison: Efficacy of Abatacept *vs*. placebo: Outcome 3: ACR 70 improvement.

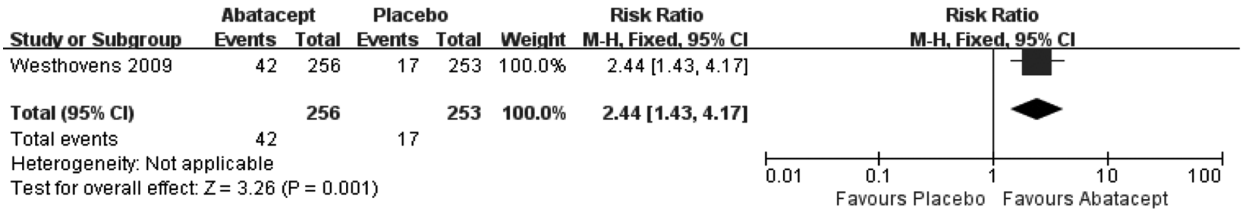


Fig. 12. Forest plot of comparison: Efficacy of Abatacept *vs*. placebo; Outcome 4: ACR 90 improvement.

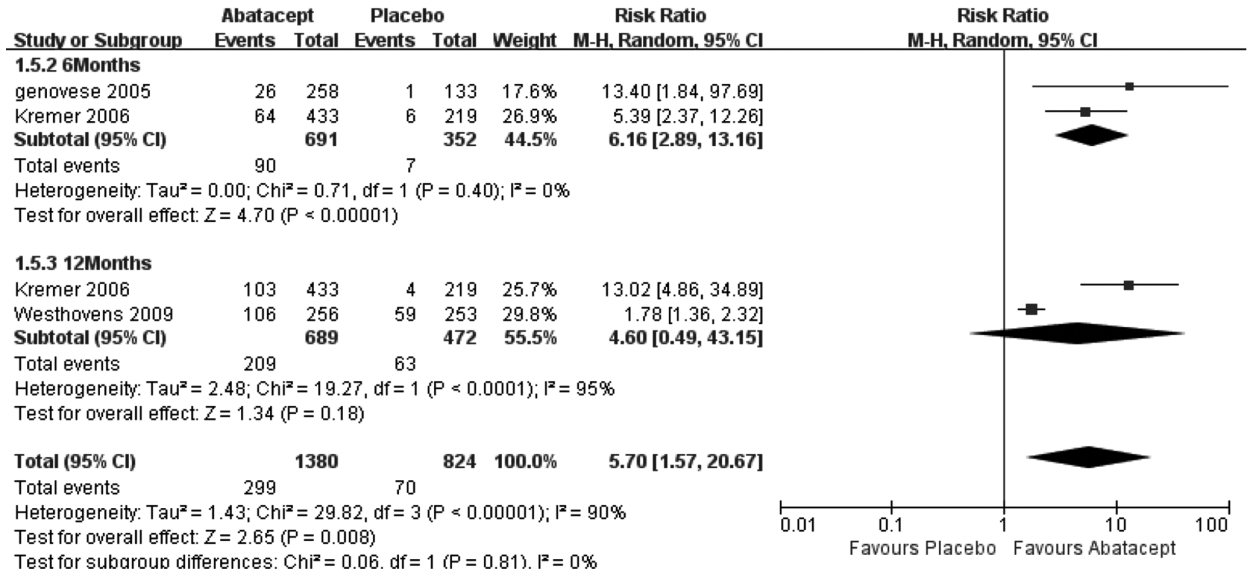


Fig. 13. Forest plot of comparison: Efficacy of Abatacept *vs*. placebo; Outcome 5: DAS28-CRP improvement

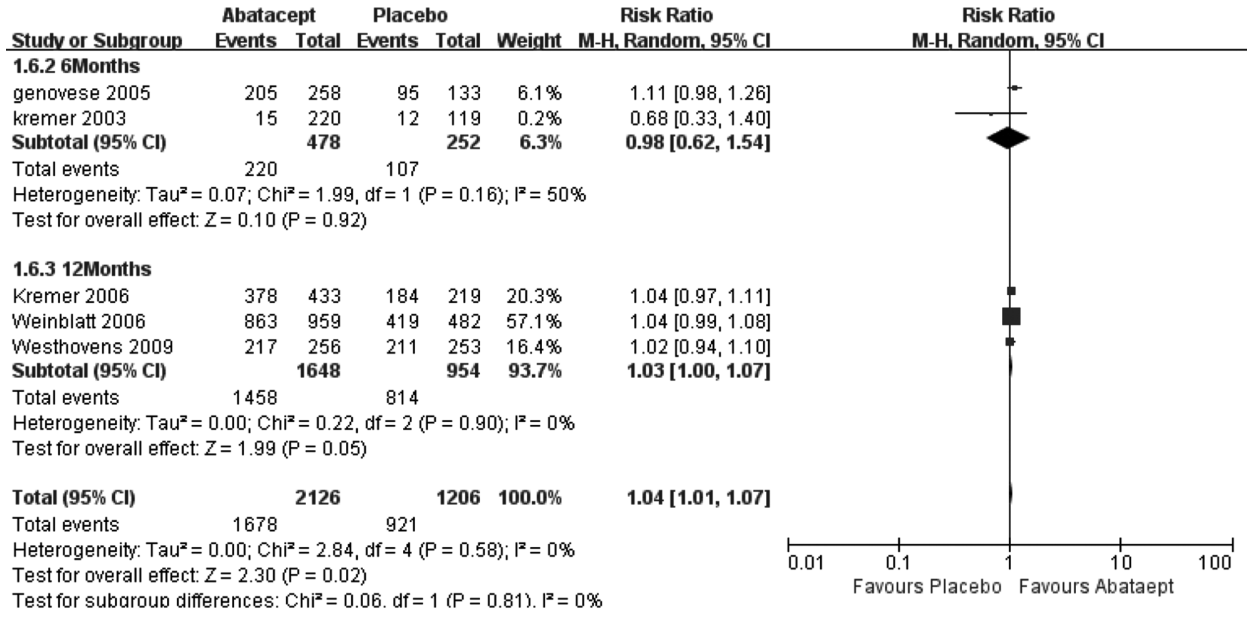


Fig. 14. Forest plot of comparison: Safety of Abatacept *vs*. placebo; Outcome 6: Adverse events.

(Fig. 13). At 6 and 12 months, the RRs were 6.16 [95%CI 2.89, 13.16] and 4.60 [95%CI 0.49, 43.15], respectively.

All 5 studies compared the adverse events between the abatacept group and placebo group and the RR was 1.04 [95%CI 1.01, 1.07] (Fig. 14). At 6 and 12 months, the RRs were 0.98 [95%CI 0.62, 1.54] and 1.03 [95%CI 1.00, 1.07] respectively.

Efficacy and safety of abatacept vs. other (b/ts) DMARDs

In total, 7 investigations (29, 34-37, 39, 40) have compared the efficacy and safety of abatacept *vs*. other b/ts DMARDs

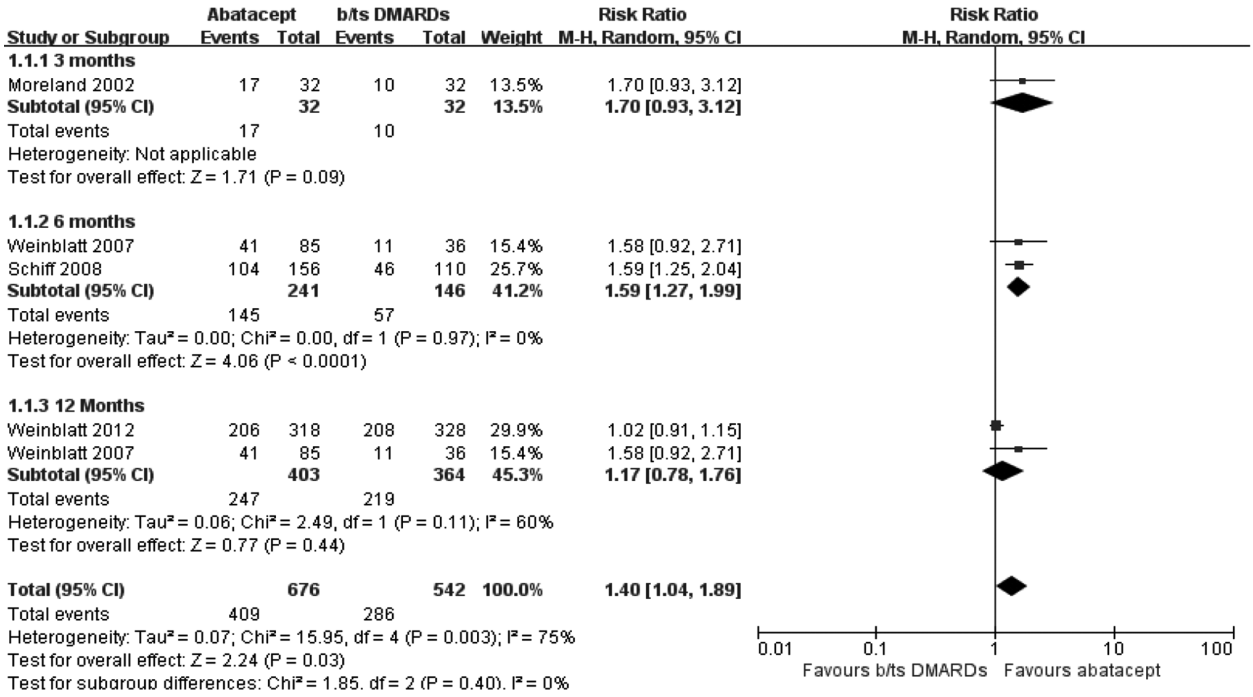


Fig. 15. Forest plot of comparison: Efficacy of Abatacept *vs*. b/ts DMARDS; Outcome 1: ACR 20 improvement.

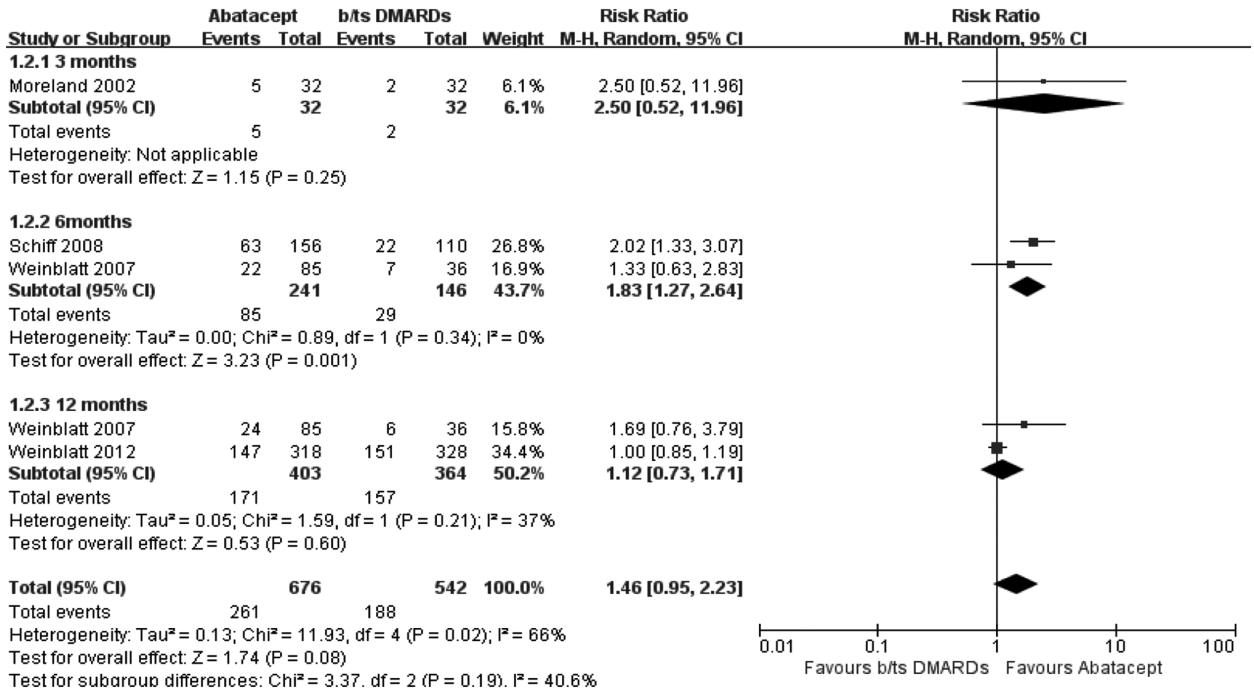


Fig. 16. Forest plot of comparison: Efficacy of Abatacept *vs*. b/ts DMARDS; Outcome 2: ACR 50 improvement.

(Fig. 15-19). Four of these articles have examined the ACR 20 response and the RR was 1.40 [95%CI 1.04, 1.89] (Fig. 15). At 3, 6 and 12 months, the RRs were 1.70 [95%CI 0.93, 3.12], 1.59 [95%CI 1.27, 1.99], and 1.17 [95%CI 0.78, 1.76], respectively.

Similarly, the ACR 50 was assessed by 4 studies and the RR was 1.46 [95%CI 0.95, 2.23] (Fig. 16). At 3, 6, and 12 months, the RRs were 2.50 [95%CI 0.52, 11.96], 1.83 [95%CI 1.27, 2.64], and 1.12 [95%CI 0.73, 1.71], respectively.

The ACR 70 was also evaluated by 4 studies and the RR was 1.64 [95%CI 0.94, 2.86] (Fig. 17). At 3, 6, and 12 months, the RRs were 5.00 [95%CI 0.25, 100.20], 2.42 [95%CI 1.26, 4.62], and 1.13 [95%CI 0.88, 1.44], respectively.

The DAS28-CRP outcome was examined by 2 articles at 3 and 12 months. The RRs were 0.44 [95%CI 0.32, 0.62] and 0.97 [95%CI 0.86, 1.10], respec-

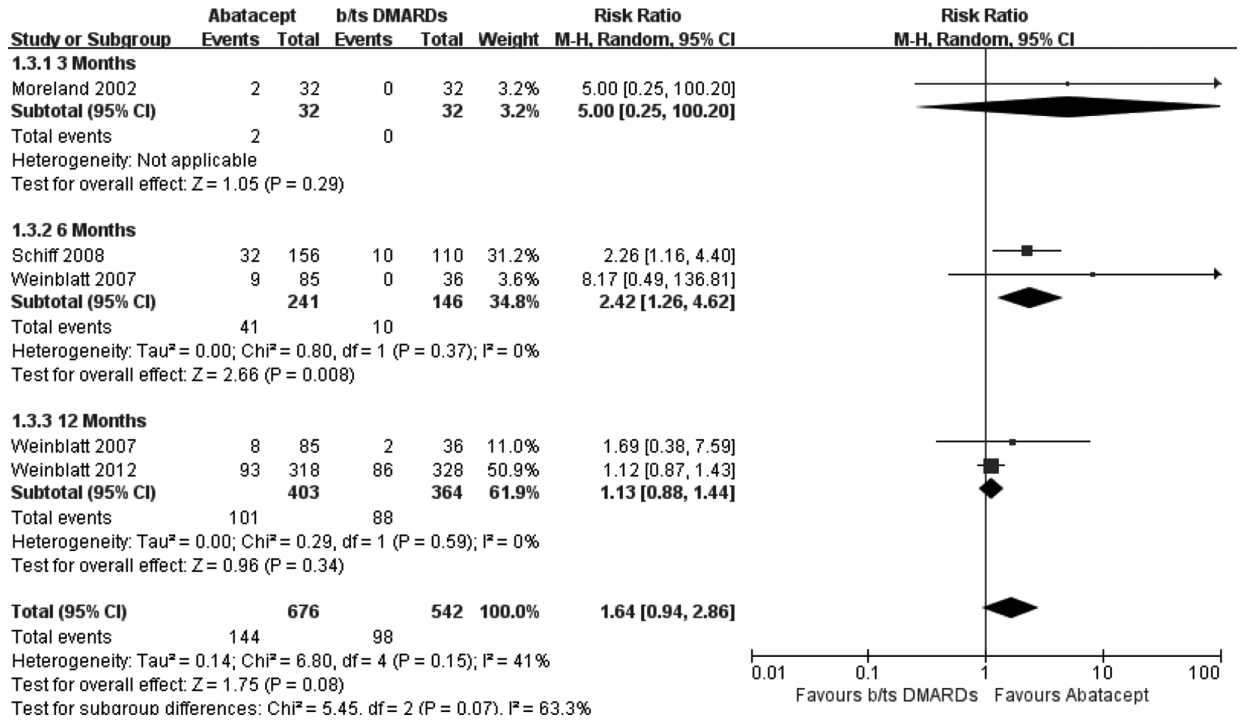


Fig. 17. Forest plot of comparison: Efficacy of Abatacept *vs*. b/ts DMARDS; Outcome 3: ACR 70 improvement.

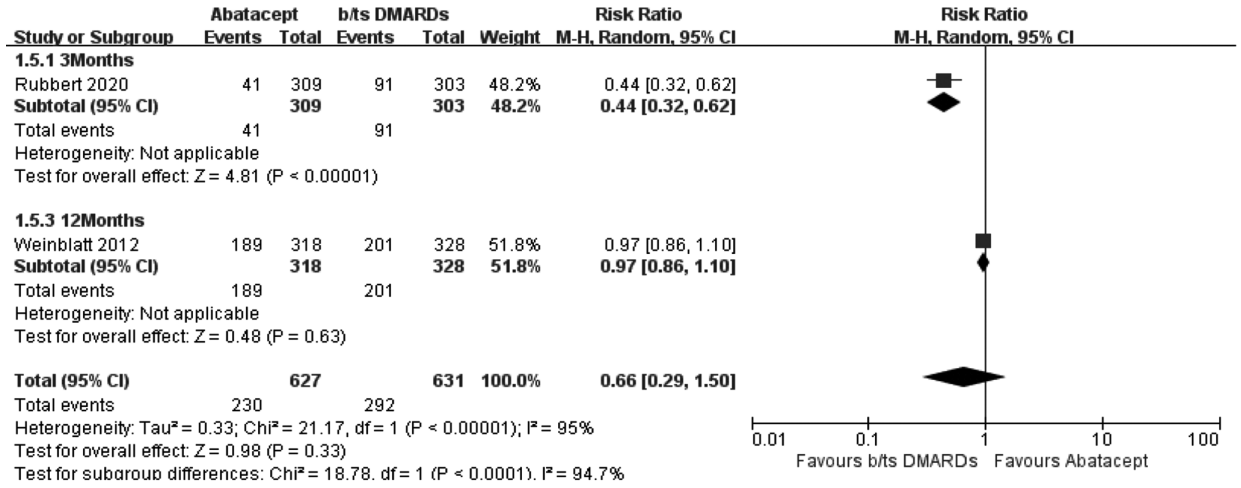


Fig. 18. Forest plot of comparison: Efficacy of Abatacept *vs*. b/ts DMARDS: Outcome 4: DAS28-CRP.

tively (Fig. 18). None of these 7 articles has reported the ACR 90 response. All 7 studies have evaluated the safety of abatacept and other b/ts DMARDs. The RR of relative adverse event was 0.71 [95%CI 0.52, 0.96] (Fig. 19).

Efficacy and safety of abatacept monotherapy vs. abatacept +csDMARDs

The efficacy of abatacept monotherapy *vs*. abatacept + csDMARDs was examined by only one study (30) (Fig. 20-25). The RRs of the ACR 20/50/70/90 responses were 1.14 [95%CI 0.96, 1.35], 1.18 [95%CI 0.95, 1.47], 1.34 [95%CI 1.01, 1.79], and 4.39 [95%CI 1.88, 10.23], respectively in favour of abatacept. Similarly, the RR of the DAS28-CRP outcome was 1.35 [95%CI 1.05, 1.73] in favour of abatacept. The RR of relative adverse events was 1.03 [95%CI 0.92, 1.15] at 12 months.

Subgroup analysis

Our results showed the presence of heterogeneity. To assess the origin of this heterogeneity, we performed a subgroup analysis based on the disease phenotype (seropositive *vs*. seronegative), drug route of administration (intravenous *vs*. subcutaneous), drug dosage (2 mg, 10 mg, or weight dependent), concomitant drugs, and the number of previous bDMARDs

Disease phenotype (seropositive vs. seronegative)

Based on the presence of rheumatoid factor (RF) or and anti-cyclic citrullinated peptide (anti-CCP), we classified our studies into 3 different categories.

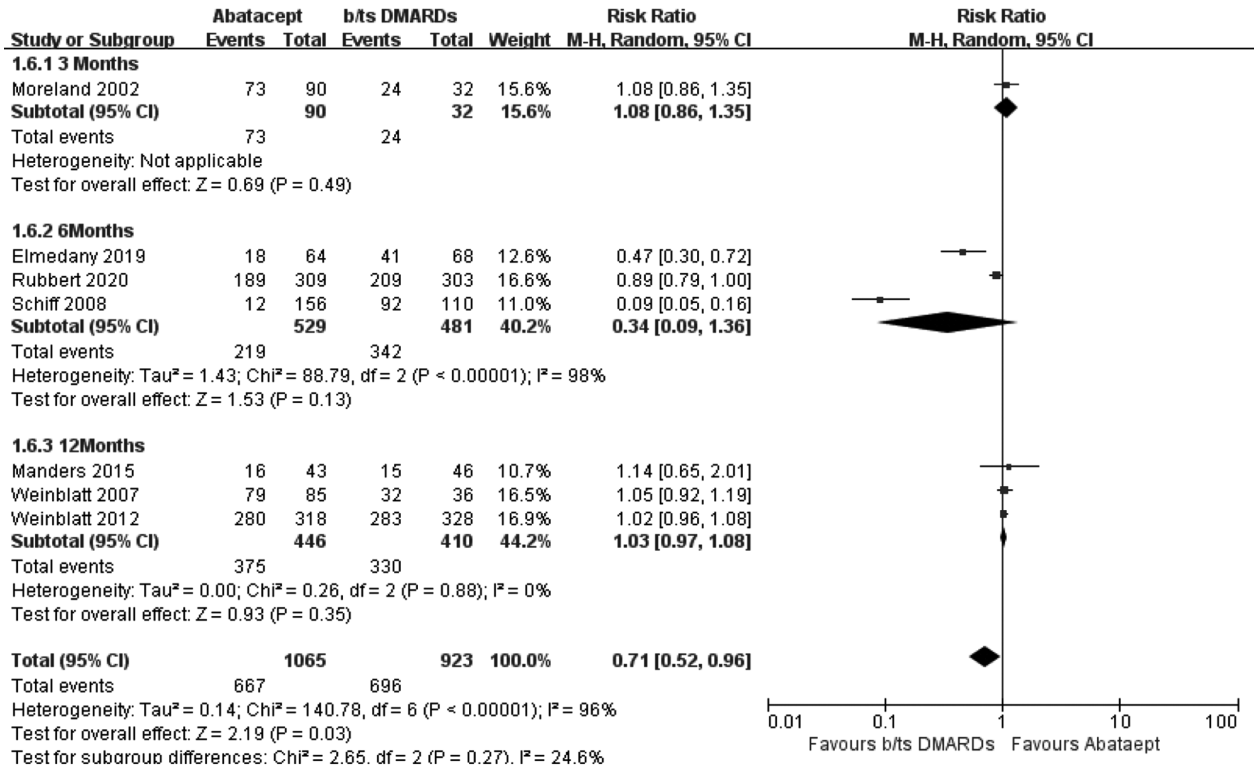


Fig. 19. Forest plot of comparison: Safety of Abatacept *vs*. b/ts DMARDS; Outcome 5: Adverse events.

The first category did not report the status of these proteins in their patients (35, 38, 39). The second group indicated both RF and anti-CCP positivity in majority of their patients (29, 30, 36, 41). And the third group only revealed RF positivity in majority of their patients (31-34, 37, 40). Since no study has exclusively enrolled seropositive/seronegative patients, we could not assess the effect of the disease phenotype on heterogeneity.

Drug administration route

While most of our studies have administered abatacept intravenously, 2 studies (30, 40), have administered the drug subcutaneously. We looked at the effect of the subcutaneous administration on ACR 20 by removing them in the combined analysis. The result showed a decrease in heterogeneity from 87% to 0%, and the RR changed from 1.57 [95%CI 1.27, 1.93] to 1.77 [95%CI 1.61, 1.94].

Drug dosage

One study (39) used a 2 mg dosage, 2 studies (30, 40) gave a 125 mg dosage, 6 studies (31-33, 35, 37, 38, 41) administered a 10 mg dosage, and 3 studies (29, 34, 36) gave three different dosages based on patients' weights (500 mg for patients <60 kg body weight, 750 mg for 60–100 kg, and 1000 mg for >100 kg).We looked at the effect of each subgroup on the heterogeneity and RR by removing them in the combined analysis. Removing the study with 2 mg dosage from the combined analysis was not followed by any major change in heterogeneity and RR.

The effect of the 2 studies with 125 mg dosage has already been assessed above. As for the 3 studies that gave different dosages, they did not report any ACR response, and only one of them (36) assessed the DAS28-CRP. Removing the latter did not result in major heterogeneity change, but the RR went from 1.92 [95%CI 1.12, 3.29] to 2.61 [95%CI 1.44, 4.75].

Concomitant drugs

Within 7 studies (29, 31-33, 36, 40, 41), patients were taking csDMARDs during abatacept therapy. In 3 studies (34, 37, 39), participants were taking TNF inhibitors, and 3 studies (30, 35, 38) did not report any concomitant drug. Removing the studies that reported TNF inhibitor as a concomitant drug from the combined analysis only affected the outcome of adverse events. It has reduced the heterogeneity from 91% to 64% and the RR changed from 0.93 [95%CI 0.84, 1.03] to 1.01 [95%CI 0.96, 1.06]. Removing the 3 studies that did not report any concomitant drug had no major effect on the heterogeneity.

Number of previous bDMARDs

Of the 13 enrolled RCTs, two (34, 39) were conducted in patients who were all previously treated with other b-DMARDs. Other 2 studies indicated that their participants were biologic naïve (30, 40), while in 5 other RCTs (29, 31-33, 36), participants received different therapies prior to abatacept administration: some were treated with bDMARDs while others were not. 4 researches on the other had did not report whether their participants were previously treated with bDMARDs. Of these 13 studies only one RCT (36) has classified their patients according to the number of previous bDMARDs but the study did not reveal the treatment

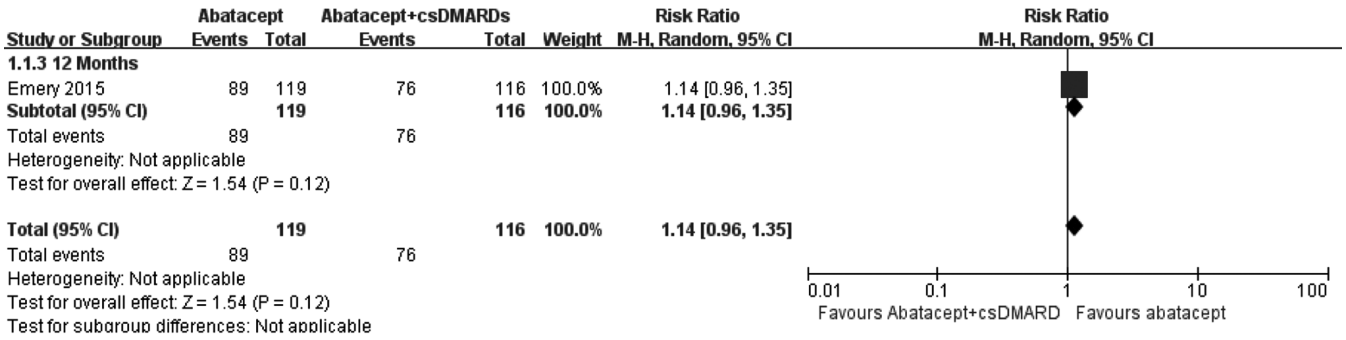


Fig. 20. Forest plot of comparison: Efficacy of Abatacept monotherapy *vs*. Abatacept + csDMARDs; Outcome1: ACR 20 improvement.

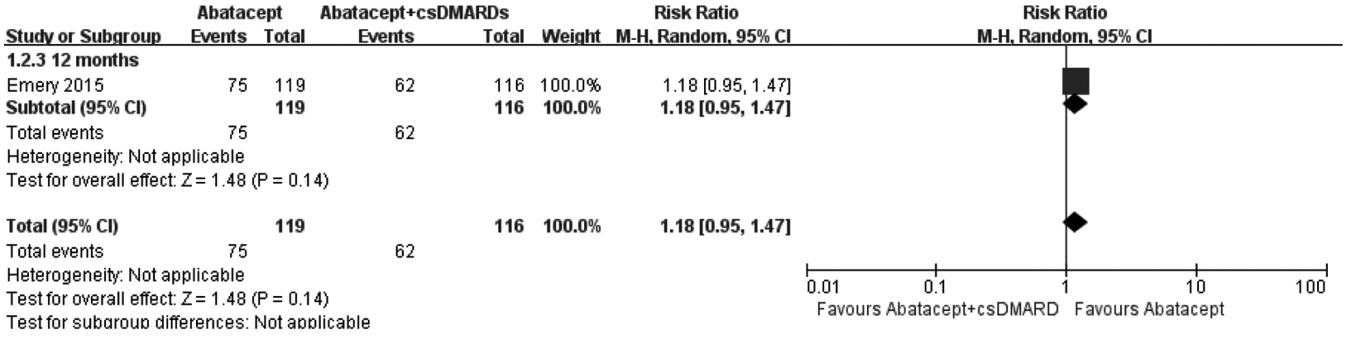


Fig. 21. Forest plot of comparison: Efficacy of Abatacept monotherapy *vs*. Abatacept + csDMARDs; Outcome 2: ACR 50 improvement.

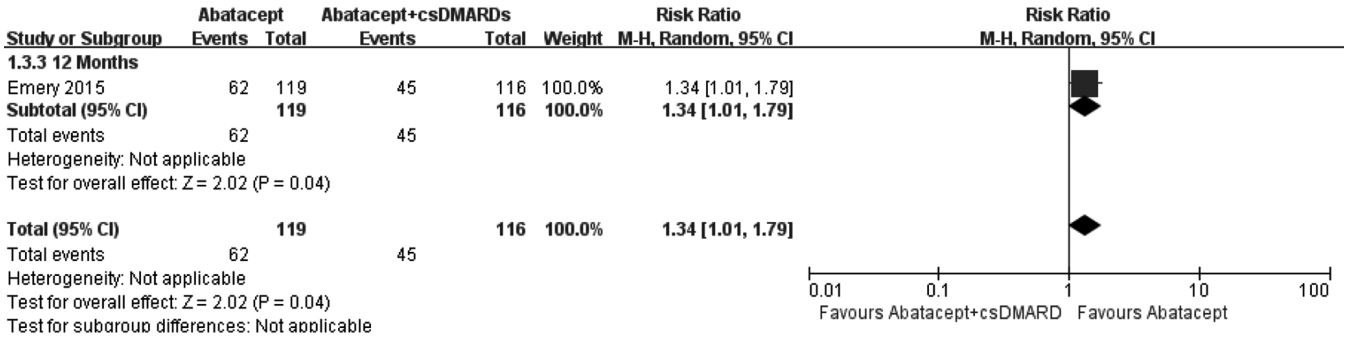


Fig. 22. Forest plot of comparison: Efficacy of Abatacept monotherapy *vs*. Abatacept + csDMARDs; Outcome 3: ACR 70 improvement.

outcome based on the number of previous bDMARDs. We looked into the effect of previous bDMARD therapy on heterogeneity by firstly removing the 2 studies that only enrolled patients with a history of bDMARD therapy. No significant change could be seen in both heterogeneity or disease outcomes (ACRs, DAS28-CRP, and adverse events). We then removed the 2 studies with biologic naive participants. The RRs of ACR 20/50/70 responses changed from 1.57 [1.27, 1.93] to 1.77 [1.61, 1.94], 1.84 [1.38, 2.44] to 2.17 [1.60, 2.93] and 2.36 [1.60, 3.47] to 3.22 [1.92, 5.41], respectively. Similarly, we could see a reduction of heterogeneity from 87% to 0%. However, since these two studies are the same studies that administered the drugs subcutaneously, it is not clear whether it is the drug administration route or the absence of other bDMARD usage prior to abatacept therapy that is responsible for this heterogeneity.

Discussion

Our study was designed to analyse the efficacy and safety of abatacept in patients with rheumatoid arthritis. Abatacept works by selectively inhibiting T-cell activation by binding to CD80/CD86. Such inhibition results in the blockage of CD28 on antigen-presenting cells, known as the costimulatory signal (42). Up to now, many RCTs of abatacept have revealed its efficacy in treating rheumatoid arthritis. However, RCTs are well-known to be limited by restricted periods and strict inclusion criteria. To overcome this limitation, we conducted a meta-analysis that combined the results of 13 RCTs comparing the efficacy and safety of abatacept to placebo and or csDMARDs or b/tsDMARDs. The search period of these studies ranged from the establishment of PubMed, Cochrane central register of controlled trials, Web of Science, and Embase databases to April 2022. Efficacy was assessed in terms of ACR20/50/70/90 responses and DAS28-CRP. Safety was evaluated in terms of side effects.

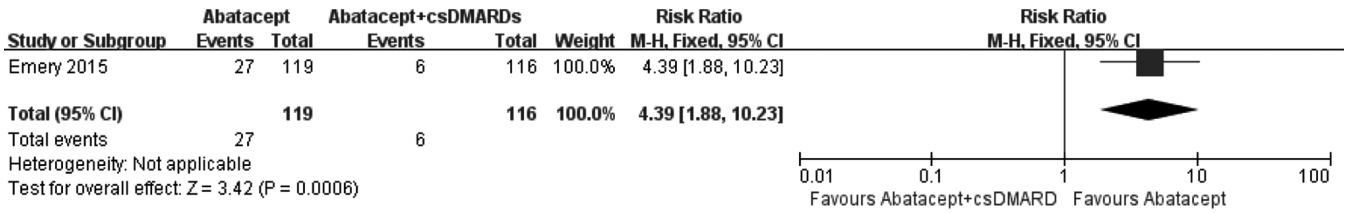


Fig. 23. Forest plot of comparison: Efficacy of Abatacept monotherapy *vs*. Abatacept + csDMARDs; Outcome 4: ACR 90 improvement.

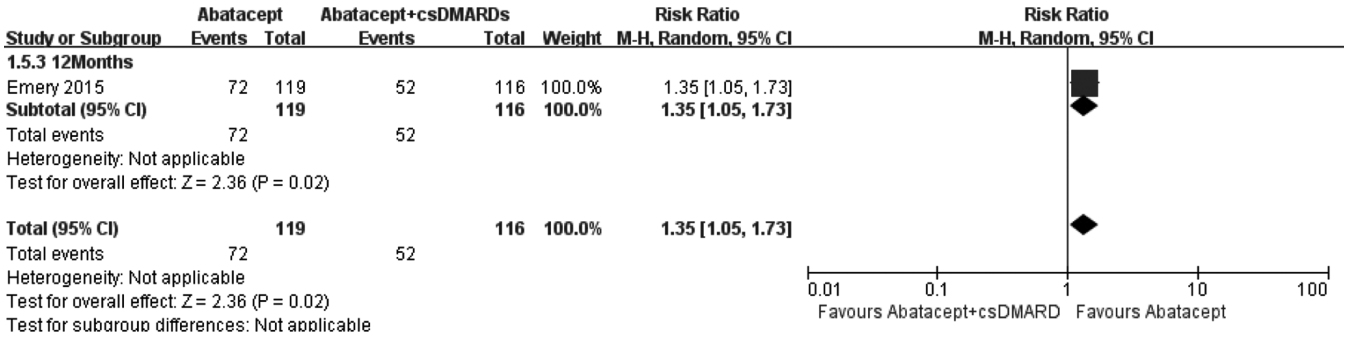


Fig. 24. Forest plot of comparison: Efficacy of Abatacept monotherapy *vs*. Abatacept + csDMARD; Outcome 5: DAS28-CRP.

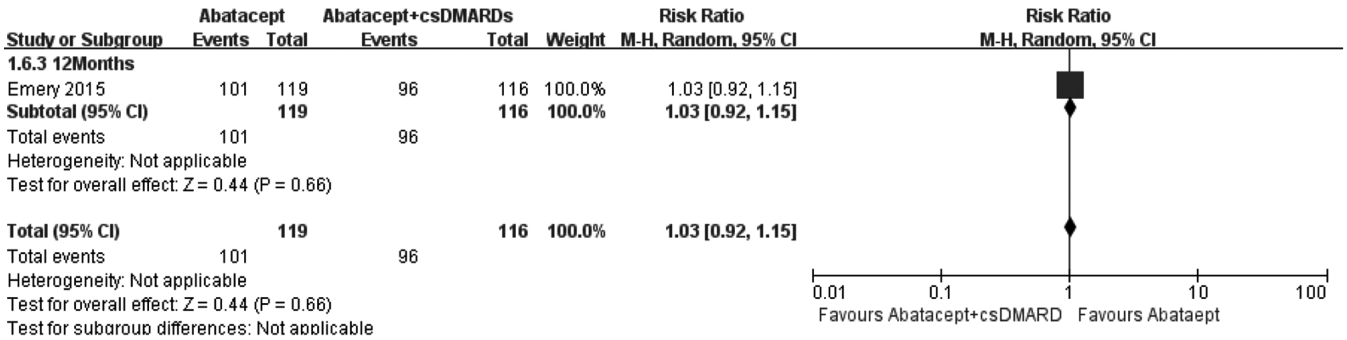


Fig. 25. Forest plot of comparison: Safety of Abatacept monotherapy *vs*. Abatacept + csDMARD; Outcome 6: Adverse events

Our work included a combined study population of 5978 adult patients from different geographic areas and ethnicities. Studies have shown that the choice of treatment for RA varies between race and ethnicity (43, 44) which influences the disease prognosis. Despite the development of highly effective therapy such as biologics, certain ethnicities were less likely to receive these drugs and therefore could not achieve a better disease outcome. This is in line with what was found in our study. In fact, while our study population was heterogenous, participants were mainly from America and Europe, and the dominant race was White. Such information highlights the need for more optimal therapeutic approach that can target the minorities.

The fact that RA is more common in women than men could also be appreciated in our work. Indeed, all our enrolled studies have indicated a female gender dominance. It was previously reported that while females with RA may have a higher disease activity, males have a better response rate to b/tsDMARDs (45). Given this impact of sex on RA, gender medicine could help strategise the treatment of this disease. Unfortunately, the nature and design of our work did not allow the analysis of the efficacy of abatacept with regard to gender differences. Future studies need to evaluate this point.

To provide more pertinent data for clinical practice, we conducted our analysis in two different aspects. First, we performed a combined analysis by comparing abatacept with other drugs, regardless of the type of intervention in the control group. Then, we performed an analysis based on the type of intervention in the control group (abatacept *vs*. placebo, abatacept *vs*. other b/ts DMARDs, and abatacept monotherapy *vs*. abatacept+csDMARDs).

Our combined analysis showed that irrespective of the treatment duration (3 months, 6 months, or 12 months), the achievement of ACR/20/50/70/90 responses were more significant in patients treated with abatacept compared to the control groups. The disease activity also highly decreased in the abatacept group compared to the control groups (Fig. 3-7). Such findings are similar to what was reported previously in 2009 (46).

For a drug to be considered effective, its safety must also be evaluated. In our combined analysis, we observed that the number of adverse events was less seen

among patients treated with abatacept than those in the control groups (Fig. 8). This result is different from what was reported previously in 2009 (46), but similar to the findings of two articles that compared abatacept with other biologics (29, 36). According to the first article, both abatacept and tocilizumab could reduce the disease activity and improve physical function in female patients with rheumatoid arthritis who failed to respond to antitumor necrosis factor therapy. However, compared to tocilizumab, abatacept had lesser side effects and better laboratory outcomes (29). The second study showed that more patients treated with upadacitinib achieved remission than those treated with abatacept. However, upadacitinib was associated with more severe adverse events than abatacept (36).

Indeed, when we exclusively compared the safety of abatacept with other b/tsDMARDs, we found that patients treated with other b/tsDMARDs were more likely to develop side effects than those who were given abatacept (Fig. 19). Moreover, participants from the abatacept group were more likely to achieve ACR 20/50/70 responses than those who were taking other b/tsDMARDs (Fig. 15-16). In terms of cost-effectiveness however, a study has revealed that rituximab, abatacept and different tumour necrosis factor inhibitors had all good RA outcomes but rituximab was more cost-effective than abatacept (34).

We also compared the efficacy of abatacept with placebo. Similar to a previous investigation (46), we observed better ACR 20/50/70/90 responses in patients treated with abatacept than those who were given placebo. Likewise, a lower disease activity could be appreciated in the abatacept group. Regarding the adverse events, there was no significant difference between the experimental and control groups (Fig. 9-14).

An additional analysis between abatacept monotherapy and abatacept+csDMARDs was conducted.

Only one enrolled study has performed this comparison and the RRs value suggest that patients treated with abatacept alone are more likely to achieve better ACR responses, and lower disease activity than those who were given abatacept+csDMARDs. The analysis also demonstrated a similar number of side effects between the two groups (Fig. 20-25). However, it should be noted that the fact that these findings derive from a single study represents a weakness, and future investigations need to assess these discoveries.

Our results showed the presence of heterogeneity. To explore the origin of this heterogeneity, we performed a subgroup analysis based on the disease phenotype (seropositive *vs*. seronegative patients), drug route of administration, drug dosage, the number of previous bDMARDs, and concomitant drugs. Among all these subgroups, only the drug administration route (intravenous *vs*. subcutaneous) or the absence of prior biologic therapy could explain this heterogeneity. Indeed, when we removed the 2 studies that administered abatacept subcutaneously from the combined analysis, the heterogeneity changed from 87% to 0%. Similarly, the removal of the 2 studies with biologic naive participants from the combined analysis reduced the heterogeneity from 87% to 0%. However, since these 2 studies are the same studies that administered abatacept subcutaneously (30, 40), it is not clear whether it is the drug administration route or the absence of prior biologic therapy that is responsible for this heterogeneity.

Strength and limitations

We have performed a rigorous search on the efficacy and safety of abatacept in treating RA. Studies included in our meta-analysis were all RCTs and were of high quality. We have carefully extracted information from these trials and evaluated different outcomes reflecting the activity of RA. Following the PRISMA checklist 20 (Supplementary file), we have ensured that our work conforms with the specification of meta-analysis. However, our study is not without limitations: The full texts of a few articles could not be retrieved and therefore were not included in our research. Even though they represent a small number, their exclusion could lead to bias. Another concern that needs to be raised is that most of our enrolled RCTs were financed by drug companies which could represent a bias.

Outstanding gaps and future direction

Our study has demonstrated that up to 12 months, abatacept can achieve better health outcomes in adult patients with rheumatoid arthritis compared to other biologics. Such evidence is clinically significant because, as with other biologics, abatacept is an expensive drug whose high cost can represent a limitation. Revealing its efficacy and safety can therefore make it acceptable to RA patients. Although our meta-analysis has shown remarkable findings, several gaps need to be addressed in the future in order to provide a better understanding of abatacept and to fully benefit from this drug. First of all, it is reported that gender has an influence on the treatment of RA. Since we still do not know how different genders respond to abatacept therapy, it would be beneficial to investigate this point in the future. Similarly, it is possible that RF/or ACCP positivity could influence the outcome of RA therapy. Therefore, studies that evaluate the treatment response of abatacept between seropositive and seronegative RA patients are needed. Thirdly, since the withdrawal treatment strategy represents a major goal in the long treatment of RA, future researches should investigate the achievement of sustained remission after withdrawal of abatacept. Finally, the drug administration route can be an important determining factor in the selection of appropriate therapy. Hence, conducting a meta-analysis that compares the safety and efficacy of subcutaneous and intravenous abatacept would be beneficial.

References

1. SMOLEN JS, ALETAHA D, MCINNES IB: Rheumatoid arthritis. *Lancet* 2016; 388(10055): 2023-38. https://doi.org/10.1016/s0140-6736(16)30173-8
2. LEE DM, WEINBLATT ME: Rheumatoid arthritis. *Lancet* 2001; 358(9285): 903-11. https://doi.org/10.1016/s0140-6736(01)06075-5
3. SPARKS JA: Rheumatoid arthritis. *Ann Intern Med* 2019; 170(1): Itc1-itc16. https://doi.org/10.7326/aitc201901010
4. GARAFFONI C, ADINOLFI A, BORTOLUZZI A *et al*.: Novel insights into the management of rheumatoid arthritis: one year in review 2022. *Clin Exp Rheumatol* 2022; 40(7): 1247-57. https://doi.org/10.55563/clinexprheumatol/1sjgyr
5. LIN YJ, ANZAGHE M, SCHÜLKE S: Update on

the pathomechanism, diagnosis, and treatment options for rheumatoid arthritis. *Cells* 2020; 9(4). https://doi.org/10.3390/cells9040880
6. SCOTT DL, WOLFE F, HUIZINGA TW: Rheumatoid arthritis. *Lancet* 2010; 376(9746): 1094-108. https://doi.org/10.1016/s0140-6736(10)60826-4
7. BULLOCK J, RIZVI SAA, SALEH AM *et al*.: Rheumatoid arthritis: a brief overview of the treatment. *Med Princ Pract* 2018; 27(6): 501-7. https://doi.org/10.1159/000493390
8. BONELLI M, SCHEINECKER C: How does abatacept really work in rheumatoid arthritis? *Curr Opin Rheumatol* 2018; 30(3): 295-300. https://doi.org/10.1097/bor.0000000000000491
9. POMBO-SUAREZ M, GOMEZ-REINO JJ: Abatacept for the treatment of rheumatoid arthritis. *Expert Rev Clin Immunol* 2019; 15(4): 319-26. https://doi.org/10.1080/1744666x.2019.1579642
10. IWAMOTO N, KAWAKAMI A: [Abatacept]. *Nihon Rinsho* 2016; 74(6): 968-73.
11. BLAIR HA, DEEKS ED: Abatacept: a review in rheumatoid arthritis. *Drugs* 2017; 77(11):1 221-33. https://doi.org/10.1007/s40265-017-0775-4
12. LIU M, YU Y, HU S: A review on applications of abatacept in systemic rheumatic diseases. *Int Immunopharmacol* 2021; 96: 107612. https://doi.org/10.1016/j.intimp.2021.107612
13. FELSON DT, ANDERSON JJ, BOERS M *et al*.: American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995; 38(6): 727-35. https://doi.org/10.1002/art.1780380602
14. WESTHOVENS R, GOMEZ-REINO JJ, GRASSI W *et al*.: Improvement in disease activity and treatment response over 2 years of abatacept treatment and shifts to improved disease states in patients with early rheumatoid arthritis who switch from MTX. *Arthritis Rheum* 2011; 63(10 Suppl. 1). Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01032654/full.
15. KREMER JM, PETERFY C, RUSSELL AS *et al*.: Longterm safety, efficacy, and inhibition of structural damage progression over 5 years of treatment with abatacept in patients with rheumatoid arthritis in the abatacept in inadequate responders to methotrexate trial. *J Rheumatol* 2014; 41(6): 1077-87. https://doi.org/10.3899/jrheum.130263
16. WESTHOVENS R, KREMER JM, EMERY P *et al*.: Long-term safety and efficacy of abatacept in patients with rheumatoid arthritis and an inadequate response to methotrexate: a 7-year extended study. *Clin Exp Rheumatol* 2014; 32(4): 553-62.
17. WEINBLATT ME, SCHIFF M, VALENTE R *et al*.: Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a phase IIIb, multinational, prospective, randomized study. *Arthritis Rheum* 2013; 65(1): 28-38. https://doi.org/10.1002/art.37711
18. RUBBERT-ROTH A, XAVIER R, HARAOUI B *et al*.: Clinical responses to upadacitinib or abatacept in patients with rheumatoid arthritis by type of prior biologic disease modifying antirheumatic drug: data from the phase 3 select-choice study. *Ann Rheum Dis* 2021; 80 (Suppl. 1): 580. https://doi.org/10.1136/annrheumdis-2021-eular.2114
19. BYKERK VP, BURMESTER GR, COMBE BG *et al*.: On-drug and drug-free remission by baseline symptom duration: abatacept with methotrexate in patients with early rheumatoid arthritis. *Rheumatol Int* 2018; 38(12): 2225-31. https://doi.org/10.1007/s00296-018-4173-3
20. FLEISCHMANN R, WEINBLATT M, AHMAD H *et al*.: Efficacy of abatacept and adalimumab in patients with early rheumatoid arthritis with multiple poor prognostic factors: post hoc analysis of a randomized controlled clinical trial (AMPLE). *Rheumatol Ther* 2019; 6(4): 559-71. https://doi.org/10.1007/s40744-019-00174-7
21. SCHIFF M, WEINBLATT ME, VALENTE R *et al*.: Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. *Ann Rheum Dis* 2014; 73(1): 86-94. https://doi.org/10.1136/annrheumdis-2013-203843
22. SCHIFF M, PRITCHARD C, HUFFSTUTTER JE *et al*.: The 6-month safety and efficacy of abatacept in patients with rheumatoid arthritis who underwent a washout after anti-tumour necrosis factor therapy or were directly switched to abatacept: the ARRIVE trial. *Ann Rheum Dis* 2009; 68(11): 1708-14. https://doi.org/10.1136/ard.2008.099218
23. KREMER JM, DOUGADOS M, EMERY P *et al*.: Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase iib, double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005; 52(8): 2263-71. https://doi.org/10.1002/art.21201
24. KREMER JM, GENANT HK, MORELAND LW *et al*.: Results of a two-year followup study of patients with rheumatoid arthritis who received a combination of abatacept and methotrexate. *Arthritis Rheum* 2008; 58(4): 953-63. https://doi.org/10.1002/art.23397
25. RUSSELL AS, WALLENSTEIN GV, LI T *et al*.: Abatacept improves both the physical and mental health of patients with rheumatoid arthritis who have inadequate response to methotrexate treatment. *Ann Rheum Dis* 2007; 66(2): 189-94. https://doi.org/10.1136/ard.2006.057018
26. EMERY P, KOSINSKI M, LI T *et al*.: Treatment of rheumatoid arthritis patients with abatacept and methotrexate significantly improved health-related quality of life. *J Rheumatol* 2006; 33(4): 681-9.
27. LI T, WELLS G, WESTHOVENS R, EMERY P, BECKER JC, TUGWELL P: Improvements in participation in usual daily activities in patients with rheumatoid arthritis treated with abatacept. *Value Health* 2011; 14(2): 361-70. https://doi.org/10.1016/j.jval.2010.10.008
28. FLEISCHMANN R, WEINBLATT ME, SCHIFF M *et al*.: Patient-reported outcomes from a two-year head-to-head comparison of subcutaneous abatacept and adalimumab for rheumatoid arthritis. *Arthritis Care Res* 2016; 68(7): 907-13. https://doi.org/10.1002/acr.22763
29. ELMEDANY SH, MOHAMED AE, GALIL SMA: Efficacy and safety profile of intravenous tocilizumab versus intravenous abatacept in treating female Saudi Arabian patients with active moderate-to-severe rheumatoid arthritis. *Clin Rheumatol* 2019; 38(8): 2109-17. https://doi.org/10.1007/s10067-019-04508-2
30. EMERY P, BURMESTER GR, BYKERK VP *et al*.: Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results from the phase 3b, multicentre, randomised, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period. *Ann Rheum Dis* 2015; 74(1): 19-26. https://doi.org/10.1136/annrheumdis-2014-206106
31. GENOVESE MC, BECKER JC, SCHIFF M *et al*.: Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N Engl J Med* 2005; 353(11): 1114-23. https://doi.org/10.1056/nejmoa050524
32. KREMER JM, WESTHOVENS R, LEON M *et al*.: Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N Engl J Med* 2003; 349(20): 1907-15. https://doi.org/10.1056/nejmoa035075
33. KREMER JM, GENANT HK, MORELAND LW *et al*.: Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2006; 144(12): 865-76. https://doi.org/10.7326/0003-4819-144-12-200606200-00003
34. MANDERS SH, KIEVIT W, ADANG E *et al*.: Cost-effectiveness of abatacept, rituximab, and TNFi treatment after previous failure with TNFi treatment in rheumatoid arthritis: a pragmatic multi-centre randomised trial. *Arthritis Res Ther* 2015; 17(1): 134. https://doi.org/10.1186/s13075-015-0630-5
35. MORELAND LW, ALTEN R, VAN DEN BOSCH F *et al*.: Costimulatory blockade in patients with rheumatoid arthritis: a pilot, dose-finding, double-blind, placebo-controlled clinical trial evaluating CTLA-4Ig and LEA29Y eighty-five days after the first infusion. *Arthritis Rheum* 2002; 46(6): 1470-9. https://doi.org/10.1002/art.10294
36. RUBBERT-ROTH A, ENEJOSA J, PANGAN AL *et al*.: Trial of upadacitinib or abatacept in rheumatoid arthritis. *N Engl J Med* 2020; 383(16): 1511-21. https://doi.org/10.1056/nejmoa2008250
37. SCHIFF M, KEISERMAN M, CODDING C *et al*.: Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multicentre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann Rheum Dis* 2008; 67(8): 1096-103. https://doi.org/10.1136/ard.2007.080002
38. WEINBLATT M, COMBE B, COVUCCI A, ARANDA R, BECKER JC, KEYSTONE E: Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and non-biologic disease-modifying antirheumatic drugs: a one-year randomized, placebo-controlled study. *Arthritis Rheum* 2006;5 4(9): 2807-16. https://doi.org/10.1002/art.22070
39. WEINBLATT M, SCHIFF M, GOLDMAN A *et al*.: Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept:

a randomised clinical trial. *Ann Rheum Dis* 2007; 66(2): 228-34. https://doi.org/10.1136/ard.2006.055111

40. WEINBLATT ME, SCHIFF MH, FLEISCHMANN R *et al*.: Head to head comparison of subcutaneous abatacept versus adalimumab in the treatment of rheumatoid arthritis: key efficacy and safety results from the ample (abatacept versus adalimumab comparison in biologic-naive RA subjects with background methotrexate) trial. *Arthritis Rheum* 2012; 64: S1031. https://doi.org/10.1002/art.37735
41. WESTHOVENS R, ROBLES M, XIMENES AC *et al*.: Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. *Ann Rheum Dis* 2009; 68(12): 1870-7. https://doi.org/10.1136/ard.2008.101121
42. SARMIENTO-MONROY JC, PARADA-ARIAS L, RODRÍGUEZ-LÓPEZ M *et al*.: Subcutaneous abatacept in rheumatoid arthritis: a real-life experience. *J Transl Autoimmun* 2019; 2: 100016. https://doi.org/10.1016/j.jtauto.2019.100016
43. YIP K, NAVARRO-MILLÁN I: Racial, ethnic, and healthcare disparities in rheumatoid arthritis. *Curr Opin Rheumatol* 2021; 33(2): 117-21. https://doi.org/10.1097/bor.0000000000000782
44. LEE SJ, KREMER J, KAVANAUGH A: Treatment disparity related to race/ethnicity and education in rheumatoid arthritis patients: comment on the article by Constantinescu et al. *Arthritis Rheum* 2009; 61(8): 1141-2. https://doi.org/10.1002/art.24727
45. FAVALLI EG, BIGGIOGGERO M, CROTTI C, BECCIOLINI A, RAIMONDO MG, MERONI PL: Sex and management of rheumatoid arthritis. *Clin Rev Allergy Immunol* 2019; 56(3): 333-45. https://doi.org/10.1007/s12016-018-8672-5
46. MAXWELL L, SINGH JA: Abatacept for rheumatoid arthritis. *Cochrane Database Syst Rev* 2009; 2009(4): Cd007277. https://doi.org/10.1002/14651858.cd007277.pub2