

Efficacy, safety and tolerability of using abatacept for the treatment of rheumatoid arthritis

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The objective is to provide an update on the clinical efficacy, safety and tolerability of the use of abatacept for treating rheumatoid arthritis. A systematic review (up to June 2011) followed by meta-analyses was performed. Randomized controlled clinical trials comparing abatacept at a dose of 10 mg/kg with a placebo, both with concomitant methotrexate, were used. Only high- or moderate-quality studies were included. The efficacy was evaluated based on changes in the ACR, DAS and HAQ; safety was assessed based on serious adverse events, serious infections, malignancies and deaths; tolerability was evaluated based on the withdrawals due to adverse events, serious adverse events and lack of efficacy. All these parameters were evaluated within one year of treatment. Nine studies met the inclusion criteria, comprising 4,219 patients. For all of the efficacy parameters, the abatacept group had better results than the placebo group, except in the case of HAQ improvement >0.3, which presented no statistically significant difference. None of the safety parameters presented a significant difference between the groups. The tolerability parameters were also similar between groups, with the exception of withdrawals due to lack of efficacy. For this criterion, the abatacept group presented favorably compared to the control group. Abatacept showed a higher efficacy compared to placebo without significant differences between the abatacept and control group in terms of safety.

Uniterms: Abatacept/efficacy. Rheumatoid arthritis/treatment. Meta-analyses.

O objetivo foi fornecer dados atualizados sobre eficácia clínica, segurança e tolerabilidade do uso de abatacepte para o tratamento da artrite reumatoide. Realizaram-se uma revisão sistemática (com dados até junho/2011) e metanálises. Somente estudos clínicos controlados randomizados comparando o abatacepte (10 mg/kg) com placebo, ambos com uso concomitante de metotrexato, foram incluídos; todos possuíam qualidade alta ou moderada. A eficácia foi avaliada baseando-se em mudanças no ACR, DAS e HAQ; a segurança foi avaliada pelos eventos adversos e infecções graves, malignidades e mortes e a tolerabilidade pelo abandono do tratamento devido a eventos adversos (graves ou não) e falta de eficácia. Todos esses parâmetros foram avaliados ao final de um ano de tratamento. Nove estudos se adequaram aos critérios de inclusão, envolvendo 4219 pacientes. Em todos os parâmetros avaliados, o grupo tratado com abatacepte obteve melhores resultados, exceto para a melhora (>0,3) no HAQ (sem diferença estatisticamente significativa). Nenhum critério de segurança ou tolerabilidade apresentou diferença significativa entre os grupos, com exceção dos abandonos devido à falta de eficácia (grupo abatacepte apresentou resultados favoráveis em relação ao controle). O abatacepte possui maior eficácia quando comparado com o placebo, sem diferença significativa entre os grupos em termos de segurança.

Unitermos: Abatacepte/eficácia. Artrite reumatóide. Metanálise.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease with a worldwide prevalence of approximately

1%. The disease leads to joint inflammation and destruction and generates a decrease in the health-related quality of life, functional limitations and work disability, mainly due to pain and fatigue (Bagust *et al.*, 2009; Singh *et al.*, 2009; Cortejoso-Fernandez *et al.*, 2012).

Cytokines, interleukins-1 β and 6 (IL-1 β and 6) and tumor necrosis factor (TNF) are known to play important roles in joint destruction in RA. The activation of T and B

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cells leads to a cascade of events, including the release of cytokines that are responsible for inflammation and joint destruction. Abatacept (ABT) modulates the stimulation of T cells, which subsequently control the function of B cells, macrophages and osteoclasts and the release of cytokines, matrix metalloproteinases and antibodies (Bruce, 2009; Falgarone *et al.*, 2009). ABT is a fusion protein made up of the Fc portion of human immunoglobulin and cytotoxic T-lymphocyte associated antigen 4. ABT blocks the cascade of activation of T cells (Smolen *et al.*, 2007; Bruce, 2009; Mola *et al.*, 2012).

ABT was shown to be safe and efficient for patients with an inadequate response to TNF antagonists and methotrexate (MTX) in some randomized controlled clinical trials (RCT). Treatment with ABT resulted in decreases in arthritis, pain, disability, fatigue and radiological joint damage, and the efficacy was maintained over time (Genovese *et al.*, 2005; Kremer *et al.*, 2005; Kremer *et al.*, 2006; Genant *et al.*, 2008; Schiff *et al.*, 2008; Falgarone *et al.*, 2009; Rubbert-Roth; Finckh, 2009; Russell *et al.*, 2009; Russell *et al.*, 2009; Mola *et al.*, 2012).

Although RTC have shown the effectiveness of ABT in treating the signs and symptoms of AR, indiscriminate use must be avoided and continued evaluations must be conducted due to the lack of information about the long-term safety (Cortejoso-Fernández *et al.*, 2012). According to a review by Cochrane, ABT presents a better safety profile than most other biologics (Malaviya, Östör, 2012). This study provides a systematic review and meta-analyses to evaluate the efficacy, safety and tolerability of ABT pharmacotherapy for RA interventions based on updated evidence, including systematic reviews and meta-analyses.

METHODS

A systematic review and meta-analyses were performed of RCT that compared the use of ABT at a dose of 10 mg/kg versus placebo, both with concomitant MTX. In the included studies, ABT was given endovenously at days 1, 15 and 29 and every 4 weeks thereafter. Only studies involving adult patients with active RA (as defined by the American College of Rheumatology - ACR - criteria) and with moderate to high quality were included (according to Jadad's Scale) (Jadad *et al.*, 1996). Other inclusion criteria were as follows: studies that reported clinical outcomes and were available as full-text publications. Interventional studies were excluded if they were not randomized or double-blind.

Two independent reviewers performed the systematic review and applied Jadad's Scale (Jadad *et al.*, 1996) for quality evaluation of the studies. The two reviewers extracted the data from the articles in pre-defined tables.

In the case of a difference between the data extracted by the reviewers, the discordant data were discussed and consensual values were adopted.

The electronic databases used in the systematic review were as follows: Medline, Embase, Chocrane Library, Scielo, Lilacs and International Pharmaceutical Abstracts. The search was performed for relevant studies up to June 2011. Language and date of study publication were not exclusion criteria. As descriptors, the following expressions were used: rheumatoid arthritis AND abatacept. No search filters were used for the type of study restriction, except for in Medline (in which we only looked for clinical trials, meta-analyses, RCT, and clinical trials) and IPA (in which we only searched for original articles).

The clinical outcomes adopted for the evaluation of treatment were the following: the response of RA to treatment with ABT according to the ACR criteria (ACR 20, 50 and 70); a Disease Activity Score in 28 joints indicating the remission of the pathology ($DAS28 \leq 2.6$) and a low disease activity ($DAS28 \leq 3.2$); and HAQ variation and improvement ($\Delta HAQ \geq 0.3$). Additionally, the safety outcomes considered were as follows: serious adverse events (SAE), serious infections (SI), malignancies and deaths. For the tolerability evaluation, withdrawals due to adverse events, SAE or lack of efficacy were measured. All parameters were evaluated after one year of treatment, according to the available data in the included studies.

For statistical analyses, the software Review Manager 5.0, from Cochrane Collaboration, was used. Dichotomous variables were evaluated using the risk ratio with the inverse variance model, with a confidence interval of 95% (random effect model). HAQ variation was the only continuous variable, and it was evaluated by the mean difference and inverse variance model, with the same confidence interval. The random effect model was chosen due to the high heterogeneity in the data that could not be explained.

Statistical heterogeneity among the results was assessed using I^2 , a common metric method for measuring the magnitude of this variable. The interpretation of I^2 is relatively simple: its value varies from 0% to 100%, and in situations where $I^2 < 25\%$, the statistical heterogeneity is considered low; it is considered moderate and high for values between 25% and 50% and for values above 50%, respectively (Hakkinen *et al.*, 2006; Huedo-Medina *et al.*, 2006).

A sensitivity analysis was also performed in this study. The method adopted for evaluating the robustness of the study was as follows: the data were reviewed with exclusion of data of studies or groups of studies. The data were also reviewed using different statistical methods.

RESULTS

In the systematic review, 42 potentially relevant articles were identified, of which 29 were excluded on the basis of the title or abstract. The remaining 13 articles were evaluated by two independent reviewers, and 4 studies were excluded upon reading the full text. The remaining 9 articles were included in the meta-analyses based on their quality and their accordance with the inclusion criteria. Figure 1 is a scheme of the systematic review, and Table I shows the main characteristics of the excluded studies and the reasons for their exclusion.

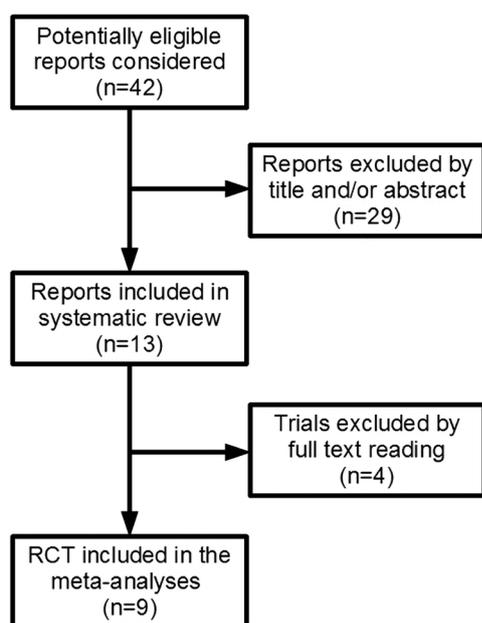


FIGURE 1 - Results of the systematic review. RCT – Randomized controlled trial.

Description of the included studies

Twelve studies met the inclusion criteria and were included in the meta-analyses. All of the included studies were sponsored by Bristol-Myers Squibb. A chronological summary of the baseline characteristics of the patients involved in the included studies is shown in Table II.

The mean age of the patients across all trials ranged from 49.1 to 54.6 years. The gender distribution was also similar across trials (all trials had a 3:1 ratio of females to males). Both the mean age and gender distribution values are consistent with the epidemiology of RA [1, 2]. The data for the mean number of swollen and tender joints were also similar across the studies; however, the mean disease duration was heterogeneous across the studies (ranged from 3.4 to 12.9 years).

TABLE I - Characteristics of the excluded studies

REFERENCE	REASON FOR EXCLUSION
Alten, 2006	
Chung, 2006	
Genant, 2008	
Genovese, 2008	
Kremer, 2008	
Maxwell, 2009	
Ostor, 2008	Not a randomized controlled clinical trial
Russell, 2009	
Schiff, 2009	
Singh, 2009	
Singh, 2009	
Vera-Llonch, 2008	
Venkateshan, 2009	
Westhovens, 2009	
Dougados, 2009	
Hasset, 2008	Analyzed data from another study (Genovese <i>et al.</i> , 2005)
Li, 2008	Involved an intervention that was not relevant for this meta-analyses
Moreland, 2002	
Ma, 2009	Pharmacokinetic study
Cole, 2008	
Emery, 2006	
Marti, 2009	
Martin, 2007	Compared outcomes that were not of interest for the meta-analyses
Russel, 2007	
Weisman, 2006	
Wells, 2008	
Westhovens, 2006	
Ruperto, 2008	Abatacept was prescribed for juvenile rheumatoid arthritis
Salliot, 2009	Adverse events meta-analysis

Meta-analyses results for efficacy

For evaluation of the efficacy of ABT, the following data were extracted from the studies: the proportion of patients who achieved ACR20, ACR50, ACR70, DAS28 \leq 3.2 and DAS28 \leq 2.6; the mean HAQ variation from baseline to the end of the follow-up; and the proportion of patients who showed an improvement of 0.3 or more in the HAQ scale. All the parameters were measured after one year of continuous treatment.

Considering the ACR outcomes, four studies provided data of the outcomes within one year of treatment (Kremer *et al.*, 2005; Kremer *et al.*, 2006; Schiff *et al.*, 2008; Westhovens *et al.*, 2009a). In two other studies, the interventions included concomitant anti-TNF agent (Genovese *et al.*, 2005; Weinblatt *et al.*, 2007). The articles

used in the meta-analyses involved the following intervention: ABT 10mg/kg+MTX versus placebo+MTX.

The Risk Ratios (RR) comparing ABT versus the control groups were as follows: 1.60 [1.28, 2.01] for ACR20, 1.98 [1.35, 2.91] for ACR50 and 2.47 [1.51, 4.03] for ACR70 (Figure 2). In total, 71% of the patients achieved ACR20 after one year of treatment with ABT compared to 43% of the control group. For ACR50 and ACR70, the values were 49% and 37% for the ABT group and 28% and 16% for the control group, respectively.

High statistical heterogeneities among the studies ($I^2 > 50\%$) were observed for the three outcomes (ACR20, 50 and 70). No clinical or methodological differences among the studies were observed to be able to cause these heterogeneities.

The proportions of patients with low disease activity

and who experienced remission were also evaluated in our meta-analyses using DAS28. The RR values comparing the ABT and control groups were 3.09 [1.68, 5.68] and 3.88 [1.48, 10.16] for the percentages of patients who achieved $DAS28 \leq 3.2$ (low disease activity) and $DAS28 \leq 2.6$ (disease remission), respectively, within one year of treatment. In total, 44% of patients achieved values of $DAS28 \leq 3.2$ in the ABT group; in the control group, this value was 14%. A total of 31% of the patients in the ABT group presented remission of the disease according to the DAS28 criteria; for the control group, this value was 13% (Figure 3).

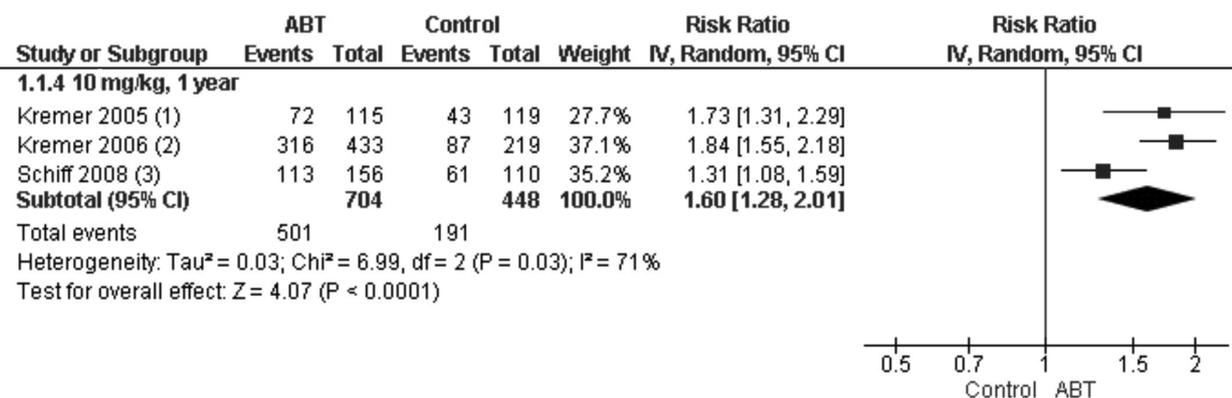
The statistical heterogeneity was high for both of the DAS28 outcomes. No clinical or methodological differences in the studies could account for this heterogeneity.

The meta-analysis of the variation of the HAQ from baseline to the end of follow-up involved only two stud-

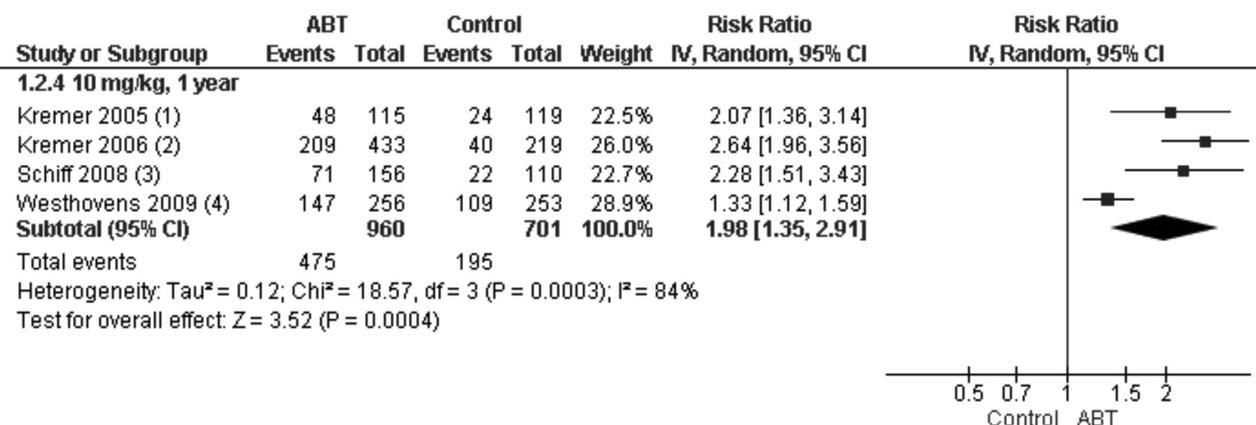
TABLE II - Patients' baseline characteristics in the included studies

Study (Jadad Score) Intervention	Number of patients	Mean age (years)	Mean disease duration (years)	Mean number of swollen joints	Mean number of tender joints	% of patients on DMARD	Mean HAQ score
Moreland, 2002 (4) ABT 10mg/kg + MTX Placebo + MTX	64	51.5	3.4	23.3	29.5	N.A.	N.A.
Kremer, 2003 (4) ABT 10mg/kg + MTX Placebo + MTX	234	54.6	9.3	21.1	28.7	N.A.	1.0
Genovese, 2005* (5) ABT 10mg/kg + MTX Placebo + MTX	391	53.2	11.9	22.2	31.7	N.A.	1.8
Kremer, 2005 (4) ABT 10mg/kg + MTX Placebo + MTX	234	54.6	9.3	21.1	28.7	N.A.	N.A.
Kremer, 2006 (4) ABT 10mg/kg + MTX Placebo + MTX	652	51.1	8.6	21.6	31.4	11.0	1.7
Weinblatt, 2006 (5) ABT 10mg/kg + DMARD Placebo + DMARD	1274	52.1	9.5	19.8	28.9	89.8	1.5
Weinblatt, 2007 (4) ABT 10mg/kg + ETA Placebo + ETA	121	51.1	12.9	19.7	28.8	N.A.	N.A.
Schiff, 2008 (5) ABT 10mg/kg + MTX Placebo + MTX	266	49.1	8.1	20.8	31.1	N.A.	1.8
Westhovens, 2009 (4) ABT 10mg/kg + MTX Placebo + MTX	509	49.9	6.4	22.4	31.1	3.3	1.7

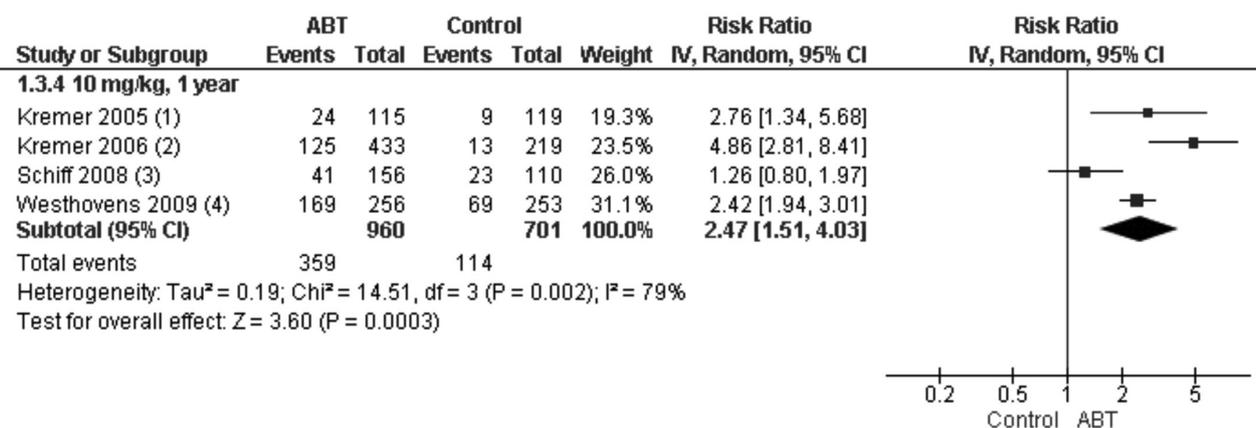
*Intervention with or without concomitant anti-TNF; DMARD: disease-modifying antirheumatic drugs; HAQ: health assessment questionnaire; N.A.: not available; ABT: abatacept; MTX: methotrexate; ETA: etanercept



- (1) ABT+MTX vs. Placebo+MTX
- (2) ABT+MTX vs. Placebo+MTX
- (3) ABT+MTX vs. Placebo+MTX



- (1) ABT+MTX vs. Placebo+MTX
- (2) ABT+MTX vs. Placebo+MTX
- (3) ABT+MTX vs. Placebo+MTX
- (4) ABT+MTX vs. Placebo+MTX



- (1) ABT+MTX vs. Placebo+MTX
- (2) ABT+MTX vs. Placebo+MTX
- (3) ABT+MTX vs. Placebo+MTX
- (4) ABT+MTX vs. Placebo+MTX

FIGURE 2 - Meta-analysis of ACR20 (top), ACR50 (middle) and ACR70 (bottom). ABT – abatacept; MTX – methotrexate. IV – inverse variance; CI – confidence interval.

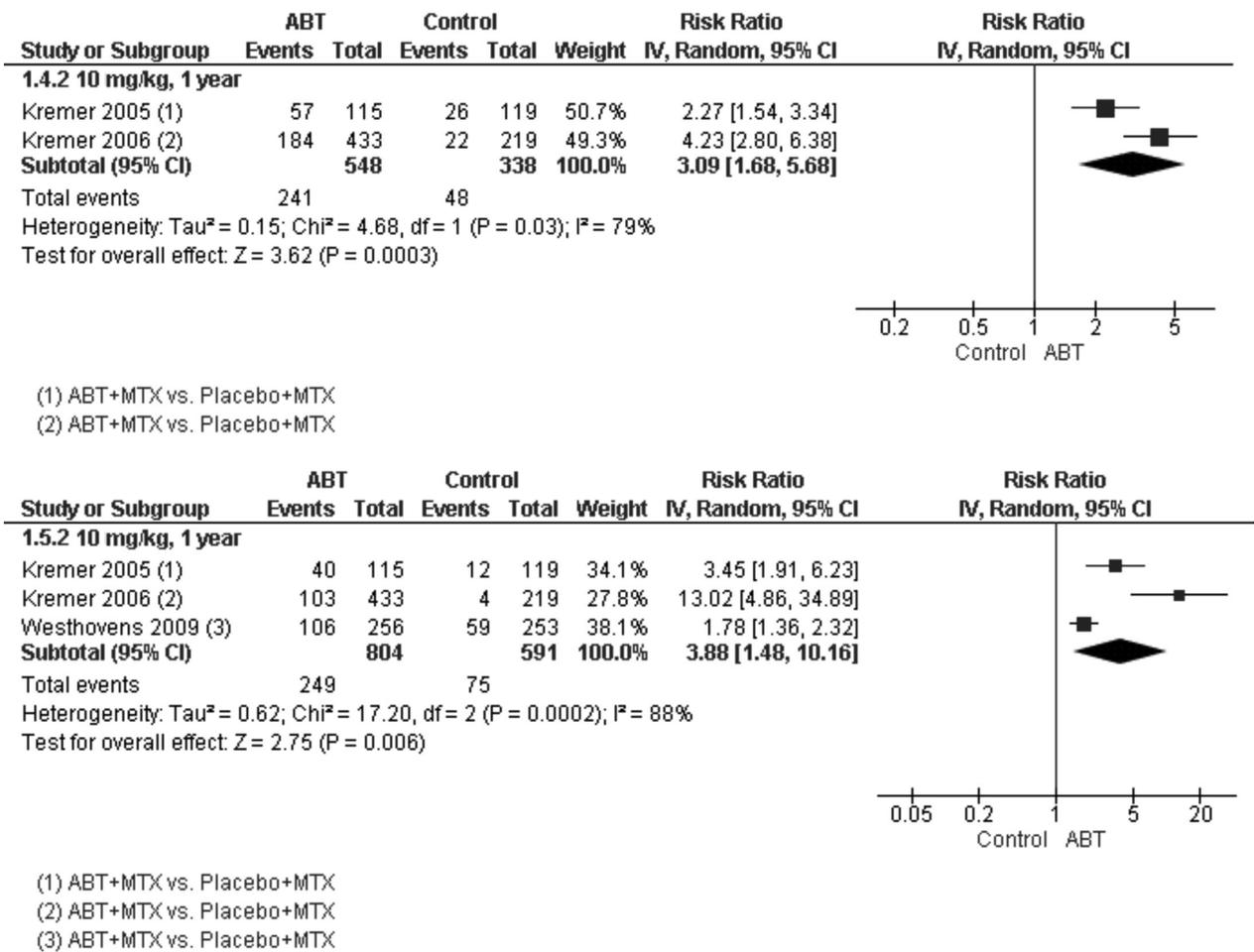


FIGURE 3 - Meta-analysis of low disease activity (DAS≤3.2) and disease remission (DAS≤2.6) – top and bottom, respectively. ABT – abatacept; MTX – methotrexate. IV – inverse variance; CI – confidence interval.

ies (Kremer *et al.*, 2006; Westhovens *et al.*, 2009a), both of which had ABT + MTX versus placebo+MTX as the intervention. The values included in the meta-analysis resulted in a mean difference of 0.19 [0.20, 0.19], favoring the ABT group. A high heterogeneity was also observed in this parameter, which could not be explained by the methodologies of the included studies (Figure 4).

For HAQ improvement ≥ 0.3, two studies were included in the meta-analysis (Kremer *et al.*, 2006; Westhovens *et al.*, 2009a). The result was an RR value of 1.36 [0.98, 1.90], favoring the ABT group; however, this difference was not statistically significant. High heterogeneity was observed (Figure 4).

Meta-analyses results for safety

Table III summarizes the results concerning safety. Three studies provided data related to the SAE and SI for one year of treatment (Kremer *et al.*, 2006; Jonsson; Kobelt; Smolen, 2008; Westhovens *et al.*, 2009a). Data on

death were available in four studies (Kremer *et al.*, 2005; Kremer *et al.*, 2006; Weinblatt *et al.*, 2006; Westhovens *et al.*, 2009a). Data on malignancies were extracted from four studies (Kremer *et al.*, 2005; Kremer *et al.*, 2006; Weinblatt *et al.*, 2006; Westhovens *et al.*, 2009a).

The RR values were not statistically significant for any of these items (p values of 0.19, 0.58, 0.82 and 0.98 for SAE, SI, malignancies and deaths, respectively).

Only the SAE data had values of I² higher than 25% (I²=39%), corresponding moderate heterogeneity. The study responsible for this heterogeneity was that of Weinblatt *et al.* (2006); the only difference between this study and the others was the possibility that the patients used other DMARD besides MTX.

Meta-analyses results for tolerability

The results concerning withdrawals due to AE, SAE and a lack of efficacy for ABT at a dose of 10 mg/kg within one year of treatment are summarized in Figure 5.

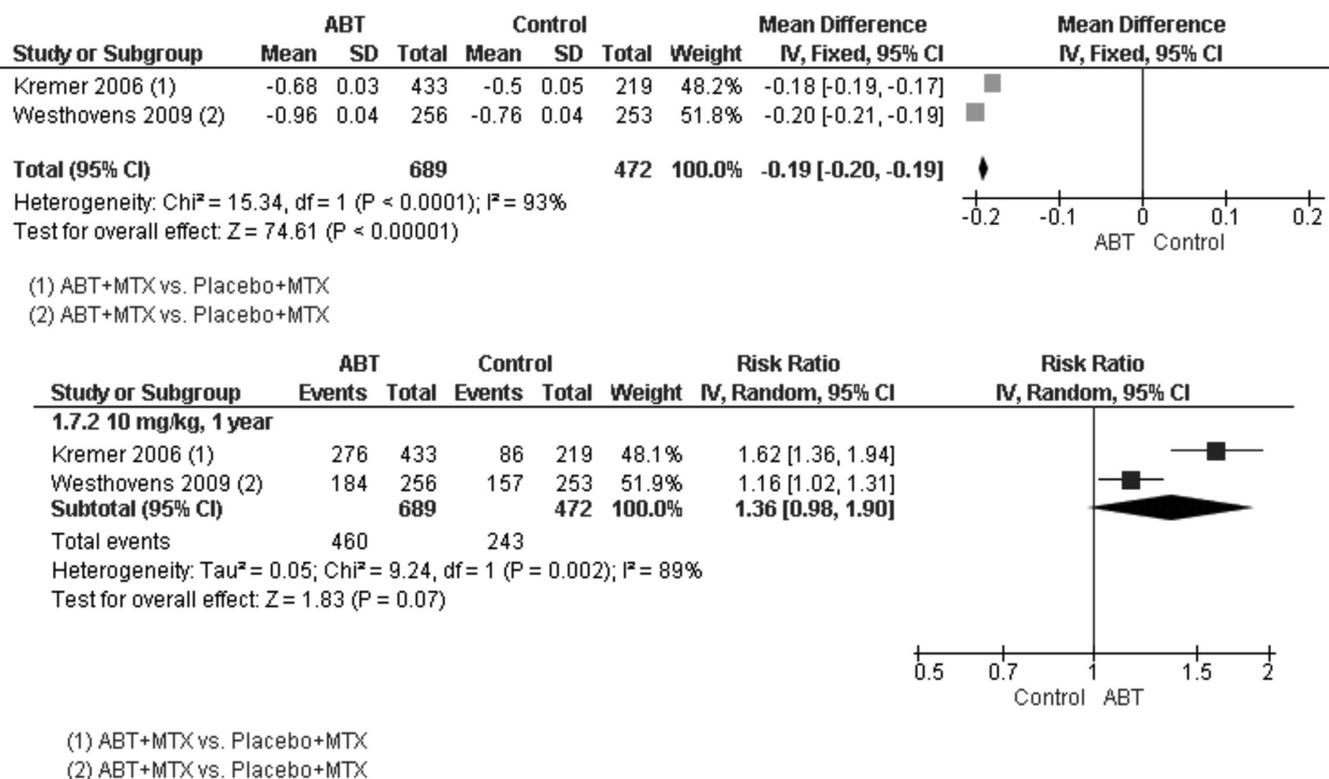


FIGURE 4 - Meta-analyses of HAQ variation (top) and HAQ improvement ≥ 0.3 (bottom). ABT – abatacept; MTX – methotrexate. IV – inverse variance; CI – confidence interval; SD – standard deviation.

TABLE III - Safety results

Outcome	Studies	Participants	Statistical Method	Effect Estimate
SAE	3	2435	Risk Ratio (IV, Random, 95% CI)	1.27 [0.76, 2.13]
SI	3	2435	Risk Ratio (IV, Random, 95% CI)	1.52 [0.81, 2.85]
Malignancies	4	2669	Risk Ratio (IV, Random, 95% CI)	0.93 [0.55, 1.57]
Deaths	4	2669	Risk Ratio (IV, Random, 95% CI)	0.56 [0.21, 1.47]

SAE: serious adverse events; SI: serious infections; IV: inverse variance; CI: confidence interval

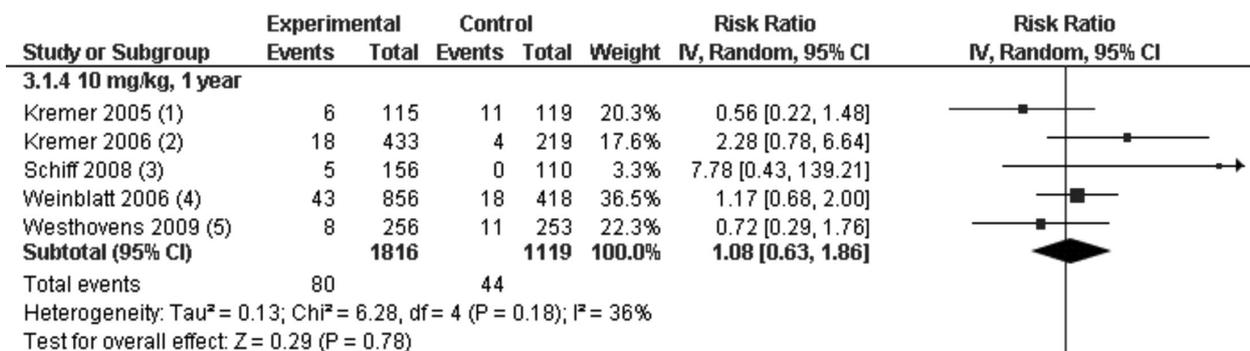
There were no statistically significant differences between the intervention and control groups in any of the evaluated parameters, except in the meta-analysis of the proportion of patients who withdrew from treatment due to a lack of efficacy (RR of 0.29 [0.12, 0.71]). This parameter exhibited high heterogeneity ($I^2=64\%$), which could not be explained by methodological differences between the studies. The value of RR of the withdrawals due to AE within one year of treatment also exhibited high heterogeneity, although the RR value was not statistically significant.

DISCUSSION

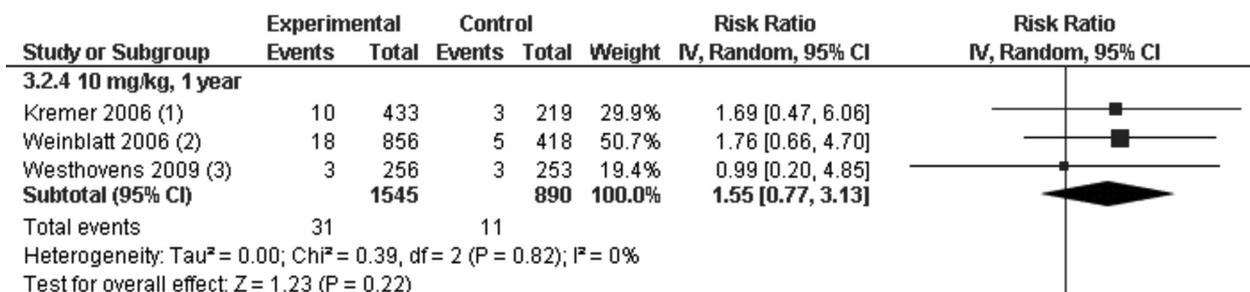
DMARDs and anticytokines, such as adalimumab, etanercept or infliximab, are used worldwide to control the

symptoms of RA, but in some patients, the results are not satisfactory (Bértolo *et al.*, 2007; Russell, A. *et al.*, 2009). Other biological agents have been developed to treat these refractory patients. Recent studies showed the effectiveness of these agents, including ABT and rituximab (RTX), for the treatment of RA. The evidence obtained from clinical trials is promising for the reduction of disease progression (Toussirot; Wendling, 2004; Smolen *et al.*, 2007). The remission of the disease is more likely when ABT is used in the early stages of RA (Tang *et al.*, 2008); in this study, only two trials (Moreland *et al.*, 2002; Westhovens *et al.*, 2009a) included patients who were within less than three years of disease onset.

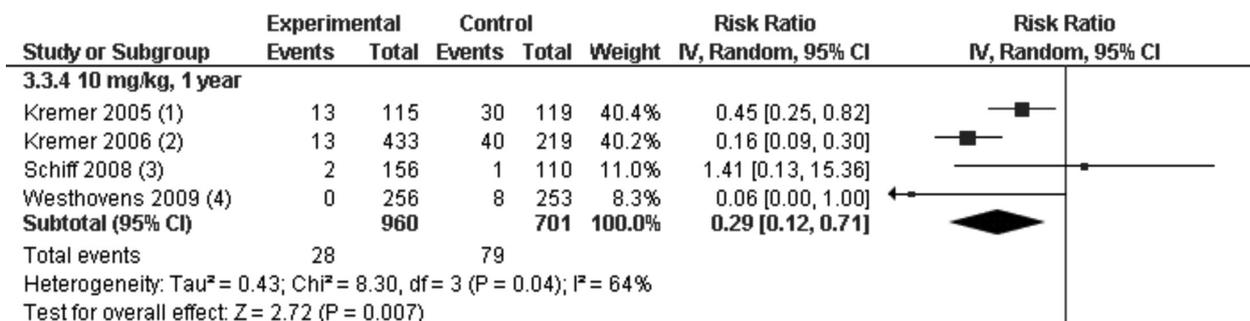
In this study, the ABT-treated patients showed better efficacy and tolerability, compared to the control group.



- (1) ABT+MTX vs. Placebo+MTX
- (2) ABT+MTX vs. Placebo+MTX
- (3) ABT+MTX vs. Placebo+MTX
- (4) ABT+DMARD vs. Placebo+DMARD
- (5) ABT+MTX vs. Placebo+MTX



- (1) ABT+MTX vs. Placebo+MTX
- (2) ABT+DMARD vs. Placebo+DMARD
- (3) ABT+MTX vs. Placebo+MTX



- (1) ABT+MTX vs. Placebo+MTX
- (2) ABT+MTX vs. Placebo+MTX
- (3) ABT+MTX vs. Placebo+MTX
- (4) ABT+MTX vs. Placebo+MTX

FIGURE 5 - Meta-analysis of withdrawals due to AE, SAE and a lack of efficacy (top, middle and bottom, respectively). ABT – abatacept; MTX – methotrexate. IV – inverse variance; CI – confidence interval.

Better efficacy after one year of treatment was observed for all of the considered parameters (ACR20, ACR50, ACR70, DAS28 \leq 3.2, DAS28 \leq 2.6, mean HAQ variation, and the proportion of patients who had an improvement of 0.3 or more in the HAQ scale). The lower efficacy of the control group was also observed in the results of the meta-analyses of the withdrawals due lack of efficacy.

Our meta-analyses included the results of studies involving patients with early RA and patients with a long disease duration (with a mean duration of disease varying from 3.2 years to 12.2 years).

The safety data showed no differences between the groups with regard to SAE, serious infections, malignancy and deaths. The results of the analysis of withdrawals due to AE confirm this data, as there were no significant differences between the groups. Some of the common AE, SAE and serious infections cited in the studies were nausea, upper respiratory tract infection, headache, flu syndrome, rash and injection site reaction (Weinblatt *et al.*, 2006; Westhovens *et al.*, 2009b).

Other meta-analyses (Singh *et al.*, 2009) have also shown benefits associated with the use of ABT instead of placebo (OR = 2.98 [1.79, 4.97]; RR = 1.03 (Zhang; Yu, 1998)), including six studies with a total of 1712 patients that considered ACR50 as the effectiveness outcome. The same study presented a value of OR equal to 1.24 [0.88, 1.76] (RR = 1.01 (Zhang; Yu, 1998)) for withdrawals due to AE; their meta-analysis included the same six studies but with a total of 1441 patients. Another meta-analysis presented similar results for the ACR50 (OR = 3.28 [2.44, 4.41]; RR = 1.04 (Zhang; Yu, 1998)) but used the Mantel-Haenszel method instead of the inverse variance method (Salliot *et al.*).

Only RCT were included in this study for the evaluation of outcomes. However, long-term observational studies can provide a more realistic long-term estimation of the outcomes, especially the safety-related ones, reflecting the risks of ABT in the "real world". RCT have insufficient numbers of patients and follow-up times to detect rare SAE.

This study included some important clinical outcomes, such as the ACR and DAS28; however, other relevant outcomes could not be analyzed (such as radiographic progression) because they were less often included in the reviewed RCT.

CONCLUSION

Our meta-analyses provided an updated comprehensive picture of the clinical efficacy, safety and tolerability of ABT, which presented a higher efficacy for all considered parameters (ACR20, ACR50, ACR70, DAS28 \leq 3.2,

DAS28 \leq 2.6, mean HAQ variation, and the proportion of patients who had an improvement of 0.3 or more in the HAQ scale) compared to placebo. However, there were no significant differences between the ABT and control groups in terms of safety and withdrawals due to AE and SAE. Furthermore, the ABT group presented fewer withdrawals due to lack of efficacy.

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