Greater remission rates in patients with early versus long-standing disease in biologic-naive rheumatoid arthritis patients treated with abatacept: a post hoc analysis of randomised clinical trial data

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Abstract

Objective

Current aim of rheumatoid arthritis (RA) treatment is to achieve remission in as many patients as possible. Rates of remission and clinical outcomes after treatment with abatacept in biologic-naive rheumatoid arthritis (RA) patients with early disease and an inadequate response to methotrexate (MTX) versus patients with ≥10 years of disease were assessed.

Methods

Data from two trials assessing the efficacy of abatacept in MTX inadequate responders were pooled for this exploratory post hoc analysis. Patients with disease duration of ≤2 years at baseline (early disease), originally assigned to an abatacept ≈10 mg/kg treatment arm and entered into a long-term extension (LTE), were compared with patients with ≥10 years of disease (long-standing RA). Remission, DAS28-CRP, ACR 70 responses and the Routine Assessment of Patient Index Data 3 (RAPID3), improvement in physical function as measured by the Health Assessment Questionnaire Disability Index (HAQ-DI).

Results

Twenty-three percent of these patients (n=108) had early disease. A higher percentage of patients with early disease achieved DAS28-CRP remission versus patients with long-standing disease (35.2% vs. 19.4% at year 1, p<0.01; 46.0% vs. 30.9% at year 3, p<0.05). In addition, a higher percentage of the subgroup with early RA achieved ACR70 responses. More patients with early RA had a meaningful improvement in their HAQ-DI (75.2% vs. 60.4%; p<0.05) and RAPID3 scores at one year (mean changes from baseline of -9.6 vs. -8.1; p=0.009)

Conclusions

These data provide additional support for the possible use of abatacept in biologic-naive patients who have had inadequate response to MTX, earlier in their disease course.

Key words

rheumatoid arthritis, abatacept, early arthritis, DAS28, RAPID3

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Abbreviations:
ACR: American College of Rheumatology
AIM: Abatacept in Inadequate Responders to Methotrexate
DAS28-CRP: 28-joint count Disease Activity Score using C-reactive protein
DMARD: disease-modifying anti-rheumatic drugs
HAQ-DI: Health Assessment Questionnaire Disability Index
LDAS: low disease activity score
LTE: long-term extension
mTSS: Genant-modified total Sharp score
MTX: methotrexate
TNF: tumour necrosis factor
RA: rheumatoid arthritis
RAPID3: Routine Assessment of Patient Index Data 3

Competing interests
Yusuf Yazici as been a consultant for Bristol-Myers Squibb, Celgene, Centocor, Genentech, Merck, Pfizer, Roche and UCB, and served on the speaker bureaus of Bristol-Myers Squibb and Genentech. Diane Moniz Reed, Christian Klem, Lisa Rosenblatt, and George Wu are full-time employees and stockholders in Bristol-Myers Squibb. Joel Kremer has been a consultant and speaker for Bristol-Myers Squibb and has also received grant support from Bristol-Myers Squibb for research activities.

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Introduction

The consequences of inadequately treated rheumatoid arthritis (RA) include severe functional decline, increased mortality, work disability, joint replacement surgery, and medical costs (1, 2). Studies have suggested that substantial and irreversible joint destruction already occurs within the first 2 years after disease onset (3, 4).

Although there is no cure for RA, most patients with early disease can be treated successfully, with some achieving increased remission rates compared with 10 to 15 years ago (5-10). The recognition of the potential for severe long-term disability and comorbidity in many patients supports the use of effective early therapeutic interventions to improve long-term outcomes (11, 12).

Abatacept is a biologic disease-modifying antirheumatic drug (DMARD) for the treatment of RA and JIA that selectively modulates the CD80/CD86: CD28 costimulatory signal required for full T-cell activation. The efficacy of abatacept in adult patients with an inadequate response to methotrexate (MTX) has been demonstrated as monotherapy and in combination with MTX (13-15). The phase 2b IM101-100 trial established the efficacy of abatacept in this patient population (15, 16), and the phase 3, randomised, double-blind, placebo-controlled Abatacept in Inadequate Responders to Methotrexate (AIM) trial confirmed the clinical benefits of abatacept in a larger population of patients with an inadequate response to MTX (14).

In the present study, data from these two double-blind, placebo-controlled trials were pooled for this exploratory post hoc analysis. The objectives of this analysis were to assess rates of remission, clinical outcomes, and x-ray progression after treatment with abatacept in biologic-naive RA patients with an inadequate response to MTX who have early disease (≤2 years duration) compared with the rates in patients with ≥10 years of disease (long-standing RA).

Methods

The details of the phase 2b and AIM trials have been published previously (14, 16). Briefly, all patients who enrolled in the long-term extension (LTE) portion of both AIM and the phase 2b trials received a fixed dose of abatacept ≈10 mg/kg in addition to background MTX. To be eligible for analysis, patients had to meet the following criteria: disease duration at baseline of ≤2 years (early disease, chosen as a common definition for early RA) or ≥10 years (long-standing RA), originally assigned to the abatacept 10 mg/kg treatment arm, and entered into the LTE.

Adjustments to background disease-modifying anti-rheumatic drugs (DMARDs) and other concomitant medications were permitted during the LTE portion at the discretion of the investigator, based on the clinical status of the patient.

Outcomes assessed at the end of years 1, 2, and 3 included American College of Rheumatology (ACR) responses, remission and low disease activity as defined by the 28-joint count Disease Activity Score using C-reactive protein (DAS28-CRP), improvement in physical function as measured by the Health Assessment Questionnaire Disability Index (HAQ-DI), and the Routine Assessment of Patient Index Data 3 (RAPID3), an index of only the patient-reported outcome measures of physical function, pain, and global assessment of disease activity that is scored on a scale of 0 to 30 (17).

Radiographic outcomes for patients from the AIM trial were available for the abatacept treatment group at baseline and at the end of years 1, 2, and 3. Genant-modified Sharp scores for joint space narrowing, erosions, and the total were determined for patients with early RA and those with long-standing disease.

Statistical analysis

Statistical methods used in the AIM and phase 2b studies have been previously described (14, 16). In this study, all efficacy analyses were performed based on the as-observed data, *i.e.* data available for the specified parameter at years 1, 2, and 3, except for the radiographic analysis. All statistical tests were based on a two-sided 5% level of significance, and all analyses were performed using

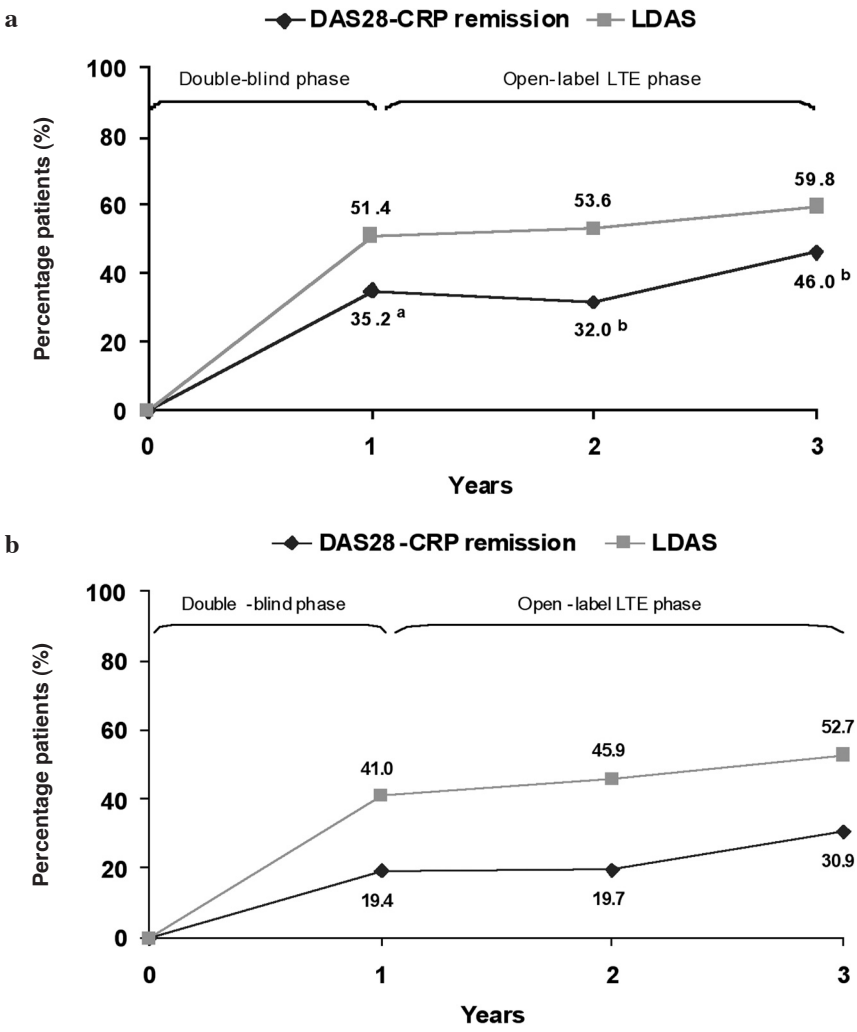

Fig. 1. Remission rates in patients with early or long-standing RA treated with abatacept. Percentage of abatacept-treated patients with early rheumatoid arthritis (RA) (**a**) or long-standing RA (**b**) who were in remission (dark diamonds) or had a low disease activity score (LDAS, light squares), measured at baseline through year 3. Remission defined as 28-joint count Disease Activity Score using C-reactive protein (DAS28-CRP) <2.6; LDAS defined as DAS28-CRP <3.2. [a]$p<0.01$; [b]$p<0.05$, both *versus* long-standing RA. LTE = long-term extension. The patients available for analysis at each time point are shown in the table below:

	LDAS		DAS < 2.6	
	≤2	≥10	≤2	≥10
Year 1, n	105	139	105	139
Year 2, n	97	122	97	122
Year 3, n	87	110	87	110

Table I. Characteristics of patients with early rheumatoid arthritis (RA) (≤2 years) or long-standing RA (≥10 years) who entered the long-term extension (LTE) of the phase 2b and phase 3 (AIM) trials of abatacept in patients with an inadequate response to MTX, and who met the inclusion criteria for this study. All patients were in the abatacept ≈10-mg/kg active therapy groups. With the exception of duration of disease, all baseline clinical characteristics were similar between the two groups. SD: standard deviation; DAS28-CRP: 28-joint count Disease Activity Score using C-reactive protein; CDAI: clinical disease activity index; RAPID3: Routine Assessment of Patient Index Data 3; HAQ-DI: Health Assessment Questionnaire Disability Index; VAS: visual analogue scale.

	Early RA (n=108)	Long-standing RA (n=159)
Age (years), mean ± SD	50.3 ± 13.4	55.4 ± 12.1
Female gender (%)	75.9	76.1
Disease duration (years), mean ± SD	1.2 ± 0.66	17.5 ± 6.87
DAS28-CRP, mean ± SD	6.3 ± 0.76	6.4 ± 0.82
CDAI, mean ± SD	44.4 ± 12.4	46.4 ± 11.7
RAPID3, mean ± SD	17.2 ± 0.54	17.6 ± 0.44
Tender joints, mean ± SD	30.7 ± 12.1	30.6 ± 13.2
Swollen joints, mean ± SD	21.4 ± 8.6	21.5 ± 9.4
HAQ-DI, mean ± SD	1.5 ± 0.66	1.6 ± 0.68
Pain (100-mm VAS), mean ± SD	60.0 ± 21.2	62.4 ± 20.2
Patient global assessment (100-mm VAS), mean ± SD	64.0 ± 20.9	61.2 ± 21.54
Physician global assessment (100-mm VAS), mean ± SD	64.0 ± 16.0	68.1 ± 15.1
Rheumatoid factor positive (%)	82.2	93.3
CRP level (mg/L), mean ± SD	33.0 ± 31.0	31.2 ± 28.0

SAS software, version 8.2 (SAS Institute, Cary, North Carolina).

The radiographic analyses included all observed data at baseline and at years 1, 2, and 3. Missing annual radio-graphic data were imputed with linear extrapolation for discontinued subjects, provided these subjects had data available at baseline and for at least 1 post-treatment time point prior to discontinuation. Summary statistics and a cumulative probability plot were generated for changes from baseline in the Genant-modified Sharp scores at years 1, 2, and 3 by disease duration cohort assignment.

Results

Of the 616 patients who were randomised to the abatacept 10 mg/kg treatment arms in the phase 2b and AIM trials, 462 enrolled in the LTE period (75% of randomised patients

who completed the double-blind phase). Twenty-three percent of these patients (n=108) had early disease (mean disease duration 14±8 months; Table I), 34% had long-standing disease (mean disease duration 17.5±6.87 years; Table I). The clinical characteristics of this early RA patient population are reported in Table I and reflect study participants with moderate-to-severe RA. With the exception of disease duration (1.2 versus 17.5 years), baseline characteristics were similar between the early RA cohort and the long-standing RA comparator cohort (subjects with disease duration ≥10 years). As would also be expected, the mean age of the early RA cohort was approximately 5 years younger than the cohort with long-standing disease (Table I).

Patients with early RA were significantly more likely to achieve DAS28-CRP remission *versus* patients with long-standing disease at year 1 (35.2% in remission *vs*. 19.4%; $p<0.01$; Fig. 1A), year 2 (32.0% in remission *vs*. 19.7%; $p<0.05$), and year 3 (46.0% in remission *vs*. 30.9%; $p<0.05$). A greater percentage of patients with early RA achieved low disease activity (DAS28-CRP <3.2) compared with patients who had long-standing disease duration (Fig. 1B).

A high percentage of study participants with early RA also attained significant clinical response as measured by ACR70 response criteria, with statistically significantly higher percentage of ACR70 responders at both year 1 and year 3 for the early RA cohort versus those with long-standing disease (36.8% *vs*. 25.0% at year 1, and 44.3% *vs*. 30.4% at year 3, $p<0.05$ for both comparisons; Fig. 2A and 2B). In addition, the percentage of patients who achieved ACR50 response criteria also tended to be higher for those with early RA.

In this sub-analysis, the change in RAPID3 scores from baseline was significantly greater at year 1 in patients with early RA treated with abatacept *versus* patients with long-standing disease treated with abatacept (mean change from baseline of -9.6 *vs*. -8.1; $p=0.009$). Furthermore, there was a trend for sustained greater benefit of abatacept treatment in the early RA patients compared with patients with long-standing disease as measured by RAPID3 scores at years 2 and 3.

Despite similar levels of functional disability at baseline as measured by the HAQ-DI, significantly more patients with early RA had a clinically meaningful improvement (HAQ-DI ≥0.3 unit) in their HAQ-DI scores at year 1 compared with the established RA cohort (assessed as the percentage of patients achieving an improvement of ≥0.3 in the HAQ-DI, exceeding the minimum clinically important difference of ≥0.22 (18)).

Radiographic progression was assessed in the subset of patients from these cohorts who participated in the AIM trial using the Genant-modified Sharp scoring system. In patients with early RA and patients with long-standing disease, abatacept therapy in combination with MTX resulted in progressively smaller increases in radiographic scores at each of the three years in this analysis, suggesting that abatacept may have an increasing disease-modifying effect on

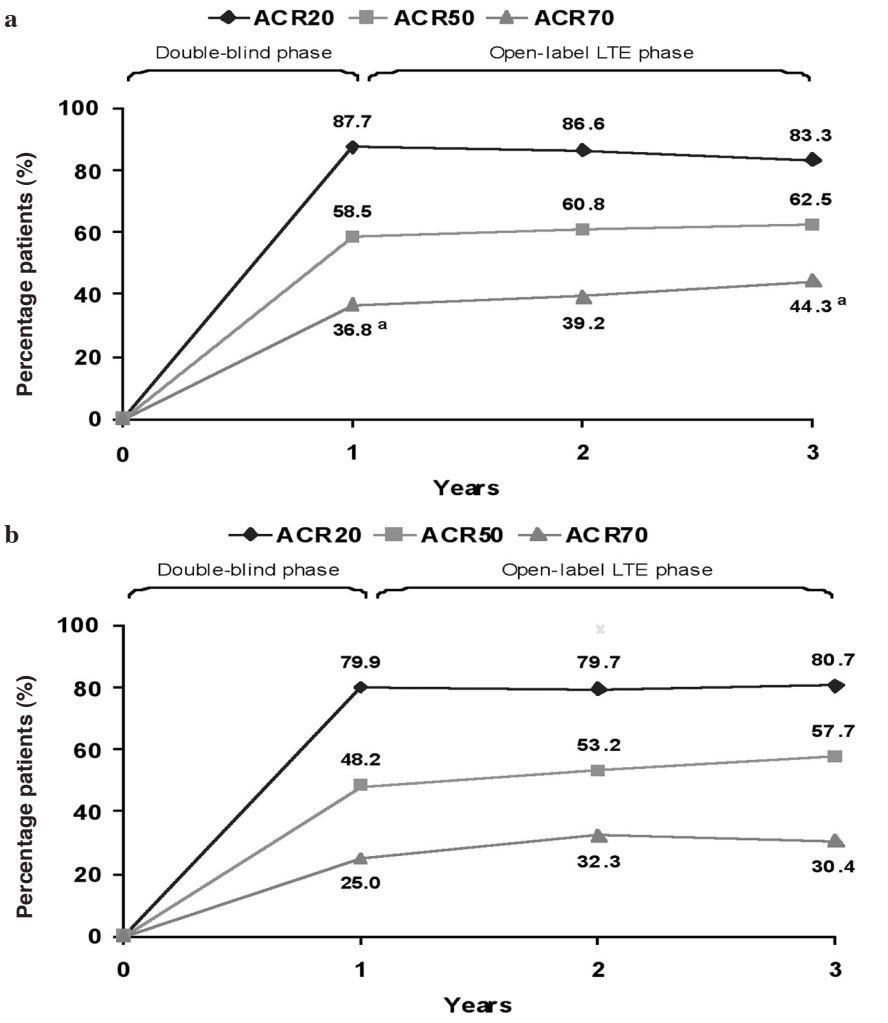

Fig. 2. ACR response in patients with early or long-standing RA treated with abatacept. Percentage of abatacept-treated patients with early RA (**a**) or long-standing RA (**b**) who achieved ACR20 (dark diamonds), ACR50 (light squares), and ACR70 (dark triangles) response criteria, measured at baseline through year 3. [a]P<0.05, both *versus* long-standing RA. The patients available for analysis at each time point are shown in the table below:

	ACR 20		ACR 50		ACR 70	
	≤ 2	≥ 10	≤ 2	≥ 10	≤ 2	≥ 10
Year 1, n	106	139	106	139	106	140
Year 2, n	97	123	97	124	97	124
Year 3, n	88	108	81	111	88	112

Table II. Mean Genant-modified total Sharp score (mTSS) at baseline, and mean changes in mTSS at years 1, 2, and 3 for abatacept-treated patients with early RA or long-standing RA.

	Mean mTSS (SD)	
	RA duration ≤2 years (n=73)	RA duration ≥10 years (n=100)
Baseline	23.8 (21.3)	69.8 (38.1)
Δ Year 1	1.07 (2.04)	0.60 (1.24)
Δ Year 2	0.54 (1.30)	0.46 (1.14)
Δ Year 3	0.22 (1.11)	0.13 (0.94)

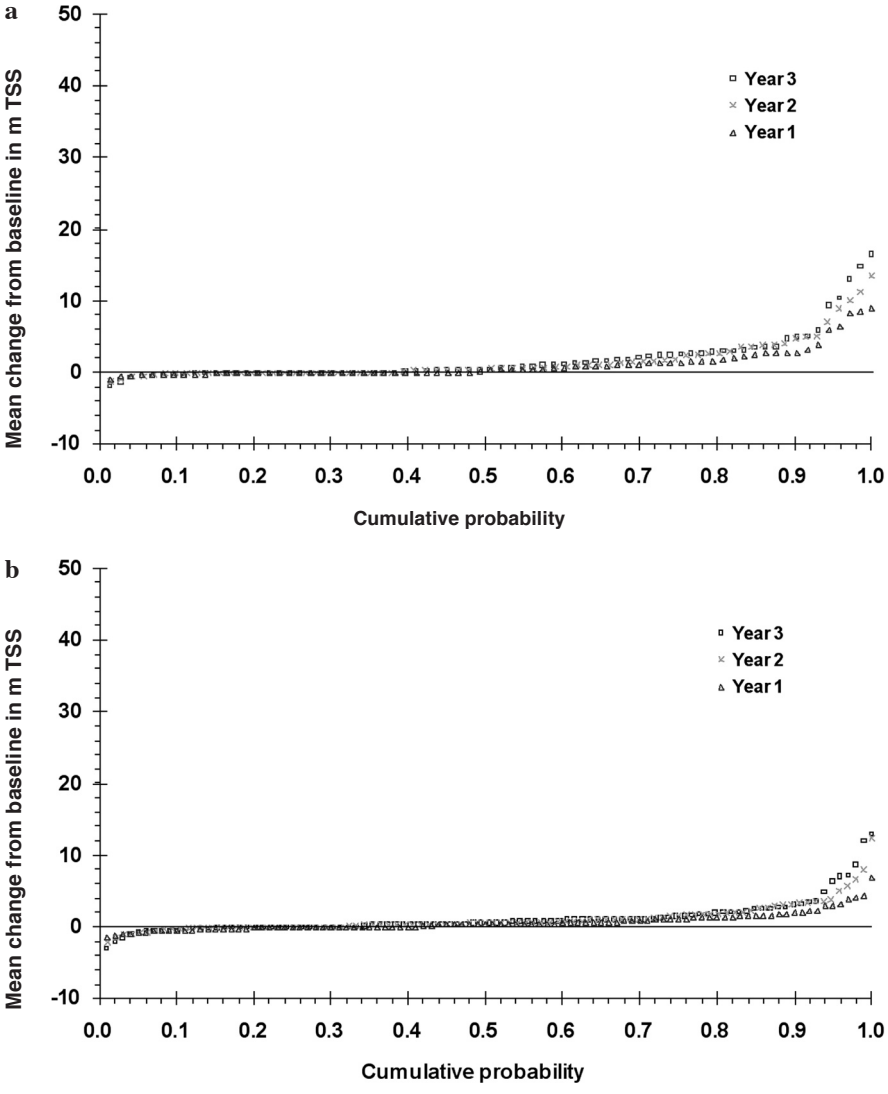

Fig. 3. Change in radiographic score in patients with early or long-standing RA treated with abatacept. Cumulative distribution of mean changes from baseline in Genant-modified total Sharp Scores (mTSS) for abatacept-treated patients with early RA (**a**) and long-standing RA (**b**) at years 1, 2, and 3. All radiographic data were obtained from participants in the active therapy group of the phase 3 (AIM) trial of abatacept in patients with an inadequate response to MTX.

structural damage over time (Table II). This benefit occurred in both groups, despite patients with long-standing disease having higher Genant-modified total Sharp scores at baseline compared with patients who had disease duration of 2 years or less (69.8 *vs*. 23.8, respectively). The cumulative distributions of changes in Genant-modified total Sharp scores (mTSS) are also similar for both treatment groups (Fig. 3) and are similar to previously reported results for the total population of patients treated with abatacept in the AIM study (19).

Discussion

The purpose of this post hoc analysis was to assess rates of remission and clinical outcomes after treatment with abatacept in biologic-naive RA patients with early disease (≤2 years) and an inadequate response to MTX, and compare these rates with those in patients with longer disease duration (≥10 years). The objective was to see if disease duration at the time of abatacept initiation made a difference in clinical response in this secondary analysis of randomised clinical trial dataset.

The group of patients with early RA had significantly higher rates of remission compared with those with long-standing disease, despite the fact that these trials were not powered to detect differences in these subsets, suggesting that the data are likely robust and the effect represents true differences in treatment response.

Greater improvements were observed in clinical measures of low disease activity (ACR70), patient-reported outcomes (RAPID3 index), and physical disability (HAQ-DI) in the early RA cohort compared to the long standing disease cohort. Radiographic measures of structural damage progression demonstrated that abatacept in combination with MTX inhibits the progression of structural damage in RA patients with both early and long-standing disease.

It should be noted that the early RA cohort analysed here was small, and neither the phase 2b trial nor the AIM trial was originally designed or powered to answer the questions asked in this subanalysis. There are several other limitations inherent in this type of analysis. The subgroups were not generated by random assignment, and although the baseline clinical disease characteristics appear similar, the sub-groups may not have had uniform disease characteristics and disease prognosis. Finally, the data analysed were as observed and, despite high completion rates (approximately 80%), may not reflect the full range of patient populations with early RA (20, 21). These factors must be considered when interpreting the results (22). However, the recent

report of the efficacy of abatacept in an early disease population provides support to the findings reported here (23).

In conclusion, RA patients with early disease (≤2 years duration) in this study appear to have more significant improvement in their disease activity compared with patients with long-standing disease (≥10 years), with about half of the patients in DAS28-CRP remission at 3 years. Taken together, these data may provide additional support for the use of abatacept in biologic-naive RA patients with early disease who have had an inadequate response to MTX.

Authors' contributions

YY helped design the analysis, interpret the data, and helped draft the manuscript. DMR helped design the analysis, interpret the data, and helped drafted the manuscript. CK helped design the analysis, interpret the data, and helped draft the manuscript. LR helped design the analysis, interpret the data, and helped draft the manuscript. GW analysed and interpreted the data and helped draft the manuscript. JMK helped design the study, collect and interpret the data, and helped draft the manuscript. All authors read and approved the final manuscript.

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