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CONCISE REPORT

Maintenance of remission following 2 years of standard treatment then dose reduction with abatacept in patients with early rheumatoid arthritis and poor prognosis

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ABSTRACT

Objectives To evaluate maintenance of response while reducing intravenous abatacept dose from ~10 mg/kg to ~5 mg/kg in patients with early rheumatoid arthritis (RA) who achieved disease activity score (DAS)28 (erythrocyte sedimentation rate, ESR) <2.6.

Methods This 1-year, multinational, randomised, double-blind substudy evaluated the efficacy and safety of ~10 mg/kg and ~5 mg/kg abatacept in patients with early RA with poor prognosis who had reached DAS28 (ESR) <2.6 at year 2 of the AGREE study. The primary outcome was time to disease relapse (defined as additional disease-modifying antirheumatic drugs, ≥2 courses high-dose steroids, return to open-label abatacept ~10 mg/kg, or DAS28 (C reactive protein) ≥3.2 at two consecutive visits).

Results 108 patients were randomised (~10 mg/kg, n=58; ~5 mg/kg, n=50). Three and five patients, respectively, discontinued, and four per group returned to open-label abatacept. Relapse over time and the proportion of patients relapsing were similar in both groups (31% (~10 mg/kg) vs 34% (~5 mg/kg); HR: 0.87 (95% CI 0.45 to 1.69)). Mean steady-state trough serum concentration for the ~10 mg/kg group was 20.3–24.1 μg/mL, compared with 8.8–12.0 μg/mL for the ~5 mg/kg group.

Conclusions This exploratory study suggests that abatacept dose reduction may be an option in patients with poor prognosis early RA who achieve DAS28 (ESR) <2.6 after ≥1 year on abatacept (~10 mg/kg).

Trial registration number NCT00989235.

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INTRODUCTION

Current recommendations support the use of biological disease-modifying antirheumatic drugs (DMARDs) in combination with methotrexate (MTX) in patients with rheumatoid arthritis (RA) who have responded insufficiently to conventional synthetic DMARDs.[1] [2] However, studies in DMARD-naïve patients with early RA have demonstrated the superiority of biological DMARDs plus MTX compared with MTX alone,[3–6] especially in patients at high risk of progression of structural damage. This creates a challenge for the rheumatologist, concerning the appropriate use of biologics while maximising cost-effectiveness and therapeutic benefit.[7]

Drug-free remission remains a therapeutic goal in RA. In established RA, withdrawal of biological therapy generally leads to loss of remission for the majority of patients.[8] [9] However, dose reduction is a feasible strategy for some patients as shown in the PRESERVE study.[10] In early RA, withdrawal of biological treatment is possible.[11–13] However, withdrawal of all therapies is less successful.[14] [15] In early RA, dose reduction is possible for the large majority of patients.[14]

There is also evidence that early biological intervention may alter the course of RA. In the ADJUST (Abatacept study to Determine the effectiveness in preventing the development of rheumatoid arthritis in patients with Undifferentiated inflammatory arthritis and to evaluate Safety and Tolerability) study, 26 patients with undifferentiated arthritis or early RA (American College of Rheumatology 1987 criteria)[16] received intravenous abatacept monotherapy (~10 mg/kg) or placebo for 6 months. Progression to RA was delayed for up to 1 year in 54% of patients treated with abatacept (vs 33% of patients treated with placebo) and inhibition of joint damage was maintained.[17] These findings suggest that initiating selectively modulating T cell therapy at an early stage could alter the course of RA.

The objective of this substudy of the AGREE (Abatacept trial to Gauge Remission and joint damage progression in methotrexate-naive patients with Early Erosive rheumatoid arthritis) trial[6] was to evaluate the impact on disease activity of reducing the dose of intravenous abatacept from the approved monthly dose of ~10 mg/kg to ~5 mg/kg, in patients who had achieved disease activity score (DAS)28 (erythrocyte sedimentation rate, ESR) of <2.6 at year 2 of treatment.

PATIENTS AND METHODS
Patients

Of the 87 sites that had enrolled patients in the initial 2-year, randomised AGREE study, 35 sites enrolled patients in the AGREE substudy. The AGREE study included patients who were MTX-naïve with early (≤2 years), erosive, seropositive RA.[6] To enter the substudy, patients were required to have achieved DAS28 (ESR) <2.6 at year 2 (day 701) of the main study and to reaffirm their informed consent.

Study design

The substudy was a 12-month, multicentre, randomised, double-blind, two-arm, parallel-dosing study (NCT00989235). Patients were randomised (1:1) to receive intravenous abatacept monthly at doses of ∼10 mg/kg or ∼5 mg/kg based on weight range. No dose adjustments were allowed. Concomitant medication was kept stable and selected conventional synthetic DMARDs were permitted. If a patient had an increase in disease activity, concomitant DMARDs or corticosteroids could be modified or the patient could discontinue the double-blind study and resume open-label intravenous abatacept ∼10 mg/kg.

DAS28 (ESR) was used for enrolment criteria, whereas DAS28 (C reactive protein, CRP) was used for all disease activity assessments, including baseline measurements (to reflect the AGREE study).

Assessments

The primary end point was the time to disease relapse (defined as additional DMARD required, or ≥two courses of high-dose steroids, or requirement for open-label intravenous abatacept ∼10 mg/kg, or DAS28 (CRP) ≥3.2 at two consecutive visits) and was presented as Kaplan-Meier cumulative percentage of events of disease relapse. Secondary end points included disease activity measured by DAS28 (CRP); proportion of patients who at any time modified therapy and/or had two consecutive DAS28 (CRP) scores ≥3.2 (therapy modification included additional DMARD required, ≥two courses of high-dose steroids, and return to open-label intravenous abatacept ∼10 mg/kg); proportion of patients who lost remission status at any time (defined as DAS28 (CRP) ≥2.6); safety and tolerability; quarterly steady-state trough serum concentrations (C_{min}) of abatacept; and quarterly immunogenicity (antiabatacept antibodies). Physical function was determined quarterly using the Health Assessment Questionnaire–Disability Index (HAQ-DI).

Statistical analysis

A specific power calculation was not performed. All patients receiving at least one dose of abatacept were evaluated monthly. The time to disease relapse was evaluated in a Kaplan-Meier curve (Cox proportional hazards model); mean changes in DAS28 (CRP) and HAQ-DI from baseline were determined together with 95% CIs for adjusted treatment difference; last observation carried forward method was used to impute missing day 365 values; and scores and/or missing values for patients who modified therapy were imputed using the last assessment prior to the first occurrence of intervention therapy. The proportion of patients who reached each relapse component or who lost remission status were evaluated using 95% CI for treatment difference; pharmacokinetics were evaluated using geometric mean and percentage coefficient of variation for C_{min}.

RESULTS

Patient disease characteristics are summarised in table 1. Mean DAS28 (CRP) at baseline was 2.1 in each group. Over the 12-month follow-up period, three patients discontinued treatment in the ∼10 mg/kg group compared with five patients in the ∼5 mg/kg group; of these, one patient discontinued due to lack of efficacy (abatacept ∼10 mg/kg group) and one patient discontinued due to an adverse event (abatacept ∼5 mg/kg group, endocarditis; figure 1).

The same number of patients (n=4) in each group returned to open-label intravenous abatacept ∼10 mg/kg (table 2). Of the four patients in the ∼5 mg/kg group who returned to open-label abatacept ∼10 mg/kg, three had regained DAS28 (CRP) <2.6 by month 12. Therapy was modified by more patients in the ∼5 mg/kg group than in the ∼10 mg/kg group; no patients in either group required concomitant high-dose corticosteroids (table 2). The Kaplan-Meier curves of relapse over time (figure 2) and the proportions of patients experiencing relapse over 12 months were similar in both groups (table 2; ∼10 mg/kg vs ∼5 mg/kg; HR: 0.87; 95% CI 0.45 to 1.69).

Changes in DAS28 (CRP) and the proportions of patients who lost DAS28 (CRP)-defined remission status were similar between groups at month 12 (table 2). Changes in the HAQ-DI score from baseline to month 12 were −0.07 in the ∼10 mg/kg group and 0.06 in the ∼5 mg/kg group.

Safety results were comparable between the two dosing groups. One death occurred (∼5 mg/kg group, acute cardiopulmonary failure). Serious adverse events were reported in three patients in the ∼10 mg/kg group (claw toe, appendicitis, pleurisy) and in three patients in the ∼5 mg/kg group (RA flare, uncontrolled diabetes mellitus, acute renal insufficiency, leucopenia, neutropenia and endocarditis (all in the same patient); osteoarthritis and acute cardiopulmonary insufficiency (in one patient); and RA flare). Infections were observed in 22 (37.9%) patients in the ∼10 mg/kg group and 13 (26.0%) in the ∼5 mg/kg group.

Table 1 Patient baseline demographics and disease characteristics

	Double-blind abatacept ∼10 mg/kg	Double-blind abatacept ∼5 mg/kg	Total
Number of patients treated	58	50	108
Age, years, mean (SD)	50.1 (11.5)	51.1 (13.4)	50.6 (12.3)
Female	44 (75.9)	41 (82.0)	85 (78.7)
White	49 (84.5)	46 (92.0)	95 (88.0)
Duration of RA,* mean (SD)	2.2 (0.4)	2.4 (0.5)	2.3 (0.5)
TJC, mean (SD)	1.4 (2.5)	1.1 (1.5)	1.3 (2.1)
SJC, mean (SD)	0.7 (1.4)	0.5 (1.1)	0.6 (1.2)
HAQ-DI, mean (SD)	0.5 (0.5)	0.6 (0.6)	0.6 (0.5)
Patient global assessment, mean (SD)	14.3 (16.8)	16.3 (12.9)	15.3 (15.0)
DAS28 (CRP), mean (SD)	2.1 (0.6)	2.1 (0.6)	2.1 (0.6)
CRP mg/dL, mean (SD)	0.5 (0.6)	0.5 (0.5)	0.5 (0.5)

Data are n (%), unless otherwise indicated.
*At the start of the sub-study.
CRP, C reactive protein; DAS, disease activity score; HAQ-DI, Health Assessment Questionnaire–Disability Index; RA, rheumatoid arthritis; SJC, swollen joint count; TJC, tender joint count.
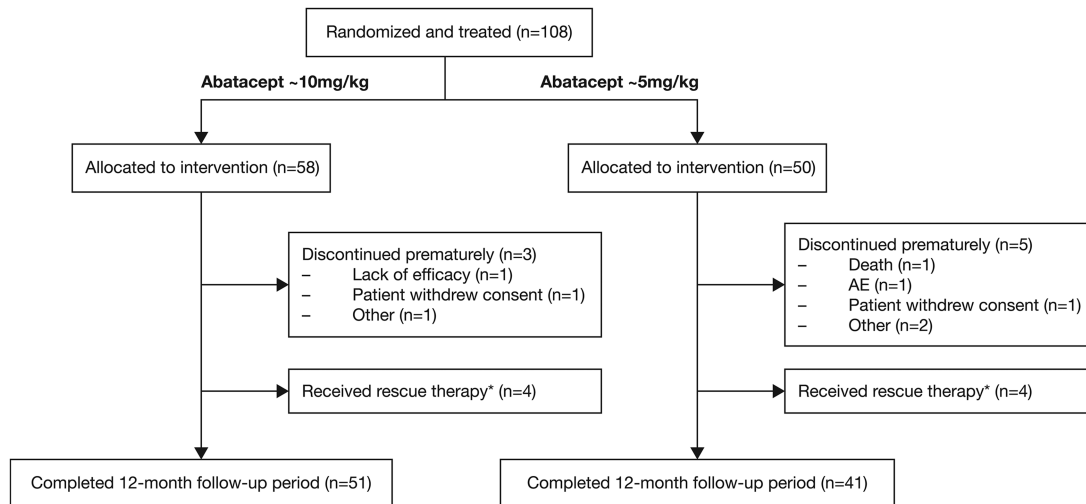
Figure 1 Patient disposition. *Open-label ~10 mg/kg abatacept. AE, adverse event.

Peri-infusional reactions (all mild-to-moderate) were seen in five and two patients, respectively. Two autoimmune events (episcleritis and Sjögren's syndrome) and one mild infusional reaction occurred (all in the ~5 mg/kg group).

In the reduced abatacept dose group (~5 mg/kg), consistent C_{min} was achieved between month 3 and month 6, with geometric mean C_{min} ranging from 8.8 μg/mL to 12.0 μg/mL; the range was 20.3 μg/mL to 24.1 μg/mL during follow-up in the ~10 mg/kg abatacept group. Six of 105 (5.7%) patients developed positive responses for antiabatacept antibodies assay (four in the ~10 mg/kg group; two in the ~5 mg/kg group); five were positive for anticytotoxic T lymphocyte antigen 4 and possibly immunoglobulin antibodies and one was positive for immunoglobulin and/or junction region antibodies.

DISCUSSION

Data from this substudy in MTX-naïve patients with early RA and poor prognosis, who had achieved DAS28 (ESR) <2.6 after 2 years of monthly abatacept (~10 mg/kg) plus MTX in the AGREE trial, demonstrate that reduced disease activity can be maintained in some patients after reducing the dose of abatacept from the approved monthly intravenous dose of ~10 mg/kg to ~5 mg/kg. There was no significant increase in disease activity, and few patients required additional DMARDs or return to open-label ~10 mg/kg abatacept. As such, the findings support those from the PRIZE study, with most patients maintaining remission following biological dose reduction.[14]

Systemic exposure was approximately 50% lower in the abatacept ~5 mg/kg group compared with the ~10 mg/kg group, which is consistent with the linear pharmacokinetic profile of abatacept.[18] Published steady-state mean (range) C_{min} values, following administration of the approved monthly intravenous dose, are 24 (1–66) μg/mL.[19] Despite lower exposure in the ~5 mg/kg group, approximately 50% of patients maintained C_{min} at ~10 μg/mL (associated with maximal inhibition of T cell proliferation and cytokine production).[20] Lower drug exposure in the ~5 mg/kg group did not appear to increase the risk of immunogenicity. In general, the number and type of safety events were as expected based on previous reports,[21] and did not differ between groups.

These findings should be interpreted with some caution owing to the small sample size and the fact that the population included only those patients with early RA who had achieved remission after 2 years of treatment with abatacept (~10 mg/kg).

Table 2 Summary of efficacy results

	Double-blind abatacept ~10 mg/kg (n=58)	Double-blind abatacept ~5 mg/kg (n=50)
Patients experiencing disease relapse	18 (31.0)	17 (34.0)
Patients with two consecutive DAS28 (CRP) scores ≥3.2	13 (22.4)	11 (22.0)
Patients with modified therapy	6 (10.3)	9 (18.0)
Additional DMARD	2 (3.4)	6 (12.0)
High-dose steroids	0	0
Return to open-label ~10 mg/kg abatacept	4 (6.9)	4 (8.0)
Patients losing remission status*	31 (53.4)	32 (64.0)
DAS28 (CRP) mean change from baseline (SE)†	0.27 (0.10)	0.25 (0.11)
Physical function (HAQ-DI) mean change from baseline (SE)†	−0.07 (0.04)	0.06 (0.05)

Data are n (%), unless otherwise indicated.
*Defined as DAS28 (CRP) ≥2.6 at any time point.
†LOCF analysis: missing day 365 values were imputed using the LOCF method. For patients with modified therapy, scores and/or missing values were imputed using the last assessment prior to the first occurrence of intervention therapy. N values for DAS28 (CRP) mean changes were 50 and 43, and for HAQ-DI were 54 and 45, for abatacept ~10 mg/kg and ~5 mg/kg, respectively.
CRP, C reactive protein; DAS, disease activity score; DMARD, disease-modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire–Disability Index; LOCF, last observation carried forward.

Figure 2 Kaplan-Meier curve of time to disease relapse. ABA, abatacept.
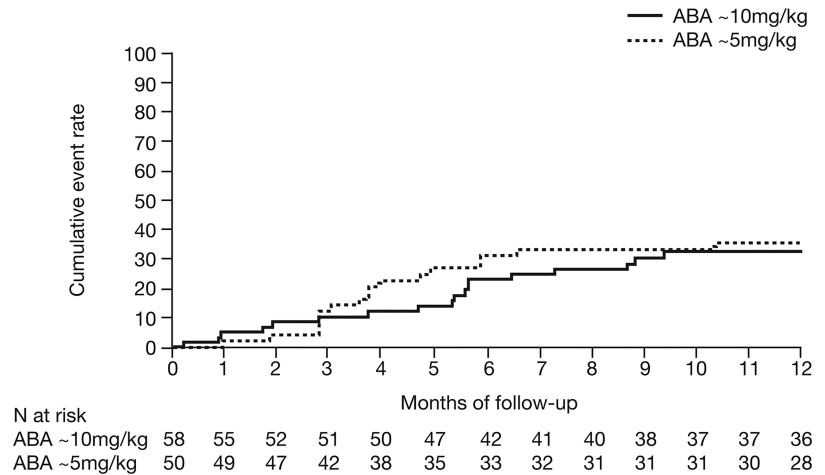
In addition, this study was designed before acceptance of the more stringent remission criteria proposed by the American College of Rheumatology and European League Against Rheumatism; the DAS28 (CRP) criteria were used in the sub-study for consistency with the original AGREE study primary end point. Another limitation was the use of two different DAS28 measures: DAS28 (ESR) to aid rapid determination of patient eligibility, and DAS28 (CRP) for all other disease activity assessment.

In summary, considering the potential to alter the course of disease in some patients with early RA, along with the safety and health economic benefits in avoiding unnecessary drug exposure, timely induction of biological agents (preferably in combination with MTX), followed by dose reduction, might be a therapeutic option in patients with early RA who have achieved DAS28 <2.6, and deserves further investigation.

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protocol of the study and helped in the interpretation of the data. BM helped in the interpretation of the data.

Competing interests RW has received speaker fees and research grants from Bristol-Myers Squibb, research grants from Roche, consulting fees from Janssen, and non-financial support (clinical trial advice) from Galapagos. MR, ACX and S-HP have no conflicts of interest to disclose. JW has received consultancy fees from AbbVie, Bristol-Myers Squibb, Chugai, MSD, Pfizer and UCB. PD, JG-R and WS have received speaker fees from Bristol-Myers Squibb. WG has received speaker and consultancy fees from AbbVie, Bristol-Myers Squibb, General Electric Medical Systems, Menarini, MSD, Pfizer, Savient and UCB. BH has received fees for advisory boards from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Roche and UCB, and consultant fees from Pfizer. HG has received consultant and/or scientific advisory board fees from Bristol-Myers Squibb, Amgen, Merck, Pfizer, Janssen, Lilly, Servier, Daiichi and Synarc. CP has received speaker's bureau fees from Amgen and is the founder and CEO of Spire Sciences, which provides central image analysis services for clinical trials to multiple pharmaceutical companies. J-CB has received consultant fees from Pfizer, and is a former employee of Bristol-Myers Squibb. BM is an employee of Bristol-Myers Squibb.

Patient consent Obtained.

Ethics approval The protocol and patients' informed consent received institutional review board/independent ethics committee approval, and the study was conducted in accordance with the Declaration of Helsinki and was consistent with the International Conference on Harmonisation Good Clinical Practice. Comite de Etica em Pesquisa do Instituto de Assistencia Medica ao Servidor Publico Estadual Avenida Ibirapuera, Sao Paulo, Brazil; Comite de Etica em Pesquisa Humana e Animal do Hospital Geral de Goiania Avenida Anhanguera, N., 6479—Setor Oeste Goiania, Brazil; Comite de Etica em Pesquisa do Hospital Heliopolis Rue Conego Xavier, Sao Paulo, Brazil; Comite de Etica em Pesquisa do Hospital Universitario Pedro Ernesto Universidade do Estado do, Rio de Janeiro, Brazil; C.C.P.P.R.B. Montpellier Saint Eloi Hopital Saint Eloi, Montpellier, France; Schulman Associates I.R.B., Inc., Cincinnati, OH, USA; Institute of Rheumatology, Russian Academy of Medical Science, Ethics Commitee at State Office, Institute of Rheumatology R.A.M.S., Moscow, Russian Federation; Ethics Committee at the Federal Agency for Control of Quality, Moscow, Russian Federation; Comite de Etica em Pesquisa do Pontifícia Universidade Catolica do Rio Grande, do Rio Grande do Sul, Brazil; Hospital Universitario Virgen Macarena C.E.I.C. Unidad De Investigación, Sevilla, Spain; E. C. Regional De Cantabria, Hospital Univ. Marques De Valdecilla, Santander, Spain; Comite Etico De Investigacion Clinica De Galicia (Sergas), Division de Farmacia y Productos Sanitarios Edificio Administrativo San Lazaro, Santiago De Compostela, A Coruna, Spain; Hanyang University Medical Center Institutional Review Board, Seoul, Republic of Korea; Institutional Review Board, Asan Medical Center, Songpa-Gu, Seoul, Republic of Korea; Eulji University Hospital, Seogu, Daejeon, Republic of Korea; Centro Medico Toluca, Barrio San Mateo, Metepec, Mexico; Comite De Etica, Col. Reforma, Toluca, Mexico; Comite Etico Hospital General, Col. Centro Morelia, Michioacan, Mexico; Komisja Bioetyczna Przy, Instytucie Reumatologiczynm, Warszawa, Poland; Hospital Regional I.S.S.S.T.E. Leon, Departura de Ensenanza y Investigacion, Guanajuazo, Mexico; Commissie Medische Ethiek, Universitaire Ziekenhuizen K. U. Leuven Campus, Leuven, Belgium; Commission D'Ethique Biomedicale Hospitalo-Facultaire, Bruxelles, Belgium; Commissie Medische Ethiek, Universitaire Ziekenhuizen K. U. Leuven Campus, Leuven, Belgium; Internal Review Board Services, Aurora, Ontario, Canada; Comite

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