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

Permalink
https://escholarship.org/uc/item/5dk7b5x4

Journal
Annals of the rheumatic diseases, 74(3)

ISSN
0003-4967

Authors
Westhovens, Rene
Robles, Manuel
Ximenes, Antonio Carlos
et al.

Publication Date
2015-03-01

DOI
10.1136/annrheumdis-2014-206149

Peer reviewed
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

Rene Westhovens, 1 Manuel Robles, 2 Antonio Carlos Ximenes, 3 Jurgen Wollenhaupt, 4 Patrick Durez, 5 Juan Gomez-Reino, 6 Walter Grasso, 7 Boulos Haraoui, 8 William Shergy, 9 Sung-Hwan Park, 10 Harry Genant, 11 Charles Peterfy, 12 Jean-Claude Becker, 13 Bindu Murthy 14

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 (DAS28) (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.

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, 3–8 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. 9

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. 3–5 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-naïve patients with Early Erosive rheumatoid arthritis) trial 18 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 (DAS28) (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. 7 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\text{min}) of abatacept; and quarterly immunogenicity (anti-abatacept 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\text{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.
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 group. Six of 105 (5.7%) patients developed positive responses for antabatacept 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. 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. Published steady-state mean (range) C_min values, following administration of the approved monthly intravenous dose, are 24 (1–66) μg/mL. 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). 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, 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 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.
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.

**Author affiliations**

1Skeletal Biology and Engineering Research Center, Department of Development and Regeneration KU Leuven, Rheumatology, University Hospitals Leuven, Leuven, Belgium
2Centro Médico Toluca, Metepec, México
3Hospital Geral de Goiânia, Goiânia, Brazil
4Schoen Klinik Hamburg Eilbek, Hamburg, Germany
5Service et Pôle de Rhumatologie, Cliniques Universitaires Saint-Luc, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium
6Hospital Clínico Universidad De Santiago, A Coruña, Spain
7Clinica Reumatologica, Università Politecnica delle Marche, Ancona, Italy
8Institut de Rhumatologie de Montréal, Montréal, Quebec, Canada
9University of Alabama, Huntsville, Alabama, USA
10The Catholic University of Korea, Seoul, South Korea
11University of California, San Francisco/Synarc, San Francisco, California, USA
12Spire Sciences, Inc., Boca Raton, Florida, USA
13Becker Clinical Research Consulting LLC, New York, New York, USA
14Bristol-Myers Squibb, Princeton, New Jersey, USA
15Bristol-Myers Squibb, Princeton, New Jersey, USA for her help in analysing the study data and Roy Helfrick (Bristol-Myers Squibb, Princeton, New Jersey, USA) for his role as study protocol manager. Professional medical writing and editorial assistance was provided by Laura McDonagh of Caudex Medical and was funded by Bristol-Myers Squibb.

**Contributors**

All authors revised the manuscript for important intellectual content, approved the final version and are accountable for all aspects of the work. In addition: RW recruited patients, performed the study, contributed to the elaboration of the protocol of the study and helped in the interpretation of the data. HM helped in the interpretation of the data.

**Funding**

The AGREE study and subsequent statistical analyses were funded and performed by Bristol-Myers Squibb.

**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, Cellgene, Janssen, Roche and UCB, and consultant fees from Pfizer. HG has received consultant and advisory board fees from Bristol-Myers Squibb, Amgen, Merck, Pfizer, Janssen, Lilly, Servier, Daichi 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. Comité de Ética em Pesquisa do Instituto de Assistência Medica ao Servidor Público Estadual Avenida Ibirapuera, Sao Paulo, Brazil; Comité de Ética em Pesquisa Humana e Animal do Hospital Geral de Goiânia Avenida Anhanguera, N., 6479—Setor Oeste Goiânia, Brazil; Comité de Ética em Pesquisa do Hospital Heliopolis Rue Conego Xavier; Sao Paulo, Brazil; Comité de Ética em Pesquisa do Hospital Universitario Pedro Ernesto Universidade do Estado do, Rio de Janeiro, Brazil; C.C.P.P.R.R. Montpellier Saint Eloi Hospital Saint Eloi, Montpellier, France; Schulman Associates I.R.B., Inc., Cincinnati, OH, USA; Institute of Rheumatology, Russian Academy of Medical Science, Ethics Committee 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; Comité de Ética em Pesquisa do Pontificia Universidade Catolica do Rio Grande, do Rio Grande do Sul, Brazil; Hospital Universitario Virgen Macarena C.E.I.C. Unidad De Investigacion, Sevilla, Spain; E. C. Regional De Cantabria, Hospital Univ. Marques De Valdecilla, Santander, Spain; Comité 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; Comité De Ética, Col. Reforma, Toluca, Mexico; Comité Etico Hospital General, Col. Centro Morelia, Michoacan, Mexico; Komisja Bioetyczna Przy, Instytucie Reumatologicznym, Warszawa, Poland; Hospital Regional I.S.S.T.E. Leon, Departura de Ensenanza y Investigacion, Guanajuato, Mexico, Comissie Medische Ethiek, Universitaire Ziekenhuizen K. U. Leuven Campus, Leuven, Belgium; Comité D’Ethique Biomedicale Hospitalo-Facultaire, Bruxelles, Belgium; Comissie Medische Ethiek, Universitaire Ziekenhuizen K. U. Leuven Campus, Leuven, Belgium; Internal Review Board Services, Aurora, Ontario, Canada; Comite
de Etica e Investigacion Christus Muguerra Del Parque, Chihuahua, Mexico; Comite de Etica e Investigacion Galeana Sur 465 Col. Obraj, Aguascalientes, Mexico; Ethikkommission Der Med., Fakultat Der Uni. Leipzig, Leipzig, Germany; Viria Jesse Ziekhuis Ethische Toetsingscommissie, Hasselt, Belgium; Commissie Medische Ethiek Klinische Onderzoek, Universitaire Ziekenhuizen K. U. Leuven Campus, Leuven, Belgium; Comite Independiente de Etica Del Centro De Estudios De Investigacion Basica Y Clinica, Col. Vallarta Norte, Guadalajara, Jalisco, Mexico; Comision de Investigacion Y Etica De La Facultad De Medicina Y Hospital Universitario, Col. Mitras Centro, Monterrey, Nuevo Leon, Mexico; Comision de Investigacion Y Etica Hospital Central, Col. Morales, San Luis Potosi, Mexico; Comitato Etico Azienda Sanitaria n.5 di Jesi (AN), Regione Marche, Italy.

Provenance and peer review Not commissioned; externally peer reviewed.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

REFERENCES

1. Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2012;64:625–39.

2. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73:492–509.

3. Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54:26–37.

4. Detert J, Bastian H, Listing J, et al. Induction therapy with adalimumab plus methotrexate for 24 weeks followed by methotrexate monotherapy up to week 48 versus methotrexate therapy alone for DMARD-naive patients with early rheumatoid arthritis; HIT HARD, an investigator-initiated study. Ann Rheum Dis 2013;72:844–50.

5. Tak PP, Rigby W, Rubbert-Roth A, et al. Sustained inhibition of progressive joint damage with rituximab plus methotrexate in early active rheumatoid arthritis: 2-year results from the randomised controlled trial IMAGe. Ann Rheum Dis 2013;72:351–7.

6. 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;68:1870–7.

7. Verschueren P, Westhovens R. Optimal care for early RA patients: the challenge of translating scientific data into clinical practice. Rheumatology (Oxford) 2011;50:1194–200.

8. Tamaka Y, Hirata S, Saleem B, et al. Discontinuation of biologics in patients with rheumatoid arthritis. Clin Exp Rheumatol 2013;31:522–7.

9. Huizinga T, Donka T, Conaghan P, et al. Clinical and radiographic outcomes at two years and the effect of tocilizumab discontinuation following sustained remission in the second year of the ACT-RAY study. Ann Rheum Dis 2013;72(Suppl 3):i63.

10. Smolen JS, Nash P, Durez P, et al. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE); a randomised controlled trial. Lancet 2013;381:918–29.

11. Kavanaugh A, Fleischmann RM, Emery P, et al. Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-week results from the randomised, controlled OPTIMA study. Ann Rheum Dis 2013;72:64–71.

12. Quinn MA, Conaghan PG, O’Connor P, et al. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52:27–35.

13. van den Broek M, Klarenbeek NB, Dirven L, et al. Discontinuation of infliximab and potential predictors of persistent low disease activity in patients with early rheumatoid arthritis and disease activity score-steered therapy: subanalysis of the BeSt study. Ann Rheum Dis 2011;70:1389–94.

14. Emery P, Spiler W, Stopinska-Polaszewska M, et al. Assessing maintenance of remission after withdrawal of etanercept plus methotrexate, methotrexate alone, or placebo in early rheumatoid arthritis patients who achieved remission with etanercept and methotrexate: The PReiz study. Arthritis Rheum 2013;65(Suppl 10):2689.

15. Emery P, Burmester G, Bykerk V, et al. Induction of clinical remission followed by drug-free withdrawal with abatacept combination and monotherapy in early RA: results from the AVEKt study Over 18 months. Ann Rheum Dis 2014;73(Suppl 2).

16. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.

17. Emery P, Durez P, Dougados M, et al. Impact of T-cell costimulation modulation in patients with undifferentiated inflammatory arthritis or very early rheumatoid arthritis: a clinical and imaging study of abatacept (the ADJUST trial). Ann Rheum Dis 2010;69:510–16.

18. Ma Y, Lin BR, Lin B, et al. Pharmacokinetics of CTLA4Ig fusion protein in healthy volunteers and patients with rheumatoid arthritis. Acta Pharmacol Sin 2009;30:364–71.

19. Orencia Prescribing Information. 2013. http://packageinserts.bms.com/pi/pi_orencia.pdf (last accessed: 28 Sept 2014).

20. Davis P, Nadler S, Rouleau K, et al. Abatacept (CTLA4-Ig) modulates human T-cell proliferation and cytokine production but does not affect lipopolysaccharide-induced tumor necrosis factor alpha production by monocytes. Arthritis Res Ther 2005;7(Suppl 1):P21.

21. Westhovens R, Kremer J, 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;32:553–62.