

Abatacept: first T cell co-stimulation modulator for severe active RA

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PRODUCT PROFILE

Proprietary name: Orencia

Constituents: abatacept

Dosage and method of administration: in combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have had an insufficient response or have intolerance to other

DMARDs including at least one TNF inhibitor; to be administered as a 30-minute iv infusion; dosage dependent on body weight, <60kg – 500mg, 60-100kg – 750mg, >100kg – 1000mg; to be given 2 and 4 weeks after the first infusion, then every 4 weeks thereafter; not recommended in children

Contraindications: hypersensitivity to the active substance or to any of the excipients; severe and uncontrolled infections such as sepsis and opportunistic infections

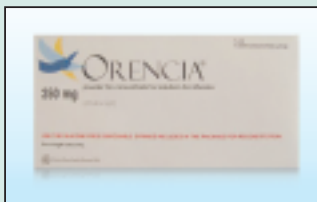
Precautions: special caution should be exercised in patients with a history of allergic reactions to abatacept or to any of the excipients; co-administration with biologic immunosuppressive or immunomodulatory agents could potentiate the effects of abatacept on the immune system; treatment should not be initiated in patients with active infections; caution should be taken in patients with a history of recurrent infections or underlying conditions that may predispose them to infections; screening for viral hepatitis before treatment should be performed in accordance with published guidelines as antirheumatic therapies have been associated with hepatitis B reactivation; live vaccines should not be given during treatment or within 3 months of its discontinuation; there is a theoretical concern that treatment may increase the risk of autoimmune processes, but in the placebo-controlled clinical trials abatacept treatment did not lead to increased autoantibody formation relative to placebo treatment; the GDH-PQQ based glucose monitoring systems may react with the maltose present in abatacept, resulting in falsely elevated blood glucose on the day of infusion – patients that require blood glucose monitoring should consider methods that do not react with maltose; abatacept contains 1.5mmol sodium per maximum dose of 4 vials, and should be taken into consideration when treating patients on a controlled sodium diet

Pregnancy and lactation: not recommended; women should use effective contraception during treatment and up to 14 weeks after the last dose; women should not breastfeed during treatment and for up to 14 weeks after the last dose

Interactions: concurrent therapy with a TNF-blocking agent is not recommended; there is insufficient evidence to assess safety and efficacy in combination with anakinra or rituximab

Side-effects: *very common:* headache; *common:* increased blood pressure, abnormal liver-function test (including increased transaminases); dizziness; cough; abdominal pain, diarrhoea, nausea, dyspepsia; rash (including dermatitis); lower respiratory tract infection (including bronchitis), urinary tract infection, herpes simplex, upper respiratory tract infection (including tracheitis, nasopharyngitis), rhinitis; hypertension, flushing; fatigue, asthenia

Presentation/cost: 250mg powder for infusion solution, 1 vial – £252.00



Abatacept (Orencia) is licensed for the treatment of severe RA in combination with methotrexate when at least one anti-TNF agent has failed. Here, Steve Chaplin presents the clinical data relating to its efficacy and adverse effects, and Dr Andrew Ostor comments on its place in RA therapy.

The British Society for Rheumatology (BSR) guideline for the management of rheumatoid arthritis (RA) during the first two years states that patients should be established on disease-modifying therapy as soon as possible after diagnosis.¹ Treatment should be provided as ‘an aggressive package of care, incorporating escalating doses, intra-articular steroid injections, parenteral methotrexate and combination therapy, rather than sequential monotherapy, progressing to biologic – antitumour necrosis factor (anti-TNF) – therapy, when required’.

An anti-TNF agent – etanercept (Enbrel), adalimumab (Humira) or infliximab (Remicade) – should be considered if an adequate trial of at least two disease-modifying antirheumatic drugs (DMARDs), one of which must be methotrexate, fails.² Analysis of the BSR Biologics Register shows that, in

the first 15 months of treatment with an anti-TNF, 28 per cent of patients with severe RA stop treatment due to lack of efficacy (45 per cent) or toxicity (55 per cent).³ The National Institute for Health and Clinical Excellence (NICE) guidance on the use of etanercept and infliximab does not recommend consecutive use⁴ but, of the patients who stopped treatment, 46 per cent were switched to an alternative anti-TNF agent. Of these, just over one quarter discontinued treatment again. Overall, therefore, about 18 per cent of patients prescribed an anti-TNF do not continue treatment.

The therapeutic options for patients unable to take an anti-TNF agent are limited. They include rituximab (Mabthera), a monoclonal antibody causing B-cell depletion; NICE does not recommend the use of the only other biologic agent, anakinra (Kineret).⁵ There is therefore a need for new treatments for patients with refractory RA.

The technology

T cells play a critical role in amplifying and maintaining inflammation in RA. Abatacept (Orencia) is a selective T cell co-stimulation modulator; to date, it is the only licensed drug with this mechanism of action. It inhibits one of the signals required for full activation of CD28 T cells, resulting in a reduction in serum levels of some cytokines associated with inflammation, including TNF- α .⁶

Abatacept is licensed for use in combination with methotrexate for the treatment of moderate to severe active RA in adult patients who have had an insufficient response or intolerance to other DMARDs, including at least one TNF inhibitor.⁷ It is administered as a 30-minute infusion at a dose of approximately 10mg per kg at 0, 2 and 4 weeks and then every four

Response*	Phase IIb		AIM	
	Abatacept	Placebo	Abatacept	Placebo
ACR20	63%	36%	73%	40%
ACR50	42%	20%	48%	18%
ACR70	21%	8%	29%	6%
Remission [†]	35%	10%	24%	2%

* The American College of Rheumatology (ACR) response categories measure improvement in the number of tender and swollen joints, plus improvement in at least 3 of:

- global disease activity assessed by observer
- global disease activity assessed by patient
- patient assessment of pain
- physical disability score, eg Health Assessment Questionnaire
- acute-phase response, eg erythrocyte sedimentation rate or C-reactive protein

Response is defined as the percentage of patients in whom 20, 50 or 70% improvement in these clinical measures is achieved (adapted from ref. 4)

[†] remission was defined as a DAS28 score <2.6. DAS28 measures disease activity on 28 joints, erythrocyte sedimentation rate and general health status

Table 1. Twelve-month response and remission rates in the phase IIb⁸ and AIM trials⁹

weeks. Alternatives should be considered if there is no response after six months.

Abatacept should not be co-prescribed with an anti-TNF agent (due to an increased risk of infection) or a live vaccine, and it is contraindicated in patients with opportunistic infection or sepsis.

Clinical trials

There are no published randomised trials comparing abatacept with other biological DMARDs. Three pivotal randomised double-blind efficacy trials have been conducted in patients with active RA despite treatment with methotrexate: a Phase IIb study,⁸ AIM⁹ (Abatacept in Inadequate responders to Methotrexate) and ATTAIN (Abatacept Trial in Treatment of Anti-TNF Inadequate responders).¹⁰ Only ATTAIN evaluated abatacept in patients whose RA was refractory to treatment with an anti-TNF agent, *ie* the licensed indication. In each, treatment with methotrexate and other drugs, including DMARDs in AIM and ATTAIN, was continued.

In the Phase IIb study, 339 patients treated with methotrexate were randomised to placebo or abatacept 2 or 10mg per kg. After 12 months, abatacept 10mg per kg was associated with significantly greater response and remission rates compared with placebo (see Table 1). Disease activity scores were significantly lower with abatacept 10mg per kg and physical function and health-related quality of life¹¹ were significantly improved compared with placebo.

In AIM,⁹ 652 patients treated with methotrexate were randomised to additional treatment with abatacept 10mg per kg or placebo. The primary end-points were the ACR20 (defined as a 20 per cent improvement in disease symptoms from baseline according to the American College of Rheumatology improvement criteria – see Table 1 for explanation) at six months and change in physical functions and joint erosion at 12 months. Eighty-nine per cent of patients treated with abatacept and 74 per cent of those assigned to placebo completed one year's treatment. Compared with

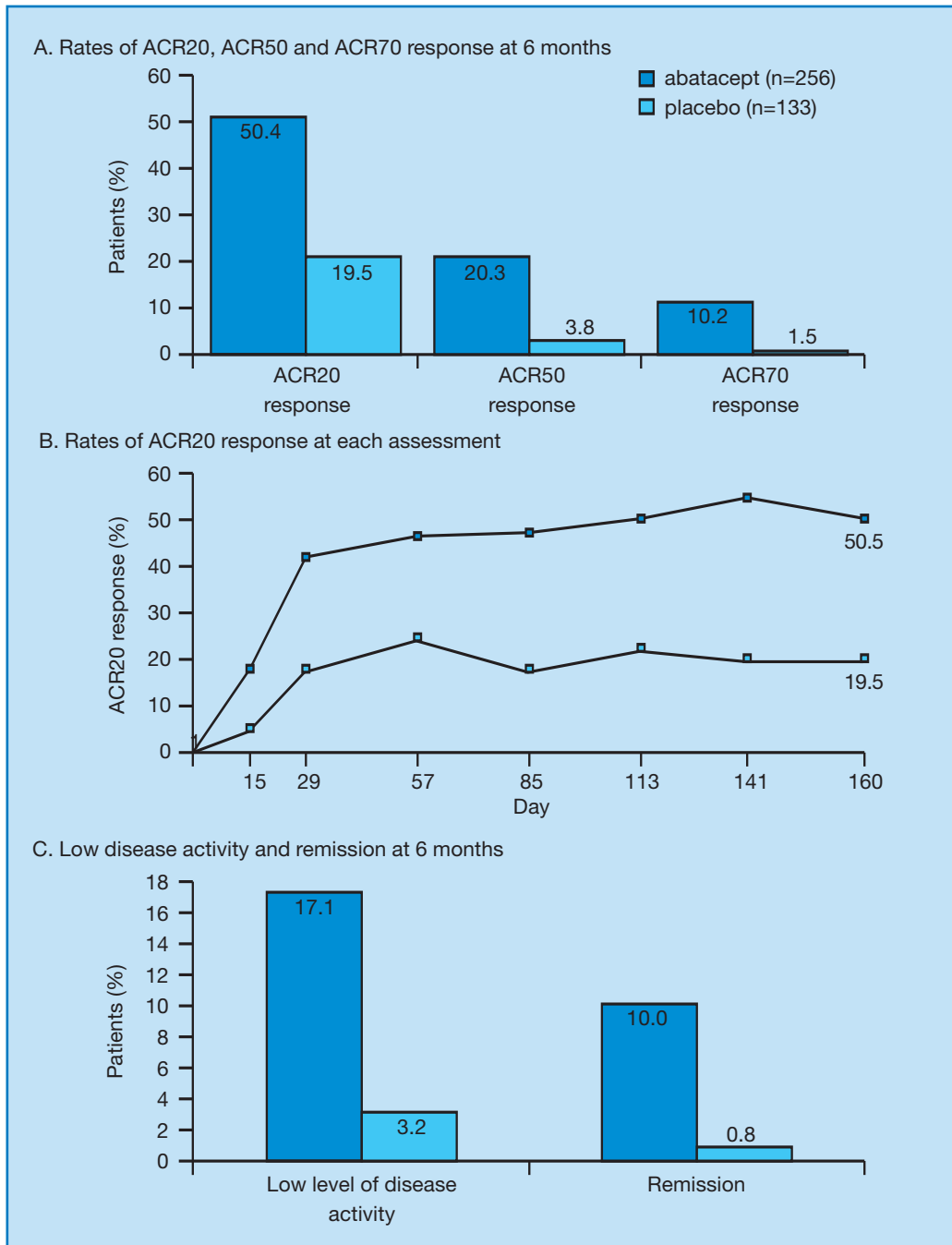


Figure 1. Primary and secondary end-points in the ATTAIN trial¹⁰

placebo, abatacept was associated with a significantly greater ACR20 response at six months (68 vs 40 per cent); significantly more patients with clinically important improvement in physical function at one year (64 vs 40 per cent); and significant slowing of joint erosion at one year: progression of structural dam-

age was reduced by approximately 50 per cent compared with placebo. There were also significantly greater improvements in secondary end-points with abatacept, including ACR20, 50 and 70 responses at one year (see Table 1), disease activity score and health-related quality of life.

Nonblinded continuation of AIM for up to two years suggested that ACR response, low disease activity and remission rates may increase with longer duration of treatment.¹² Of patients with disease progression increased slightly overall; of the patients whose disease had not been arrested in the first year, progression was arrested in 45 per cent during the second year.¹³

ATTAIN randomised 393 patients who had not responded to at least three months' treatment with an anti-TNF agent (mostly etanercept or infliximab) to treatment with abatacept 10mg per kg or placebo.¹⁰ Eighty-six per cent of patients taking abatacept plus methotrexate and 74 per cent of those assigned to methotrexate alone completed six months' treatment. The ACR20 response at six months (the primary end-point) was significantly greater with abatacept than with placebo (50 vs 20 per cent); the difference between the groups was statistically significant after 15 days (see Figure 1). Abatacept/methotrexate was also significantly superior on secondary end-points (ACR50, ACR70 and disease activity scores, see Figure 1) and improved physical function and health-related quality of life compared with methotrexate alone.

A nonblinded extension of ATTAIN for up to two years suggested that response rates increased between 6 and 12 months, then remained approximately stable.¹⁴

Safety

Safety data are available from 2778 patients treated with any dose of abatacept in the clinical trials programme, of whom 83 per cent were treated for at least one year and 50 per cent for at least two years.¹⁵ Compared with methotrexate alone, abatacept plus methotrexate

was associated with slightly higher rates of serious adverse reactions (14 *vs* 12.5 per cent) and discontinuation due to serious adverse reactions (2.8 *vs* 1.6 per cent).

Reactions more commonly reported with abatacept included headache (18.3 *vs* 12.7 per cent), dizziness (9.5 *vs* 7.0 per cent – about half cases within 24 hours of the infusion period), hypertension (6.6 *vs* 4.6 per cent) and aphthous ulcers (1.9 *vs* 1.0 per cent).

Abatacept plus methotrexate was associated with an increased risk of infections overall (54 *vs* 49 per cent with methotrexate alone), but not with an increased risk of serious infection or malignancy,¹⁵ though the duration of trials has been too short to exclude a risk of malignancy. The incidence of these events did not increase during the second year of treatment in patients taking DMARDs.¹⁶ It is unclear from published pooled data whether the risk of these reactions is higher at the licensed dose. By contrast, concurrent treatment with a biological DMARD, *eg* an anti-TNF agent, increases the risk of serious adverse events and this combination is contraindicated.¹⁷

Summary

Abatacept, the first T cell co-stimulation modulator, is licensed for the treatment of severe active RA in combination with methotrexate when at least one anti-TNF agent has been unsuccessful. There are no published trials comparing abatacept with other biological agents. In placebo-controlled clinical trials lasting up to two years, it has been shown to increase the proportions of patients responding to treatment and with low disease activity; it also reduces disease progression and improves physical function and quality of life. Treatment with abatacept plus methotrexate appears to be relatively well tolerated, with no

evidence so far of an increased risk of malignancy or serious infections.

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Key points

- abatacept is licensed for the treatment of severe active RA, in combination with methotrexate, when treatment with a DMARD is unsuccessful
- it is not been compared with other biological agents in randomised trials
- in placebo-controlled trials lasting up to 2 years, abatacept increased the proportions of patients responding to treatment and the proportion with low disease activity
- it reduced disease progression and improved physical function and quality of life
- treatment with abatacept appears to be relatively well tolerated, with no increase in the risk of malignancy or serious infections in trials of short duration

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By Steve Chaplin, a pharmacist who specialises in writing on therapeutics

Place in therapy

Despite the unprecedented advances in the management of RA over the last decade, a group of patients remain whose disease is insufficiently controlled. Furthermore, if the goal of treatment for severe RA is complete disease remission, few patients achieve this state. In relation to anti-TNF agents, up to 30 per cent of patients do not continue treatment beyond 18 months and it would appear that this proportion increases with time. The reasons for this include lack of initial response, secondary loss of efficacy or poor tolerability, and in addition anti-TNF therapy is contraindicated in certain patients.

Faced with such an individual what can a clinician do? Until recently the answer was very little. Patients would be recommended on drugs that had previously been ineffective or poorly tolerated, and steroids would frequently be necessary with the inevitable concern regarding long-term toxicity. Thankfully this hiatus in the therapeutic armamentarium has recently been bridged by newer biologic agents such as rituximab and now abatacept. Clinical trials have demonstrated a clear advantage for abatacept in exactly the patients who were facing a bleak future, namely those who had failed anti-TNF agents.

The benefits included all the parameters that matter to clini-

cians, such as disease activity scores, ACR responses and radiographic changes, and those particularly important to patients such as improvements in quality of life and physical function. This gain appears to increase with time in some patients, and reassuringly the side-effect profile is well within what would be deemed acceptable.

NICE is currently considering the place of abatacept in the treatment of RA, with its final guidance expected shortly.

By Dr Ostor, a consultant rheumatologist and associate lecturer, School of Clinical Medicine, University of Cambridge