REVIEW

Comparative clinical utility of once-weekly subcutaneous abatacept in the management of rheumatoid arthritis

Chadi Rakieh
Philip G Conaghan

Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK

Abstract: Biologic therapies in rheumatoid arthritis are now part of standard practice for disease that proves difficult to control with conventional disease-modifying anti-rheumatic drugs. While anti-tumor necrosis factor therapies have been commonly used, other targeted biologic therapies with different mechanisms of action are becoming increasingly available. Abatacept is a recombinant fusion protein that inhibits the T-cell costimulatory molecules required for T-cell activation. Intravenous abatacept has good clinical efficacy with an acceptably low toxicity profile in rheumatoid arthritis, but the subcutaneous mode of delivery has only recently become available. In this article, we examine key efficacy and safety data for subcutaneous abatacept in rheumatoid arthritis, incorporating evidence from five large Phase III studies that included people with an inadequate response to methotrexate and an inadequate response to biologic disease-modifying anti-rheumatic drugs. The results demonstrate that subcutaneous abatacept has efficacy and safety comparable with that of intravenous abatacept and adalimumab. In addition, inhibition of radiographic progression at year 1 in relatively early rheumatoid arthritis is consistent with that of adalimumab. Subcutaneous abatacept is well tolerated, with very low rates of discontinuation in both short-term and long-term follow-up.

Keywords: rheumatoid arthritis, therapy, abatacept, T-cell

Background: biologic strategies in rheumatoid arthritis

Recent therapeutic strategies focusing on early aggressive introduction of disease-modifying anti-rheumatic drugs (DMARDs) have led to improved physical, functional, and structural outcomes for patients with rheumatoid arthritis (RA).[1–4] Methotrexate, as monotherapy or in combination with other nonbiologic DMARDs, is usually part of the first-line treatment.[5] However, if the treatment target is not achieved with the first DMARD strategy, a biological DMARD should be considered.[5]

Biologic treatment strategies in RA include interference with cytokine function, depletion of B-cells, and inhibition of the second signal required for T-cell activation (costimulation blockade).[6] Anti-cytokine agents that have been approved for the treatment of RA include five anti-tumor necrosis factor alpha (TNF) agents (infliximab, etanercept, adalimumab, certolizumab, and golimumab), one interleukin-1 inhibitor (anakinra), and one interleukin-6 blocker (tocilizumab). Rituximab, a chimeric monoclonal anti-CD20 antibody, is the only B-cell-depleting agent licensed for treatment of RA. Finally, T-cell-targeted therapy has been introduced with abatacept,

Correspondence: Philip G Conaghan
Leeds Institute of Rheumatic and Musculoskeletal Medicine, Chapel Allerton Hospital, Leeds LS7 4RX, UK
Tel +44 113 3924883
Fax +44 113 3924991
Email P.Conaghan@leeds.ac.uk

which blocks the full activation of T-cells by inhibiting the costimulation mechanism.

Mechanism of action: CD28/CTLA4 blockade pathway

Abatacept is a recombinant fusion protein that inhibits the T-cell costimulatory molecules required for T-cell activation. T-cells are activated by antigen-presenting cells through two distinct signals: antigen-specific, ie, binding of the T-cell receptor on the antigen-presenting cell to the complex formed by an antigenic peptide and major histocompatibility complex II; and the costimulatory pathway, ie, binding of T-cell surface receptors (CD28) with specific ligands on the antigen-presenting cell (CD80/CD86), which provides the essential "second signal" needed for T-cell activation.[7–9]

Abatacept consists of an extracellular inhibitory receptor (cytotoxic T-lymphocyte-associated antigen 4 [CTLA4]) on the T-cell surface combined with the Fc portion of immunoglobulin G1 heavy chain. CTLA4-Ig acts as a competitive inhibitor of CD28 on the T-cell surface by binding with either CD80 (ligand B7-1) or CD86 (ligand B7-2) on the antigen-presenting cell. As a result, the second signal essential for T-cell activation is blocked.[10,11]

Pharmacokinetics of subcutaneous abatacept

Subcutaneous abatacept is administered as a flat dose of 125 mg weekly. In a double-blind, randomized, placebo-controlled Phase IIa trial, steady-state trough serum concentrations were comparable across subcutaneous abatacept single (125 mg) and weight-tiered (75–200 mg) dosing regimens from days 71–85.[12] With flat dosing (125 mg/week for all patients), the geometric mean of the trough serum concentration (23 µg/mL) was comparable with that observed in patients receiving the intravenous dose of approximately 10 mg/kg (trough serum concentration 12 µg/mL) in an integrated analysis of 149 patients.[12]

Until recently, abatacept has only been available as an intravenous infusion and is approved by the US Food and Drug Administration (FDA) as a second-line treatment for active RA. A subcutaneous self-injectable formulation became available later, and was also approved for use in RA by the FDA in 2011. Subcutaneous abatacept is administered weekly at a fixed dose of 125 mg with or without a single loading dose given by intravenous infusion (approximately 10 mg/kg). In this review, we assess the clinical efficacy and safety of subcutaneous abatacept using the available clinical data.

Efficacy of subcutaneous abatacept in RA

Intravenous abatacept is approved for the treatment of moderate-to-severe RA, and its efficacy has been well established.[13–18] This review addresses the efficacy of the subcutaneous formulation of abatacept from the published clinical data. A literature search of all clinical studies of subcutaneous abatacept was undertaken in January 2014 and retrieved one dose-ranging Phase II study with a small number of patients (n=68)[12] and five Phase III trials, ie, ACQUIRE (Abatacept Comparison of Subcutaneous versus Intravenous in Inadequate Responders to Methotrexate),[19] ACCOMPANY (Abatacept in Subjects with Rheumatoid Arthritis Administered Plus or Minus Background Methotrexate Subcutaneously),[20] ALLOW (Evaluation of Abatacept Administered Subcutaneously in Adults With Active Rheumatoid Arthritis: Impact of Withdrawal and Reintroduction on Immunogenicity, Efficacy and Safety),[21] ATTUNE (Abatacept in subjects who switch from intravenous to subcutaneous therapy),[22] and AMPLE (Abatacept Versus Adalimumab Comparison in Biologic-Naïve rheumatoid arthritis [RA] Subjects With Background Methotrexate).[23] This review focuses on the Phase III studies, and Table 1 summarizes their key findings.

ACQUIRE study

This was a 6-month, double-dummy, noninferiority study comparing the efficacy and safety of subcutaneous and intravenous abatacept in patients with active RA on a background of methotrexate.[19] A total of 693 patients were randomized to receive subcutaneous abatacept 125 mg weekly plus an intravenous loading dose on day 1 (~10 mg/kg), while 676 patients received intravenous abatacept (~10 mg/kg) on days 1, 15, and 29 and every 4 weeks thereafter. The primary endpoint (American College of Rheumatology 20% improvement criteria [ACR] 20 response) at month 6 was achieved in 76% of patients who received subcutaneous abatacept versus 75.8% of those who received intravenous abatacept.[19] Secondary endpoints were also comparable between the two groups. ACR50 response rates were 50.2% and 48.6% and ACR70 response rates were 25.8% and 24.2% in the subcutaneous and intravenous abatacept-treated groups, respectively. The mean changes from baseline in 28-Joint Disease Activity Score using C-reactive protein (DAS28-CRP) were similar in both groups.[19] At month 6, a low disease activity state (LDAS), defined as DAS28-CRP ≤3.2, was achieved in 39.5% (95% confidence interval [CI] 35.8–43.1) and 41.3%

(95% CI 37.6–45.1) of patients in the subcutaneous and intravenous groups, respectively, and remission, defined as DAS28-CRP <2.6, was achieved in 24.2% and 24.8% of the subcutaneous and intravenous abatacept-treated groups, respectively.[19]

ACCOMPANY study

ACCOMPANY was an open-label Phase IIIb study assessing subcutaneous abatacept 125 mg weekly with or without methotrexate in patients with active RA.[20] At month 4, the mean change in DAS28-CRP from baseline was −1.67 in the combination group and −1.94 in the monotherapy group.[20] This study also had a long-term extension phase, and mean change in DAS28-CRP from baseline at month 18 was −1.84 (95% CI −2.23, −1.34; combination) and −2.86 (95% CI −3.46, −2.27; monotherapy).[20] DAS28-CRP LDAS was achieved in 72.8% and 84.5% and remission in 57.8% and 74.4% of patients in the combination and monotherapy groups, respectively, at month 18.[20]

ALLOW study

This was a Phase IIIb trial designed to examine the effects of temporary withdrawal of subcutaneous abatacept on immunogenicity, after a 12-week open-label introduction (period 1) in which patients on background methotrexate received an intravenous abatacept loading dose and weekly fixed-dose subcutaneous abatacept 125 mg. In period 2, patients were randomized 2:1 to double-blind subcutaneous placebo or subcutaneous abatacept for 12 weeks. Finally, in period 3, patients who received subcutaneous placebo in period 2 were switched to subcutaneous abatacept, while those who were on subcutaneous abatacept continued on the same treatment for another 12 weeks.[21] Coprimary endpoints in this trial were the immunogenicity and safety of subcutaneous abatacept. Efficacy endpoints were monitored throughout the study. At month 6 and following the withdrawal phase (period 2), mean reductions from baseline in DAS28-CRP were −2.03 in patients who continued subcutaneous abatacept compared with −1.49 in patients who received placebo during period 2. At the end of period 3 (reintroduction phase), the reduction in DAS28-CRP was similar between the two groups, ie, −2.22 (95% CI −2.5, −1.94) and −2.32 (95% CI −2.56, −2.09) in patients who continued subcutaneous abatacept and those who were reintroduced to subcutaneous abatacept, respectively.[21] Similar results were observed in DAS28-defined LDAS and remission (≤3.2 and <2.6, respectively).[21] At month 9, LDAS was achieved in 69.2% (95% CI 54.7–83.7)

and 79.7% (95% CI 70.6–88.9) of patients who continued versus those who were reintroduced to subcutaneous abatacept after period 2, respectively.[21] The proportions of patients in DAS28 remission at month 9 were 51.3% and 63.5% in the subcutaneous abatacept continuous group versus the withdrawal and reintroduction group, respectively.[21]

ATTUNE study

ATTUNE was a 12-month, open-label single-arm trial that assessed switching from intravenous abatacept monotherapy to subcutaneous abatacept monotherapy in RA patients with inadequate response to methotrexate (71 patients), or anti-TNF (52 patients) and who had been stable on intravenous abatacept monotherapy for ≥4 years.[22] The primary endpoint was safety through month 3, while secondary endpoints included immunogenicity through month 3 and efficacy up to month 12. Clinical efficacy was maintained throughout the study and DAS28-CRP scores remained stable through month 12 of subcutaneous abatacept. Mean DAS28-CRP at month 12 was 3.21 compared with a score of 3.39 at baseline.[22] The states of DAS28-CRP low disease activity and remission were also maintained through month 12 at 51.3% (43.4% at baseline) and 39.8% (32% at baseline), respectively.[22]

AMPLE study

This was a 2-year head-to-head, noninferiority, randomized, investigator-blinded Phase IIIb trial.[23,24] Biologic-naïve patients with active RA and an inadequate response to methotrexate were randomized 1:1 to receive 125 mg of subcutaneous abatacept weekly (318 patients) or adalimumab 40 mg every 2 weeks (328) plus a stable dose of methotrexate.[24] The primary endpoint was ACR20 response rate at year 1 and was met, with 64.8% of abatacept-treated patients achieving this mark compared with 63.4% of those given adalimumab.[24] ACR50, 70, and 90 responses were also comparable between the groups through 2 years; a major clinical response (ACR70) at year 2 was achieved in 31.1% (95% CI 26–36.2) and 29.3% (95% CI 24.3–34.2) in the abatacept and adalimumab groups, respectively.[24] DAS28-CRP scores demonstrated mean changes from baseline of −2.4 and −2.3 in the abatacept and adalimumab groups, respectively.[24] At year 2, LDAS (DAS28-CRP ≤3.2) and DAS28-CRP remission (<2.6) were achieved in 65.3% and 50.6% of abatacept-treated patients, respectively, versus 68% and 53.3% of adalimumab-treated patients, respectively.[24]

Table 1 Summary of Phase III trials of subcutaneous abatacept in rheumatoid arthritis

	ACQUIRE[19]		AMPLE[23]	
Entry requirements: disease activity	≥12 tender joints ≥10 swollen joints CRP ≥0.8 mg/dL		DAS28 (CRP) ≥3.2 Anti-CCP or RF Elevated ESR or CRP	
Entry requirements: previous therapy	IR to MTX		IR to MTX biologic-naïve	
Study design	Phase IIIb, double-blind, double-dummy, noninferiority study		Phase IIIb, double-blind, noninferiority study	
Study duration	6 months		24 months	
Primary endpoint(s)	ACR 20 at month 6		ACR 20 at month 12	
Treatment	SC ABT + MTX	IV ABT + MTX	SC ABT + MTX	ADA + MTX
Patients (n)	736	721	318	328
Disease duration: years (mean, SD)	7.6 (8.1)	7.7 (7.8)	1.9 (1.4)	1.7 (1.4)
% ACR 20	76%	75.8%	64.8%	63.4%
DAS28-CRP mean change (95% CI)	−2.57 (−2.67, −2.47)[a]	−2.55 (−2.65, −2.45)[a]	−2.30 (−2.46, −2.14)[c]	−2.27 (−2.43, −2.11)[c]
DAS28-CRP remission % (95% CI)	24.2 (20.9, 27.4)	24.8 (21.5, 28.1)	43.3 (37.3, 49.1)	41.9 (36, 47.9)
HAQ-DI change (mean, 95% CI)	−0.69 (−0.73, −0.65)[a]	−0.70 (−0.74, −0.66)[a]	−0.60 (−0.68, −0.52)[a]	−0.59 (−0.67, −0.51)[a]
Pain VAS (mean, 95% CI)	49.1%[c] (45.7, 52.5)[c]	44.9%[c] (41.4, 48.4)[c]	53%[c] (41.4, 65)	39.2%[c] (27.4, 51)
Retention rate	94.2%	93.8%	86.2%	82%
Radiographic progression: SHS (mean ± SD)	NR		0.58 (3.22)	0.38 (5)

Notes: [a]Maintained improvement in DAS28-CRP at month 3 after switching from IV abatacept; [b]adjusted improvement from baseline; [c]calculated 95% CI.
Abbreviations: CRP, C-reactive protein; DAS28, disease activity score in 28 joints; anti-CCP, anti-citrullinated peptide; RF, rheumatoid factor; VAS, visual analog scale; RA, rheumatoid arthritis; IV, intravenous; ABT, abatacept; IR, inadequate response; SC, subcutaneous; MTX, methotrexate; DMARDs, disease-modifying anti-rheumatic drugs; anti-TNF, anti-tumor necrosis factor; SD, standard deviation; NR, not reported; ACR 20, American College of Rheumatology 20% improvement criteria; ADA, adalimumab; LTE, long-term extension; CI, confidence interval; SHS, modified Sharp/van der Heijde score.

Radiologic progression

Structural damage was assessed in the AMPLE study and demonstrated similar inhibition of radiographic progression rate between subcutaneous abatacept and adalimumab at year 1.[23] Changes in the total modified Sharp/van der Heijde score[25] (mean ± standard deviation) from baseline through year 1 were similar between the subcutaneous abatacept-treated and adalimumab-treated patients at 0.58±3.22 versus 0.38±5, respectively. Furthermore, radiographic nonprogression, defined as a change from baseline in the total modified Sharp/van der Heijde score ≤ the smallest detectable change, was also comparable at 84.8% with subcutaneous abatacept versus 88.6% with adalimumab at year 1.[23]

Patient-focused outcomes
Physical function and pain

Physical function assessed by the Health Assessment Questionnaire Disability Index (HAQ-DI) across the Phase III subcutaneous abatacept trials demonstrated persistent improvement comparable with that of intravenous abatacept and adalimumab.

At month 4 after starting treatment, HAQ-DI scores in the ACCOMPANY study showed improvements in both the combination (−0.6) and monotherapy (−0.3) groups. Similarly, HAQ-DI scores at month 6 in the ACQUIRE study showed comparable improvements in both the subcutaneous and intravenous groups of −0.69 and −0.70, respectively. Studies with longer-term follow-up showed a similar pattern. For example, the adjusted mean changes in HAQ-DI from baseline through year 2 in the AMPLE trial were comparable at −0.6 and −0.58 in the abatacept and adalimumab groups, respectively.[24] The improvement in physical function was maintained when switching from intravenous to subcutaneous abatacept in the ATTUNE study, with a mean HAQ-DI score of 0.9 at month 12 compared with 0.94 at baseline after switching to subcutaneous abatacept.[22]

ACCOMPANY[20]		ALLOW[21]		ATTUNE[22]	
Global VAS >20		DAS28 (CRP) ≥3.2 and ≤5.1		Active RA ≥4 years treatment with IV ABT	
IR to ≥1 DMARD (IR to MTX or MTX-naïve)		IR to MTX		IR to anti-TNF	
Phase III open-label study		Phase IIIb, 3 × 12-week periods: open-label SC ABT double-blind SC placebo/ABT open-label reintroduced SC ABT		Phase IIIb, open-label, single-arm study	
4 months		9 months		12 months	
Immunogenicity rate of SC ABT at month 4		Immunogenicity and safety of SC ABT at month 6		Safety through month 3 after switching from IV to SC ABT	
SC ABT	SC ABT + MTX	SC ABT + MTX (withdrawal/reintroduction)	SC ABT + MTX (continuous)	SC ABT in MTX IR	SC ABT in anti-TNF IR
49	51	80	40	71	52
All patients: 10.1 (11.1)		6.2 (5.8)	7.4 (7.7)	NR	NR
NR		NR		NR	
−1.94 (−2.46, −1.42)	−1.67 (−2.06, −1.28)	−2.03 (−2.4, −1.66)	−1.49 (−1.77, −1.2)	−0.37[b] (NR)	−0.11[b] (NR)
LTE month 18	LTE month 18	Month 9	Month 9	48.6 (NR)	24.5 (NR)
58.3 (42.2, 74.4)	42.5 (27.2, 57.8)	51.3 (35.6, 67)	63.5 (52.5, 74.5)		
−0.58 (−0.74, −0.42)	−0.31 (−0.43, −0.19)	−0.50 (−0.63, −0.37)	−0.72 (−0.95, −0.50)	−0.09 (NR)	−0.06 (NR)
NR		NR		NR	
All patients 96% at month 4, 83% up to month 18 LTE		98.8%	100%	All patients 91.1%	
NR		NR		NR	

Patient-reported VAS for pain was reported in the ACQUIRE study. At month 6, the adjusted mean improvement from baseline in pain VAS was 49.1% and 44.9% in the subcutaneous and intravenous abatacept groups, respectively.[19] Similarly, comparable improvements in pain VAS of 53% and 39.2% were demonstrated in the AMPLE trial at month 12 for the subcutaneous abatacept and adalimumab groups, respectively.

Patient retention with subcutaneous abatacept

Subcutaneous abatacept demonstrated high retention rates of >86% in the short-term follow-up of the Phase III trials. Patient retention was maintained in the long term, with 1,134/1,372 (82.7%) of patients remaining on subcutaneous abatacept after a median exposure of 33 months in the long-term extension period of the ACQUIRE study, reflecting good tolerability.[26] In the AMPLE trial, patient retention rates were numerically higher in the subcutaneous abatacept group (86.2%) versus the adalimumab group (82%) at month 12.[24]

Immunogenicity on subcutaneous abatacept

Immunogenicity is a drug-induced antibody response, and has been reported with biologic DMARDs, leading to reduced drug concentrations and reduced efficacy.[27–30] Therefore, immunogenicity has been studied as a primary endpoint in a number of subcutaneous abatacept trials.

In the ACQUIRE study, subcutaneous and intravenous abatacept demonstrated similar immunogenicity, with 0.4% of patients in the subcutaneous group positive for anti-abatacept antibodies versus 0.7% in the intravenous group.[19] In the ATTUNE study, the risk of immunogenicity after switching from intravenous to subcutaneous abatacept was low and did not impact the efficacy or safety of abatacept.[22]

Withdrawal and reintroduction of subcutaneous abatacept in the ALLOW study led to a transient nonsignificant increase in immunogenicity in period 2 (9.6% subcutaneous placebo versus 0% subcutaneous abatacept), which was reversed after reintroduction of the drug at the end of period 3 (2.7% versus 2.6%, respectively).[21] Finally, immunogenicity rates with subcutaneous abatacept were similar in the monotherapy group and combination with methotrexate group through the 4-month double-blind period (2% versus 3.9%).[20] At the end of the double-blind period, no immunogenicity was reported with either monotherapy or combination subcutaneous abatacept.[20]

Safety of subcutaneous abatacept in Phase III trials

Alten et al assessed the pooled safety data from five subcutaneous abatacept clinical trials in RA, ie, one Phase IIa[12] and two Phase IIIb (ACQUIRE, ALLOW) randomized controlled trials and two open-label Phase IIIb studies (ATTUNE, ACCOMPANY). In total, 1,879 patients with up to 4.5 years and 3,086 patient-years of exposure were studied.[31,32]

Only 3.5% of patients treated with subcutaneous abatacept developed injection site reactions. Most events (94%) were mild in intensity and only two patients discontinued due to local reactions.[31] In the head-to-head AMPLE trial, injection site reactions occurred significantly less frequently with subcutaneous abatacept (3.8%) than with adalimumab (9.1%). Three patients in the adalimumab group discontinued treatment due to injection site reactions versus none in the abatacept group.[24]

Injection site reactions occurred in 66 patients (3.5%) with an incidence rate (patients with events per 100 patient-years of exposure) of 2.22 (95% CI 1.74–2.82). These reactions occurred most commonly in the first 6 months, and only two patients discontinued treatment as a result. The most frequent local reactions were erythema, hematoma, pain, and pruritus. The incidence rate of serious infections was reported at 1.94 (95% CI 1.50–2.50). The most frequent serious infections were pneumonia, urinary tract infection, and gastroenteritis. Pulmonary tuberculosis and peritoneal tuberculosis were recorded in one patient each.[31] Malignancies excluding nonmelanoma skin cancer occurred at an incidence rate of 0.68 (95% CI 0.45–1.05) in 21 (1.1%) patients. The most frequent (incidence rate >0.10) malignancies were basal cell carcinoma (0.46 [95% CI 0.27–0.77]), breast cancer and squamous cell carcinoma of skin (0.16 [95% CI 0.07–0.39] each).[31] Psoriasis (0.29 [95% CI 0.15–0.56]) and Sjögren's syndrome (0.19 [95% CI 0.09–0.43]) were

the most frequent autoimmune events.[31] The incidence of serious infections, malignancies, and autoimmune events did not increase with increasing exposure.[31] Seventeen deaths occurred in the reported subcutaneous abatacept studies, with an incidence rate of 0.55 (CI 0.34–0.89), which is comparable with that reported with intravenous abatacept (0.6 [95% CI 0.47–0.76]).[32]

Discussion

An increasing number of biologic agents with different administration routes and mechanisms of action is now available for clinicians and patients to choose from in RA.[5] In this article, we have presented an overview of the key efficacy and safety data of a newly available agent, ie, subcutaneous abatacept. The data suggest that abatacept as a subcutaneous formulation has clinical efficacy comparable with that of its intravenous formulation. Further, the AMPLE study, which was the first head-to-head trial between abatacept and an anti-TNF therapy (adalimumab) in a biologic-naïve group with relatively early RA, demonstrated similar efficacy and radiographic inhibition rates.[23] This is particularly interesting given that previous studies of abatacept were largely performed in cohorts with more advanced disease and in patients who had often failed a number of biologics. Clinically meaningful improvements in patient-reported functional and pain scores were reported with subcutaneous abatacept. Comparable reductions in HAQ-DI scores and pain VAS were observed with subcutaneous abatacept versus adalimumab[23] and intravenous abatacept.[19]

Patient preference for self-administered therapy can be an important factor in choosing a biologic therapy. In one study of 90 patients with RA, 41% of those receiving anti-TNF therapy and 52.5% of those receiving nonbiologic DMARD agents preferred subcutaneous administration of treatment over intravenous or intramuscular routes. Furthermore, 62.5% of patients in the anti-TNF group preferred to receive treatment at home, rather than as an inpatient or on a day ward compared with 52% of patients in the nonbiologic DMARD group.[33] The data reviewed suggest that patients can be switched from intravenous to subcutaneous abatacept without loss of efficacy and with no increased risk of side effects.[22]

Immunogenicity has received increased attention recently because it can be linked to loss of efficacy of biologic agents.[27–30] ACCOMPANY[20] and ALLOW[21] demonstrated an excellent immunogenicity profile for subcutaneous abatacept, with antibodies against the drug detected in <5% of patients either in combination with methotrexate or as monotherapy.

The results from the pooled safety data available to date demonstrated acceptable safety for subcutaneous abatacept, with rates of side effects similar to those for intravenous abatacept,[31,32] although long-term data with more patient-years of exposure are needed.

This review is limited by the small number of Phase III studies available for subcutaneous abatacept. Only three of the reviewed studies were randomized controlled trials, and the remaining two were open-label studies. In addition, data for structural damage were only available from one study. More long-term trials and post-marketing studies with larger numbers of patients are required to assess the long-term efficacy and safety of subcutaneous abatacept.

Conclusion

This paper has reviewed the efficacy and safety data for subcutaneous abatacept from the clinical studies available to date. Subcutaneous abatacept in combination with methotrexate has demonstrated efficacy in RA, reducing the signs and symptoms of the disease, inhibiting the progression of structural damage, and improving physical function in patients with moderate to severe RA. The number of patients receiving subcutaneous abatacept monotherapy in the trials is small and more data are needed to assess the efficacy of subcutaneous abatacept as monotherapy. Head-to-head studies showed subcutaneous abatacept to be noninferior to intravenous abatacept and adalimumab in active RA. Immunogenicity rates to subcutaneous abatacept were very low and the safety profile was acceptable and consistent with that of intravenous abatacept. Subcutaneous abatacept is a new option for patients with RA and could be particularly useful for those who are unable or unwilling to receive an intravenous infusion.

Disclosure

The authors report no conflicts of interest in this work.

References
1. Munro R, Hampson R, McEntegart A, Thomson EA, Madhok R, Capell H. Improved functional outcome in patients with early rheumatoid arthritis treated with intramuscular gold: results of a five year prospective study. *Ann Rheum Dis*. 1998;57(2):88–93.
2. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum*. 2005;52(11):3381–3390.
3. van der Heide A, Jacobs JW, Bijlsma JW, et al. The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized, controlled trial. *Ann Intern Med*. 1996;124(8):699–707.
4. Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. *Rheumatology (Oxford)*. 2004;43(7):906–914.
5. 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(3):492–509.
6. Nam JL, Ramiro S, Gaujoux-Viala C, et al. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2013 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis*. 2014;73(3): 516–528.
7. Sayegh MH, Turka LA. The role of T-cell costimulatory activation pathways in transplant rejection. *N Engl J Med*. 1998;338(25): 1813–1821.
8. Foy TM, Aruffo A, Bajorath J, Buhlmann JE, Noelle RJ. Immune regulation by CD40 and its ligand GP39. *Annu Rev Immunol*. 1996;14: 591–617.
9. Lenschow DJ, Walunas TL, Bluestone JA. CD28/B7 system of T-cell costimulation. *Annu Rev Immunol*. 1996;14:233–258.
10. Quattrocchi E, Dallman MJ, Feldmann M. Adenovirus-mediated gene transfer of CTLA-4Ig fusion protein in the suppression of experimental autoimmune arthritis. *Arthritis Rheum*. 2000;43(8):1688–1697.
11. Larsen CP, Elwood ET, Alexander DZ, et al. Long-term acceptance of skin and cardiac allografts after blocking CD40 and CD28 pathways. *Nature*. 1996;381(6581):434–438.
12. Corbo M, Valencia X, Raymond R, Summerill R, Agrawal S, Townsend R. Subcutaneous administration of abatacept in patients with rheumatoid arthritis: pharmacokinetics, safety and immunogenicity. *Ann Rheum Dis*. 2009;68:S574.
13. Schiff M, Pritchard C, Huffstutter JE, et al. The 6-month safety and efficacy of abatacept in patients with rheumatoid arthritis who underwent a washout after anti-tumour necrosis factor therapy or were directly switched to abatacept: the ARRIVE trial. *Ann Rheum Dis*. 2009;68(11):1708–1714.
14. Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N Engl J Med*. 2005;353(11):1114–1123.
15. Westhovens R, Kremer JM, Moreland LW, et al. Safety and efficacy of the selective costimulation modulator abatacept in patients with rheumatoid arthritis receiving background methotrexate: a 5-year extended Phase IIB study. *J Rheumatol*. 2009;36(4):736–742.
16. Kremer JM, Russell AS, Emery P, et al. Long-term safety, efficacy and inhibition of radiographic progression with abatacept treatment in patients with rheumatoid arthritis and an inadequate response to methotrexate: 3-year results from the AIM trial. *Ann Rheum Dis*. 2011;70(10):1826–1830.
17. Kremer JM, Genant HK, Moreland LW, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann Intern Med*. 2006;144(12):865–876.
18. 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(12): 1870–1877.
19. Genovese MC, Covarrubias A, Leon G, et al. Subcutaneous abatacept versus intravenous abatacept: a Phase IIIb noninferiority study in patients with an inadequate response to methotrexate. *Arthritis Rheum*. 2011;63(10):2854–2864.
20. Nash P, Nayiager S, Genovese MC, et al. Immunogenicity, safety, and efficacy of abatacept administered subcutaneously with or without background methotrexate in patients with rheumatoid arthritis: results from a Phase III, international, multicenter, parallel-arm, open-label study. *Arthritis Care Res (Hoboken)*. 2013;65(5):718–728.
21. Kaine J, Gladstein G, Strusberg I, et al. Evaluation of abatacept administered subcutaneously in adults with active rheumatoid arthritis: impact of withdrawal and reintroduction on immunogenicity, efficacy and safety (Phase IIib ALLOW study). *Ann Rheum Dis*. 2012;71(1):38–44.
22. Keystone EC, Kremer JM, Russell A, et al. Abatacept in subjects who switch from intravenous to subcutaneous therapy: results from the Phase IIIb ATTUNE study. *Ann Rheum Dis*. 2012;71(6):857–861.

23. Weinblatt ME, Schiff M, Valente R, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a Phase IIIb, multinational, prospective, randomized study. *Arthritis Rheum*. 2013;65(1):28–38.

24. Schiff M, Weinblatt ME, Valente R, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. *Ann Rheum Dis*. 2014;73(1):86–94.

25. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. *J Rheumatol*. 2000;27(1):261–263.

26. Genovese M, Pacheco-Tena C, Covarrubias A, Leon G, Mysler E, Keiserman M. Subcutaneous abatacept: long-term data from the ACQUIRE trial. *Arthritis Rheum*. 2012;64(Suppl 10):S201.

27. Schellekens H. Factors influencing the immunogenicity of therapeutic proteins. *Nephrol Dial Transplant*. 2005;20 Suppl 6:vi3–vi9.

28. Haggerty HG, Abbott MA, Reilly TP, et al. Evaluation of immunogenicity of the T-cell costimulation modulator abatacept in patients treated for rheumatoid arthritis. *J Rheumatol*. 2007;34(12):2365–2373.

29. Dore RK, Mathews S, Schechtman J, et al. The immunogenicity, safety, and efficacy of etanercept liquid administered once weekly in patients with rheumatoid arthritis. *Clin Exp Rheumatol*. 2007;25(1):40–46.

30. Bartelds GM, Wijbrandts CA, Nurmohamed MT, et al. Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. *Ann Rheum Dis*. 2007;66(7):921–926.

31. Alten R, Kaine J, Keystone E, et al. Safety profile of subcutaneous abatacept focusing on clinically relevant events in patients with rheumatoid arthritis (RA) and up to 4.5 years of exposure. *Arthritis Rheum*. 2011;63:S150.

32. Alten R, Kaine J, Keystone E, Nash P, Delaet I, Qi K. Safety of subcutaneous abatacept in patients with rheumatoid arthritis (RA): integrated analysis of five clinical trials up to 4.5 years. *Ann Rheum Dis*. 2011; 70 Suppl 3:617.

33. Williams EL, Edwards CJ. Patient preferences in choosing anti-TNF therapies-R1. *Rheumatology (Oxford)*. 2006;45(12):1575–1576.