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Abatacept reduces disease activity and ultrasound power Doppler in ACPA-negative undifferentiated arthritis: a proof-of-concept clinical and imaging study

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Abstract

Objectives. No proven treatment exists for ACPA-negative undifferentiated arthritis (UA). The aim of this study was to evaluate whether abatacept is effective in treating poor prognosis, ACPA-negative UA, including its effect on power Doppler on US (PDUS).

Methods. A proof-of-concept, open-label, prospective study of 20 patients with DMARD-naïve, ACPA-negative UA ($\geqslant$2 joint synovitis) and PDUS $\geqslant$ 1 with clinical and 20-joint US (grey scale/PDUS) assessments at baseline, 6, 12, 18 and 24 months. All patients received 12 months of abatacept (monotherapy for minimum first 6 months). The primary end point was a composite of the proportion of patients that at 6 months achieved DAS44 remission, a maximum of one swollen joint for at least 3 consecutive months and no radiographic progression (over 0–12 months).

Results. Twenty of the 23 patients screened were enrolled [14 female; mean (S.D.) age 53.4 (11.2) years, symptom duration 7.5 (0.9) months]. Two (10%) achieved the composite primary end point. A reduction in the mean (S.D.) DAS44 was observed from a baseline value of 2.66 (0.77) to 2.01 (0.81) at 6 months and to 1.78 (0.95) at 12 months. The DAS44 remission rates were 6/20 (30%; 95% CI: 15, 51%) at 6 months and 8/20 (40%; 95% CI: 22, 62%) at 12 months. A striking decrease in the median (interquartile range; IQR) total PDUS score was noted from 10 (4–23) at baseline to 3 (2–12) and 3 (0–5) at 6 and 12 months, respectively.

Conclusion. This report is a first in potentially identifying an effective therapy, abatacept monotherapy, for poor-prognosis, ACPA-negative UA, supported by a clear reduction in PDUS. These data justify evaluation in a controlled study.

Key words: abatacept, undifferentiated arthritis, inflammatory arthritis, ACPA, ultrasound

Rheumatology key messages

- In ACPA-negative undifferentiated arthritis, abatacept led to clinical improvements, particularly in swollen joint count and CRP.
- Reduction in ultrasound PDUS was observed within 6 months of commencing abatacept.
- Following abatacept withdrawal, clinical and US measures were maintained, implying a possible modulatory role.

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Introduction

An emerging aim in the management of RA is to identify patients at the pre-RA stage and intervene with immunomodulatory therapies to prevent its progression to RA. Undifferentiated arthritis (UA) is defined as an inflammatory

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oligo- or poly-arthritis that does not fulfil criteria for a definitive diagnosis.

RF and APCA are key elements that enable the classification of RA [1, 2] with different rates of progression and response to treatment observed [3, 4]. They are associated with persistence of inflammatory arthritis and are the best predictors of radiographic progression [5–7]; thus, they are considered to be factors associated with poor prognosis. ACPA-negative RA, however, is also associated at baseline with a high level of disease activity, poor functional outcome and erosive disease [8, 9]. Power Doppler US (PDUS) is a powerful predictive factor of persistent inflammatory arthritis in autoantibody-negative UA [10], and thus is a poor prognosis factor that can be used as a tool to select ACPA-negative UA at highest likelihood of persistence. The structural outcomes and pathological distinction between PD-positive and -negative ACPA-negative UA have, however, not been determined to date.

Several studies have suggested the ability of abatacept and/or MTX to delay progression of patients with ACPA-positive UA [11, 12] or improve outcomes [13]. There is no proven therapy for ACPA-negative UA.

The hypothesis underlying this proof-of-concept study was that 12 months open-label abatacept would be effective in reducing persistent disease in adult subjects with ACPA-negative UA, characterized by presence of PDUS, previously shown to be strongly predictive of persistence—the Abatacept in ACPA Sero-negative Undifferentiated arthritis study.

Patients and methods

The study was sponsored by the University of Leeds (Sponsor Ref: RR08/8686; EudraCT: 2008-004878-41), approved by the Leeds (East) Research Ethics Committee (REC reference no. 09/H1306/33) and conducted in accordance with the International Conference on Harmonization Good Clinical Practice and local regulations. All patients provided written informed consent for this ACPA Sero-negative Undifferentiated arthritis study.

Patients

Patients that satisfied the following key eligibility criteria were considered for this study: patients with UA defined as symptomatic synovitis of two or more joints (who did not meet diagnostic criteria for any other rheumatic disease); symptom duration [defined as the time from the onset of symptoms (joint pain, swelling, or significant stiffness) of UA to enrolment] of >12 weeks and $\leqslant 18$ months; being negative for ACPA (CCP2); and US evidence of a PD-positive signal of $\geqslant 1$ (in at least one of 20 joints scanned); no prior therapy with any DMARD therapy before screening; and no i.m. or IA steroid within 6 weeks prior to baseline was permitted. To minimize the risk of including self-limiting UA, particularly in the absence of autoantibodies, the PDUS criterion was included as a poor-prognosis factor of persistence [10], thus ensuring subjects with definite, active, synovitis with likelihood of persistence of arthritis were recruited.

Study design

The study period was 24 months. Enrolled subjects received intravenous abatacept monotherapy (as per the standardized body weight–based dosing regimen of: <60 kg: 500 mg; 60–100 kg: 750 mg; >100 kg: 1000 mg) for the first 12 months of the study. Abatacept was administered on days 1, 15 and 29, and every 28 days thereafter for a total of 14 doses, with subsequent 12-month follow-up. Subjects were permitted to take NSAIDs throughout the study. Single i.m. or IA corticosteroid medication could be utilized at a maximum frequency of every 3 months during the trial, at the discretion of the investigator; but was not permitted within 8 weeks of a disease activity assessment.

Subjects with persistent UA after 6 months of study medication received additional DMARD treatment at the discretion of the investigator. Subjects who developed RA at any point during the trial were discontinued from the study and allowed to receive DMARDs at the discretion of the investigator.

Laboratory analyses

The Human Leucocyte Antigen (HLA)–DRB1 subtyping with HLADR 1, 4 and 10 serotypes that recognize the *HLADRB1*01, HLADRB1*04* and *HLADR10*1001* genes, respectively, were tested. Patients that tested positive for any of these three genotypes were assigned shared-epitope–positive status. Anti-CCP antibody levels [anti-CCP2; ImmunoCap 250 (Phadia)] were also measured, with a cut-off of <7 U/ml.

PDUS

Two rheumatologists (C.R., J.E.F.) performed blinded PDUS; both received training in our Institution that included reproducibility and reliability testing before contributing to research studies. US scanning was performed (using a GE E9 machine equipped with a 6–15 MHz linear transducer) to determine the presence of synovitis at baseline and at 6-monthly intervals to study completion (24 months). Specifically, grey scale (GS) and PDUS assessments, and erosions at baseline and 12 and 24 months were scored according to the OMERACT definition [14]. Bilateral wrist, knee and second to fifth MCP and PIP joints (20 joints in total) were scanned and each assigned a GS and PDUS score (maximum of 3), giving a maximum total scores of 60 for each.

Radiographic assessment

Plain radiographs of bilateral hands (carpal, MCP and PIP joints) were performed at baseline and 6, 12 and 24 months after the start of study medication to assess structural damage. Radiographs were scored as per the modified Genant-modified Sharp scoring system [15] by a single reader, with re-reading of baseline radiographs to ensure acceptable reproducibility. All time points for individual patients were viewed simultaneously but in random order and with the acquisition dates masked in order to blind the reader to chronology.

Patient-reported outcomes

Assessments to determine self-reported functional status (Disability Index of HAQ), health status (EQ-5D) and

health-related quality of life were undertaken at the following time points: 3, 6, 12, 18 and 24 months following the start of open-label abatacept.

Statistical analysis

This was a proof-of-concept, open-label study. All available data from all subjects who received at least one infusion of study medication at any time were included in the safety and efficacy analyses, unless otherwise specified.

The primary outcome of the study was the proportion of subjects that at 6 months achieved DAS44 remission (DAS44 <1.6), had a maximum of one swollen joint for at least 3 consecutive months and had no radiographic progression (defined as change that did not exceed the smallest detectable difference) over the first year.

Secondary efficacy outcome measures included the proportion of subjects that achieved: DAS44 remission, DAS28 remission, ACR remission and modified remission, and the mean DAS28 and Persistent Inflammatory Symmetrical Arthritis (PISA) score at 3, 6, 12, 18 and 24 months. Spearman's rank correlation (rho) was used to explore for an association between baseline PDUS score and DAS44 remission.

Adverse events (AEs) and serious AEs (SAEs) were summarized as the total number of events and number of unique events (with recurring events summarized per patient as the most severe occurrence of that event).

Handling of missing data

Screening values were imputed for missing baseline values. Patients who withdrew due to lack of efficacy were considered non-responders for the primary end point. Patients with missing data for an individual variable at any visit (with the exception of the 6-month visit) were excluded from the analysis of that variable at that visit.

Results

Baseline characteristics

Twenty-three patients were screened, of which the target 20 patients were enrolled. One subject who was negative for ACPA prior to screening had a positive titre at screening and was inadvertently included, constituting a protocol violation. The data were analysed twice: the first analysis included all 20 patients, then it was repeated with this subject excluded. The other baseline characteristics and outcome of the analyses did not differ significantly. Results from all 20 are thus presented (and the analyses with the CCP-positive subject excluded are available in the supplemental file; Tables S1–S5, available at *Rheumatology* Online, corresponding to Tables 1–5 in this report). Baseline characteristics are summarized in Table 1. At the time of study protocol development and patient recruitment, the 2010 RA classification criteria [16] had not been established. Retrospectively applying these criteria to our cohort, nine patients would satisfy the criteria for RA classification.

Table 1 Baseline characteristics

Characteristic	ACPA-negative UA (n = 20)
Age at baseline, mean (S.D.), years	53.4 (11.2)
Female, *n*/*N* (%)	14/20 (70)
RF positive, *n*/*N* (%)	1/20 (5)
ACPA positive, *n*/*N* (%)	1/20 (5)[a]
SE positive,[b] *n*/*N* (%)	11/18 (61.1)[c]
Single allele: 01	2/18 (11.1)
Single allele: 04	6/18 (33.3)
Single allele: 10	0
Double allele: 01/04	2/18 (11.1)
Double allele: 01/10	0
Double allele: 04/10	1/18 (5.6)
TJC28/RAI, mean (S.D.)	7 (0–18)/6 (0–18)
SJC28/44, mean (S.D.)	2 (0–12)/2 (0–14)
CRP, mg/l, mean (S.D.)	9 (0–117)
DAS28-ESR, mean (S.D.)	4.22 (1.12)
DAS44-ESR, mean (S.D.)	2.65 (0.75)
Baseline total GS, median (IQR)	30.5 (18–40)
Baseline total PDUS, median (IQR)	10 (4–23)

[a]One subject that was negative for ACPA prior to screening had a positive titre at screening and was inadvertently included. This was not the same patient who was RF positive (which was not an exclusion criterion). [b]HLADR 1, 4 and 10 serotypes that recognize HLADRB1*01, HLADRB1*04 and HLADR10*1001 genes, respectively, were tested. Patients that tested positive for any of these three genotypes were assigned SE-positive status. [c]Sample not taken (n = 1); incorrect sample sent for processing (n = 1). *n*/*N*: denotes number of subjects positive for the characteristic/total number of subjects; RF, positive >20 μ/ml; SE: shared epitope; TJC: tender joint count; SJC: Swollen joint count; GS: grey scale; PDUS: power Doppler US.

Missing data

An ESR that was unavailable at 12 months for one subject and 18 months for another was imputed using a published nomogram [17] for converting CRP to ESR.

Withdrawals

Two patients withdrew after 6 and 12 months for an AE and SAE (see AEs later). A further three subjects were lost to follow-up after 12 months (reasons unknown).

Primary end point

Only 2/20 (10%) subjects achieved the composite primary endpoint (DAS44 remission, a maximum of one swollen joint for at least 3 consecutive months and no radiographic progression defined) at 6 months.

Evaluating the individual components, the majority, 15/18 (83%; 95% CI: 61, 94%) had no radiographic progression (baseline radiograph missing in 1 and follow-up radiographs missing in 2) and 12/20 (60%; 95% CI 39, 78%) had a maximum of one swollen joint or less for at least 3

Table 2 Clinical efficacy variables over 2-year study[a]

Variable	Baseline	3 months	6 months	12 months[b]	18 months	24 months
DAS44-ESR rem,*n*/*N*(%)	2/20(10.0)	4/18(22.2)	6/20(30.0)	8/20(40.0)	7/17(41.2)	6/15(40.0)
(<1.6)95% CI	2.8, 30.1%	9.0, 45.2%	14.5, 51.9%	21.9, 61.3%	21.6, 64.0%	19.8, 64.3%
DAS28-ESR rem,*n*/*N*(%)	0/20(0)	5/18(27.8)	6/20(30.0)	10/20(50.0)	8/17(47.1)	6/15(40.0)
(<2.6)95% CI	0, 16.1%	12.5, 50.9%	14.5, 51.9%	29.9, 70.1%	26.2, 69.0%	19.8, 64.3%
mACR rem,*n*/*N*(%)	1/20(5.0)	2/20(10.0)	4/20(20.0)	4/20(20.0)	3/17(17.6)	3/15(20.0)
(Boolean)95% CI	0.9, 23.6%	2.8, 30.1%	8.1, 41.6%	8.1, 41.6%	6.2, 41.0%	7.0, 45.2%
DAS44-ESR, mean(S.D.)	2.65(0.75)	2.16(0.85)	2.04(0.84)	1.82(0.94)	1.84(0.86)	2.07(1.07)
N	20	18	20	20	17	15
DAS28-ESR,mean(S.D.)	4.22(1.12)	3.25(1.31)	3.08(1.22)	2.71(1.20)	2.90(1.31)	3.03(1.40)
N	20	18	20	20	17	15
SJC44, median(IQR)	2(1–6)	0(0–3)	0(0–1)	0(0–1)	0(0–1)	1(0–4)
N	20	19	20	20	17	15
SJC28, median(IQR)	2(1–5)	0(0–2)	0(0–0)	0(0–1)	0(0–1)	0(0–4)
n	20	19	20	20	17	R
RAI, median(IQR)	6(4–10)	3(1–9)	4(1–8)	3(1–6)	4(1–6)	4(0–13)
N	20	19	20	20	17	15
TJC28, median(IQR)	7(5–15)	3(1–6)	3(1–9)	3(1–5)	4(1–7)	4(0–8)
n	20	19	20	20	17	15
Symptomatic,*n*/*N*(%)	15/20(75.0)	8/19(42.1)	5/20(25.0)	6/20(30.0)	6/17(35.3)	7/15(46.7)
Synovitis,95% CI	53.1, 88.8%	23.1, 63.7%	11.2, 46.9%	14.5, 51.9%	17.3, 58.7%	24.8, 70.0%
CRP, mg/l						
Median(IQR)	9(0–21)	0(0–15)	0(0–8)	0(0–6)	0(0–7)	0(0–0)
n	20	19	20	20	16	15
ESR, mm/h						
Median(range)	12(5 to 27)	7(3 to 16)	8(7 to 11)	8(4 to 12)	5(4 to 14)	10(4 to 14)
n	20	19	20	20	17	15
PISA score, *n*/*N*(%)						
0	1/20(5.0)	1/20(5.0)	1/19(5.3)	1/19(5.3)	1/16(6.3)	1/14(7.1)
1	6/20(30.0)	6/20(30.0)	5/19(26.3)	6/19(31.6)	4/16(25.0)	4/14(28.6)
2	4/20(20.0)	6/20(30.0)	6/19(31.6)	6/19(31.6)	4/16(25.0)	5/14(35.7)
3	6/20(30.0)	5/20(25.0)	5/19(26.3)	6/19(31.6)	6/16(37.5)	4/14(28.6)
4	3/20(15.0)	2/20(10.0)	2/19(10.5)	–	1/16(6.3)	–

[a]Abatacept stopped at month 12. [b]Imputing withdrawal values for one patient who withdrew after 35 weeks due to AE. DAS44: DAS incorporating SJC44, RAI and ESR; EMS: Early Morning Stiffness; mACR: modified ACR; Max: Maximum; Min: Minimum; Phys: Physician; RAI: Ritchie Articular Index; Rem: remission; SJC28: 28-Swollen Joint Count; SJC44: 44-Swollen Joint Count; TJC28: 28-Tender Joint Count; VAS: Visual Analogue Scale; *n*/*N*: denotes number of subjects positive for the characteristic/total number of subjects.

consecutive months. Only 6/20 (30%; 95% CI: 15, 52%) subjects achieved DAS44 remission.

Secondary end points

Clinical outcomes

Table 2 details the clinical efficacy variables over the 2-year study period.

Persistent synovitis

At 6 and 12 months, 25% (5/20) and 32% (6/19) patients, respectively, demonstrated persistent clinical synovitis (two or more tender and swollen joints).

Disease activity scores and remission rates

Reduction in mean (S.D.) DAS44/DAS28 was observed from baseline values of 2.66 (0.77)/4.26 (1.13), respectively, to 2.01 (0.81)/3.07 (1.26) at 6 months; with further notable reduction to 1.78 (0.95)/2.64 (1.19) at 12 months, respectively.

At 6 months, DAS28 remission was achieved in 6/20 (30%; 95% CI: 14.5, 52%). At 12 months, DAS44 and DAS28 remission rates (withdrawal visit data from ~9 months imputed for one patient) were observed in 8/20 (40%; 95% CI: 22, 61%) and 10/20 (50%; 95% CI: 30,70%) subjects, respectively.

PISA score

At baseline, 9/20 (40%) of patients had a PISA score of $\geqslant 3$, consistent with poor prognosis; this was reduced to 7/19 (36.8%) at month 6 and 6/19 (37.5%) at both months 12 and 24.

Changes in individual DAS components

Table 2 provides the values of all clinical variables at baseline and subsequent time points. Immediate suppression

Table 3 Power Doppler US findings over the 2-year study period

Variable	Baseline	6 months	12 months	18 months	24 months
Total GS score					
Median (IQR)	30 (18–40)	22 (16–32)	19 (12–29)	18 (13–29)	20 (13–30)
n	20	20	19	14	14
Total number of joints scoring GS > 0					
Median (IQR)	14 (10–22)	12 (10–19)	13 (8–17)	14 (8–16)	14 (8–19)
n	20	20	19	14	14
Total number of joints scoring GS > 1					
Median (IQR)	10 (6–15)	7 (6–12)	7 (5–10)	5 (4–11)	6 (3–12)
n	20	20	19	14	14
Total PDUS score					
Median (IQR)	10 (4–23)	3 (2–12)	3 (0–5)	3 (0–7)	2 (1–5)
n	20	20	19	14	14
Total number of joints scoring PDUS>0					
Median (IQR)	6 (4–12)	2 (2–6)	2 (0–4)	2 (0–5)	2 (1–3)
n	20	20	19	14	14
Total number of joints scoring GS > 1&PDUS>0					
Median (IQR)	5 (2–11)	2 (1–5)	1 (0–3)	1 (0–3)	1 (0–3)
n	20	20	19	14	14
Total number of joints with erosions					
Median (IQR)	1 (0–3)		1 (0–4)		2 (0–2)
n	20		19		14
Total erosion count					
Median (IQR)	1 (0–3)		1 (0–5)		2 (0–3)
n	20		19		14

of median (IQR) CRP was observed from 9 mg/l (0–21) at baseline to 0 mg/l (0–15) at 3 months and 0 mg/l (0–8) at 6 months [corresponding to a 3-month change in median (IQR)/range CRP of −3 (−15, 0)/−43, 5; a 6-month change of −1 (−14, 0)/−90 to 7]. Similarly, effective reduction in joint counts was observed with median (IQR) swollen joint count 28 (SJC28) of 2 (1, 5) at baseline to 0 (0, 1) and 0 (0, 1) at 6 and 12 months respectively [corresponding to a median (IQR/range) change in SJC28 at 6 months of −1 (−3, 0/−10, 8) and at 12 months of −1 (−5, 0/−11 to 8)]. The median (IQR) tender joint count 28 changed from 7 (5–15) at baseline to 3 (1–9) and 2 (1–5) at 6 and 12 months, respectively [corresponding to a median (IQR/range) change in tender joint count 28 at 6 months of −5 (−7, −1/−13, 10) and at 12 months of −6 (−9, −2/−17 to 6)]. A modest reduction was observed for the patient visual analogue scale (VAS) general health, with median (IQR) values of 49 (24–59) at baseline to 25 (9–50) and 16 (3-33) at 6 and 12 months respectively [corresponding to a median (IQR/range) change at 6 months of −14 (−35, −3/−40, 52) and at 12 months of −19 (−43, −9/−58, 62)].

Patient-reported outcomes

A reduction in the median (IQR) HAQ disability index (HAQDI) was noted from a baseline value of 0.88 (0.32–1.63) to 0.69 (0–1.38) at 6 months and 0.57 (0–1.38) at 12 months. Similar to the general health, a smaller reduction in median (IQR) patient VAS disease activity was observed, from 52 (36–63) at baseline to 28 (18–41) and 24 (4–29) at 6 and 12 months, respectively. The median (IQR) health-related quality of life improved from 12 at baseline to 8 (1–11) and 4 (0–15) at 6 and 12 months, respectively.

PDUS findings

A striking decrease in the median (IQR) total PDUS score was noted from 10 (4–23) at baseline to 3 (2–12) and 3 (0–5) at 6 and 12 months, respectively. A more modest reduction in the median (IQR) total GS score was recorded; 30 (18–40) at baseline, 22 (16–32) at 6 months and 19 (12–29) at 12 months. This was mainly attributable to reduction in the median (IQR) total number of joints with GS >1 [from 10 (6–15) to 7 (6–12) and 7 (5–10) at baseline, 6 and 12 months, respectively (Table 3). The median (IQR) number of joints with GS >1 and PDUS >0 at baseline was 5 (2–11), and this was reduced to 2 (1–5) and 1 (0–3) at 6 and 12 months, respectively (the results are detailed in Table 3).

Analysis of PDUS by joint site

Table 4 details the maximum GS and PDUS scores by each joint site. The wrist joint was the most resistant to reduction in GS and PDUS. All patients had a GS of two or more in the wrist at baseline and 12 months. One patient achieved a GS of 0 by 24 months. A reduction in wrist PDUS score was observed in a small proportion. At baseline, 45% (9/20) and 25% (5/20) had PDUS of two and one, respectively, in the wrist; with 32% (6/19) and 37% (7/19), respectively, by 12 months. In contrast, notable reductions in both GS and particularly PDUS were seen

Table 4 Individual joint (maximum) power Doppler US scores over 2-year study period

Variable	Baseline	6 months	12 months	18 months	24 months
Wrist (maximum)					
GS score					
0				–	1/14(7.1)
1	–	–	–	8/14(57.1)	5/14(35.7)
2	4/20(20.0)	5/20(25.0)	6/19(31.6)	6/14(42.9)	7/14(50.0)
3	9/20(45.0)	10/20(50.0)	11/19(57.9)	–	1/14(7.1)
	7/20(35.0)	5/20(25.0)	2/19(10.5)		
PDUS score					
0	6/20(30.0)	6/20(30.0)	6/19(31.6)	9/14(64.3)	10/14(71.4)
1	5/20(25.0)	5/20(25.0)	7/19(36.8)	4/14(28.6)	2/14(14.3)
2	9/20(45.0)	9/20(45.0)	6/19(31.6)	1/14(7.1)	2/14(14.3)
3	–	–	–	–	–
Erosion present	7/20(35.0)		11/19(57.9)		7/14(50.0)
Erosion count					
0	13/20(65.0)		8/19(42.1)		7/14(50.0)
1	5/20(25.0)		7/19(36.8)		5/14(35.7)
2	1/20(5.0)		4/19(21.1)		2/14(14.3)
3	1/20(5.0)		–		–
MCP (maximum)					
GS score					
0	1/20(5.0)	–	1/19(5.3)	–	1/14(7.1)
1	4/20(20.0)	2/20(10.0)	–	2/14(14.3)	4/14(28.6)
2	5/20(25.0)	15/20(75.0)	17/19(89.5)	9/14(64.3)	4/14(28.6)
3	10/20(50.0)	3/20(15.0)	1/19(5.3)	3/14(21.4)	5/14(35.7)
Total PDUS score					
0	4/20(20.0)	8/20(40.0)	11/19(57.9)	8/14(57.1)	10/14(71.4)
1	5/20(25.0)	5/20(25.0)	4/19(21.1)	2/14(14.3)	1/14(7.1)
2	6/20(30.0)	5/20(25.0)	4/19(21.1)	3/14(21.4)	2/14(14.3)
3	5/20(25.0)	2/20(10.0)	–	1/14(7.1)	1/14(7.1)
Erosion present	5/20(25.0)		5/19(26.3)		4/14(28.6)
Erosion count					
0	15/20(75.0)		14/19(73.7)		10/14(71.4)
1	3/20(15.0)		4/19(21.1)		4/14(28.6)
2	2/20(10.0)		1/19(5.3)		–
PIP (maximum)					
GS score					
0	6/20(30.0)	8/20(40.0)	9/19(47.4)	6/14(42.9)	4/14(28.6)
1	1/20(5.0)	–	–	2/14(14.3)	4/14(28.6)
2	2/20(10.0)	3/20(15.0)	7/19(36.8)	2/14(14.3)	2/14(14.3)
3	11/20(55.0)	9/20(45.0)	3/19(15.8)	4/14(28.6)	4/14(28.6)
Total PDUS score					
0	9/20(45.0)	13/20(65.0)	15/19(78.9)	12/14(85.7)	11/14(78.6)
1	4/20(20.0)	1/20(5.0)	3/19(15.8)	–	–
2	2/20(10.0)	5/20(25.0)	1/19(5.3)	2/14(14.3)	3/14(21.4)
3	5/20(25.0)	1/20(5.0)	–	–	–
Erosion present	6/20(30.0)		6/19(31.6)		2/14(14.3)
Erosion count					
0	14/20(70.0)		13/19(68.4)		12/14(85.7)
1	5/20(25.0)		6/19(31.6)		1/14(7.1)
2	1/20(5.0)		–		1/14(7.1)
Knee (maximum)					
GS score					
0	2/20(10.0)	–	2/19(10.5)	–	1/14(7.1)
1	2/20(10.0)	6/20(30.0)	2/19(10.5)	4/14(28.6)	5/14(35.7)
2	11/20(55.0)	10/20(50.0)	14/19(73.7)	8/14(57.1)	6/14(42.9)
3	5/20(25.0)	4/20(20.0)	1/19(5.3)	2/14(14.3)	2/14(14.3)
Total PDUS score					
0	11/20(55.0)	14/20(70.0)	13/19(68.4)	11/14(78.6)	11/14(78.6)
1	5/20(25.0)	3/20(15.0)	4/19(21.1)	2/14(14.3)	2/14(14.3)
2	4/20(20.0)	2/20(10.0)	2/19(10.5)	1/14(7.1)	1/14(7.1)
3	–	5.0 (1/20)	–	–	–

All values presented are *n*/*N* (%).

Table 5 Radiographic scores over 2-year study period

Variable	Visit			
	Baseline (n = 18)	6 months (n = 16)	12 months (n = 17)	24 months (n = 10)
JSN score				
Mean (S.D.)	3.4 (6.0)	3.7 (6.4)	3.9 (7.0)	3.7 (4.8)
Median (IQR)	1 (0–5)	1 (0–5)	0.5 (0–5)	2 (0–5)
Erosion score				
Mean (S.D.)	4.3 (5.2)	4.7 (6.6)	4.6 (6.6)	3.5 (3.0)
Median (IQR)	3 (0–6)	3 (0–4)	3 (0–5)	3 (1–5)
Total Genant-modified Sharp score				
Mean (S.D.)	7.5 (10.9)	8.1 (12.6)	8.3 (13.2)	7.2 (7.1)
Median (IQR)	4 (1–9)	4 (1–9)	4 (1–8)	4 (3–11)

IQR: Interquartile Range; JSN: Joint Space Narrowing.

in the MCPs and PIPs by 6 months, with continued improvement by 12 months. At 6 and 12 months, PDUS = 0 in the wrist, MCP, PIP and knee joints was observed in 30, 40, 65, 70% and 32, 58, 79, 68% of subjects, respectively (compared with 30, 20, 45 and 55% at baseline, respectively). Absence of GS was infrequent except in the PIP joint in nine subjects; none in the wrist, one subject in the MCP and two in the knee.

Baseline PDUS and DAS44 remission

There was no evidence of an association between baseline PDUS score and change in DAS44 (Spearman's $\rho = -0.16$, $n = 19$). Baseline PDUS score was slightly lower in those who achieved DAS44 remission at 6 months [median (IQR) 9 (3–14), $n = 6$] than in those who did not [12 (5–23), $n = 13$].

Radiographic progression

The re-read of baseline radiographs for reproducibility was excellent (ICC = 0.98 [0.95–0.99]). The mean and median joint space narrowing, erosion and Genant-modified Sharp scores at baseline, months 6, 12 and 24 are presented in Table 5. Of note, 18/20 patients had baseline radiographs, with only half the patients having repeat evaluation at month 24. Median joint space narrowing and erosion scores remained unchanged throughout. Mean and median total modified Sharp scores remained stable throughout the study period.

Additional medication

None of the patients were prescribed oral steroids within the first 12 months, and no additional synthetic DMARDs were commenced in the first 6 months of the study, in line with the study protocol.

Months 0–6

One patient received an IA shoulder injection at week 11 by their GP, which constituted a protocol violation.

Months 6–12

One patient received two IA injections (80 mg depomedrone each time) for a Baker's cyst/right knee effusion at weeks 25 and 28. Two patients required synthetic DMARDs within the first 12 months; one subject was prescribed MTX (20 mg weekly) at week 32 and withdrew 3 weeks later, and the second received HCQ (400 mg daily) at week 29.

Months 12–24 following abatacept cessation

Ten patients received synthetic DMARDs after abatacept was stopped at 12 months. Seven of these were prescribed MTX (one of whom was the subject already taking HCQ, prescribed at week 29 as indicated above) and the other three received HCQ.

Outcomes following cessation of abatacept

Disease activity outcomes

By 24 months, 47% (7/15) of patients with evaluable data had persistent clinical synovitis. Following cessation of abatacept, small increases in DAS44/28 values were observed, but with a plateau at 24 months (similar values to those seen 6 months into the study). The DAS44 and DAS28 remission states were broadly maintained at 18 and 24 months (see Table 2). The CRP reduction described above in the first year was maintained throughout the follow-up time points; as were joint counts (Table 2).

AEs

There were no serious AEs during the first 12 months. Subsequent to abatacept cessation, one patient was diagnosed with an upper right lobe lung tumour shortly after the 12-month infusion. This SAE was thought to be unrelated to the study medication. Surgery to remove the tumour was successful. There were no infections requiring i.v. treatment/hospitalization and no abnormal liver enzyme tests. Another patient was found to be neutropaenic at 1300/mm3 after starting MTX. In total, there were 131 AEs (including 102 unique AEs) during the course of the 2-year study. These are detailed in Table 6.

Discussion

This proof-of-concept, open-label study is the first to evaluate the scope for biological immunomodulatory therapy in poor-prognosis, ACPA-negative UA, an important but understudied group. The findings suggest abatacept monotherapy confers clinical improvement in poor-prognosis, ACPA-negative UA and demonstrates the ability of abatacept to reduce the PDUS signal.

ACPA-negative UA, when persistent, is also associated with functional impairment and erosive damage [18]. We have previously demonstrated the utility of PDUS in identifying persistence in seronegative disease [10]. Studies to date in an UA patient group have been relatively limited, although an earlier study in early oligoarthritis by our group demonstrated that disease-modifying intervention (IA corticosteroid and SSZ) reduced clinical synovitis

Table 6 Summary of adverse events

Total number of AEs:					131
Number of unique AEs:					102
Severity	Mild:				49% (50/102)
	Moderate:				49% (50/102)
	Severe:				2% (2/52)
AE type by relation to study drug (all events):	**Possible**	**Probable**	**Unlikely**	**Unrelated**	**Total**
Endocrine disorders	0	0	0	1	1
Eye disorders	0	0	0	2	2
Gastrointestinal disorders	6	0	1	15	22
General disorders	1	0	0	1	2
Immune system disorders	0	0	0	1	1
Infections and infestations	35	0	0	14	49
Injury, poisoning and procedural	0	0	0	1	1
Investigations	0	0	0	1	1
Musculoskeletal	3	0	0	15	18
Neoplasms: benign, malignant and unspecified	0	0	0	1	1
Nervous system disorders	4	3	0	5	12
Reproductive system and breast disorders	2	0	0	0	2
Respiratory, thoracic and mediastinal disorders	5	0	0	2	7
Skin and subcutaneous tissue disorders	5	0	0	5	10
Vascular disorders	0	0	0	2	2
Total	61	3	1	66	131

[19]. The PROMPT study failed to indicate any benefit of MTX in seronegative UA on any outcome (preventing the development of RA, the signs and symptoms or radiographic progression) [12]. Thus, there is a lack of effective therapies in this group. The ADJUST study suggested abatacept could delay progression from ACPA-positive UA to RA [11]. These observations stimulated the basis for this study in a similar ACPA-negative group, with a proof-of-concept study designed to support our hypothesis before embarking on a larger, randomized study. Interestingly, almost two-thirds of our cohort was shared-epitope positive, and half of those tested positive for HLA–DRB1*0401, which confers the highest risk in predisposition to anti-CCP antibodies [20]. The basis for this remains unclear.

A three-composite primary end point (encompassing clinical, disease activity composite and radiographic components) was chosen to acknowledge the modern expectations of treatment of inflammatory arthritis. A low proportion ($n = 2$) achieved this with abatacept therapy, and under half achieved DAS28/44 remission rates at 6 months (30–40%), albeit with half achieving these outcomes by 12 months. This appears to have been driven by the more modest reduction in patient-reported outcomes compared with the more objective indicators of synovitis. Incremental reduction in disease activity over time was observed, with efficient reduction in swollen joint counts and ESR and CRP recorded.

The blinded PDUS assessments provide further evidence of a significant effect on synovial inflammation. A considerable reduction in PDUS was observed within 6 months, and this was maintained over the 2-year period, including following cessation of abatacept. Improvements in GS were more modest, consistent with prior reports of a relative lack of correlation [21, 22] (even at this early stage). Limited radiographic data were available, but suggested no change over the study period, including following abatacept cessation (in line with early use in ACPA-positive disease [11]).

The open-label nature of the study is a potential weakness, introducing a bias that could have influenced the apparent discrepancy between patient-reported outcomes and SJCs. However, the rapid suppression of inflammation as evidenced by the inflammatory markers (and small deterioration after abatacept cessation) implies a clear biological effect. The absence of a control group means it is not possible to determine whether these improvements would also be seen in a placebo ± synthetic DMARD arm. However, the poor outcomes observed in UA cohorts [8], together with the selection of poor-prognostic (PD-positive) UA in this study, which in a comparable cohort had an inferior outcome [10], is suggestive of a benefit over and above placebo. Finally, the distinct genetic associations of ACPA-negative (and -positive) disease means that these data could not necessarily be applied to other ethnic populations.

The clinical, US and radiographic outcomes were maintained in the second year of the study, following cessation of 12 months of abatacept therapy, although half the patients required a synthetic DMARD to maintain this state. Overall, these data suggest that in the vast majority of patients (18/20), abatacept therapy prevented further progression of disease, but on cessation, additional therapy was indicated to maintain this. The proportion that did not

require additional therapy following abatacept cessation might imply the possibility of drug-free disease control; additional follow-up would be able to clarify longer-term outcomes.

In established RA, an association between autoantibody-positive RA and abatacept response has been recently reported in registry data (albeit with relatively marginal differences). Whether this is causal or has a mechanistic basis remains speculative, but the latter relies on the B cell antibody response with enhanced B cell antigen presentation and T-dependent B cell activation. An autoantibody-mediated interaction, however, is not solely required for T cell effector function and development of inflammatory pathology. The anticipated reduction in T cell–activated cytokine production and abrogated activation of other key effector cells, such as dendritic cell, monocyte and synovial fibroblasts (leading to reduced cytokine, chemokine and MMP production, etc.) would be postulated to underlie the benefits we observed in our cohort. It might also be possible that some of our cohort have an as yet undetermined autoantibody status.

In summary, this first report of abatacept therapy in PD-positive ACPA-negative UA provides an initial indication of its ability to improve both clinical disease activity and US parameters of synovial inflammation. These data justify evaluation in a larger, controlled cohort. Further work may also identify biomarkers predictive of greater therapeutic responsiveness.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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