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CONCISE REPORT

Abatacept treatment reduces disease activity in early primary Sjögren's syndrome (open-label proof of concept ASAP study)

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ABSTRACT

Objective To assess the efficacy and safety of abatacept in patients with early and active primary Sjögren's syndrome (pSS).

Methods All 15 patients (12 women, three men) included in the open-label Active Sjögren Abatacept Pilot study met the revised American-European Consensus Group criteria for pSS and were biological disease-modifying antirheumatic drug-naïve. Patients were treated with eight intravenous abatacept infusions on days 1, 15 and 29 and every 4 weeks thereafter. Follow-up was conducted at 4, 12, 24 (on treatment), 36 and 48 weeks (off treatment). Disease activity was assessed with European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) and EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI). Several other functional, laboratory and subjective variables were analysed. Generalised estimating equations were used to analyse parameters over time.

Results ESSDAI, ESSPRI, rheumatoid factor and IgG levels decreased significantly during abatacept treatment and increased post-treatment. Salivary and lacrimal gland function did not change during treatment. Fatigue and health-related quality of life (HR-QoL) improved significantly during treatment. No serious side effects or infections were seen.

Conclusions In this open-label study, abatacept treatment is effective, safe and well tolerated, and results in improved disease activity, laboratory parameters, fatigue and HR-QoL in patients with early and active pSS.

Trial registration number 2009-015558-40.

INTRODUCTION

Traditional disease-modifying antirheumatic drugs (DMARDs) have limited effects in primary Sjögren's syndrome (pSS). Biological agents that target specific cells or cytokines involved in immune responses have been introduced in the treatment of various systemic autoimmune diseases. No biological agent has yet been approved for pSS treatment. TNF- α inhibitors, IFN- α , B cell depletion therapy (anti-CD20 (rituximab) and anti-CD22 (epratuzumab)) have been studied in pSS, of which rituximab showed the most promising results.¹

Abatacept is a fully human fusion molecule of IgG-Fc and cytotoxic T lymphocyte antigen 4 that modulates CD28-mediated T cell co-stimulation. Co-stimulation between antigen-presenting cells and

T cells and between B cells and T cells is an essential step in T cell-dependent immune responses including autoimmune responses.² Abatacept demonstrated consistently good safety and efficacy profiles in rheumatoid arthritis and polyarticular juvenile idiopathic arthritis.³

Given the mechanism of action of abatacept and the recognised role of T cells and B cells in pSS, selective modulation of co-stimulation represents a rational therapeutic option. Therefore, the aim of this open-label proof of concept study was to investigate the efficacy and safety of abatacept in patients with early and active pSS.

METHODS

The Active Sjögren Abatacept Pilot study, a prospective, single-centre, open-label study, was performed in 15 pSS patients. The study protocol was approved by the institutional review board of the University Medical Center Groningen (METc2009.371). All patients provided written informed consent and fulfilled the revised American-European Consensus Group criteria for pSS.⁴ Eligibility criteria were: disease duration ≤ 5 years, secretion rate of stimulated whole saliva (SWS) ≥ 0.10 mL/min, positivity for autoantibodies (rheumatoid factor (RF) ≥ 10 IU/mL, presence of anti-SSA/La and/or anti-SSB/Ro autoantibodies in serum) and availability of a parotid salivary gland biopsy with characteristic pSS features. Patients previously treated with biological agents and traditional DMARDs were excluded. Prednisone and hydroxychloroquine had to be discontinued >1 month before baseline. Symptomatic medication for sicca symptoms and non-steroidal anti-inflammatory drugs were allowed. Female patients had to use reliable methods of contraception. Patients with a history of any malignancy or with underlying cardiac, pulmonary, metabolic, renal or gastrointestinal conditions, chronic or latent infectious diseases, or with immune deficiency were excluded.

Abatacept was administered intravenously on days 1, 15 and 29, and then every 4 weeks (total treatment period 24 weeks). Dosing was 10 mg/kg of body weight according to the patient's weight at study entry.

All variables were assessed at baseline, at 4, 12 and 24 weeks (on treatment) and at 36 and 48 weeks (post-treatment). Disease activity was assessed with European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) and patients' symptoms with EULAR Sjögren's

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Clinical and epidemiological research

Syndrome Patient Reported Index (ESSPRI).^{5–10} A visual analogue scale was used for rating global disease activity (GDA) by both the attending rheumatologist and patients. (Un)stimulated whole, parotid and submandibular/sublingual saliva samples were collected in a standardised manner.¹¹ Lacrimal gland function was evaluated by unanaesthetised Schirmer's test and tear breakup time. Laboratory tests included serum RF and IgG levels. Multidimensional Fatigue Inventory (MFI)¹² and Short Form-36 health survey (SF-36)¹³ were completed to evaluate fatigue and health-related quality of life (HR-QoL), respectively.

All patients were evaluated for adverse events (AE) and serious AE (SAE), classified according to the Medical Dictionary for Regulatory Activities (V14.0). Injection and infusion reactions were prespecified and classified as injection site reactions, acute infusion AE (<1 h of the start of infusion), late AE (>1 h of the start of infusion) and infections.

Statistical analysis was performed with IBM SPSS Statistics V.20 (SPSS, Chicago, Illinois, USA). Generalised estimating equations were used to analyse variables over time within subjects. Data from baseline up to week 24 were used to assess change over time compared with baseline during treatment. Data from week 24 up to week 48 were used to assess change over time compared with week 24 during the post-treatment period. *p* Value<0.05 was considered statistically significant.

RESULTS

Inclusion of 15 patients was completed between August 2010 and May 2012 (see online supplementary figure S1). All patients completed follow-up. One patient did not complete questionnaires (ESSPRI, MFI and SF-36). Patients were relatively young, predominantly women (80%) and had a short disease duration (table 1). In retrospect, one patient had disease duration ≥ 5 years at inclusion; however, none of the outcomes changed significantly by this patient.

Abatacept treatment resulted in significant reduction of disease activity (table 2). During treatment, median ESSDAI decreased from 11 at baseline to 2, 24 weeks after treatment ($p<0.001$; figure 1A). ESSDAI returned to baseline in the post-treatment period (weeks 24–48; $p<0.001$). ESSDAI at week 48 did not differ significantly from baseline ($p=0.137$). When looking at the ESSDAI domains separately, most improvement was found in the articular, biological, constitutional and glandular domains (see online supplementary figure S2A and online supplementary table S1). Median ESSPRI decreased from 7.7 at baseline to 5.8 at week 24 ($p=0.015$), indicating significant improvement in patient symptoms, followed by a non-significant increase in ESSPRI post-treatment ($p=0.151$) (figure 1B). At subscale level, most improvement was seen on pain ($p=0.001$) and fatigue ($p=0.021$) (see online supplementary figure S2B). Reduced disease activity after abatacept treatment was supported by physician's and patient's GDA scores (figures 1C,D).

SWS did not change during treatment, while a small decrease ($p=0.018$) was seen post-treatment. Unstimulated whole saliva, parotid flow rate and lacrimal gland function did not change, both on and off treatment (figures 1E,F). RF and IgG levels decreased significantly on treatment and increased significantly post-treatment (figures 1G,H).

Patients receiving abatacept felt less tired. As mentioned before, the subscale for fatigue of ESSPRI decreased significantly during treatment. When assessing MFI in more detail, a reduction of fatigue during treatment was found for general fatigue ($p=0.009$), reduced activity ($p=0.011$) and reduced motivation ($p=0.013$) (see online supplementary figure S3A), while physical fatigue increased ($p=0.032$). During treatment, there was a

Table 1 Baseline characteristics of the ASAP study population

Variable	Median (IQR) or n (%)
Age (years)	43 (32–51)
Female gender, n (%)	12 (80)
Disease duration (months)	11 (7–36)
IgG (g/L)	20.2 (15.3–26.7)
RF (kIU/L)	43 (20–184)
Anti-Ro/SSA positive, n (%)	15 (100)
Anti-La/SSB positive, n (%)	12 (80)
UWS (mL/min)	0.12 (0.07–0.23)
SWS (mL/min)	0.39 (0.24–0.57)
ESSDAI	11 (8–14)
Articular domain, n (%)*	13 (87)
Biological domain, n (%)*	11 (73)
CNS domain, n (%)*	0 (0)
Constitutional domain, n (%)*	5 (33)
Cutaneous domain, n (%)*	4 (27)
Glandular domain, n (%)*	11 (73)
Haematological domain, n (%)*	2 (13)
Lymphadenopathy domain, n (%)*	1 (7)
Muscular domain, n (%)*	0 (0)
PNS domain, n (%)*	1 (7)
Pulmonary domain, n (%)*	3 (20)
Renal domain, n (%)*	0 (0)
ESSPRI	7.5 (6.0–8.0)
Use of artificial tears, n (%)	15 (100)
Use of artificial saliva, n (%)	1 (7)
Use of prednisone, n (%)†	1 (7)
Use of hydroxychloroquine, n (%)†	2 (13)

Values are presented as median (IQR) unless otherwise indicated.

*Number (%) of patients having any degree of activity per ESSDAI domain (score of at least 1).

†Discontinued before study entry.

ASAP, Active Sjögren Abatacept Pilot; CNS, central nervous system; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI, EULAR Sjögren's Syndrome Patient Reported Index; PNS, peripheral nervous system; RF, rheumatoid factor; SWS, stimulated whole salivary flow rate; UWS, unstimulated whole salivary flow rate.

trend towards improved HR-QoL in most scales of SF-36, which reached significance for vitality ($p=0.001$), social functioning ($p=0.004$) and mental health ($p=0.015$) (see online supplementary figure S3B).

No abatacept-related deaths, cancers, opportunistic infections or atypical presentations of infections were observed during this trial. No SAEs occurred, and no patients withdrew from the study due to AEs. One patient experienced a mild infusion reaction not requiring discontinuation of treatment (see online supplementary table S2). Six patients (40%) experienced mild acute AEs (in total 17 events) with dizziness and hypotension being the most commonly reported events. During treatment, 18 self-reported infections were seen in 10 patients (67%), the most common being upper respiratory tract infections. No infection required hospitalisation.

During treatment, two patients received rescue medication because they developed subacute cutaneous lupus after extreme sun exposure without protection, namely, treatment with steroids for 1 week (during week 10) or treatment with prednisone for 18 weeks (weeks 22–40).

DISCUSSION

Abatacept treatment was shown to be effective and safe in early and active pSS patients. Disease activity decreased, RF and IgG

Table 2 Results of disease activity, glandular function and laboratory assessments in pSS patients treated with abatacept

Variable	Week 0	Week 4	Week 12	Week 16	Week 24	Week 36	Week 48
ESSDAI	11±5 (11)	6±4 (6)*	6±8 (3)*	—	3±3 (2)*	10±6 (7)†	14±8 (11)†
ESSPRI	7.0±1.5 (7.5)	6.0±1.7 (6.0)*	5.6±1.6 (6.0)*	—	5.8±2.3 (5.8)*	5.7±2.2 (5.7)	6.6±1.8 (7.0)
Patient's GDA	59±15 (58)	53±19 (53)	48±21 (50)*	—	48±26 (54)	54±24 (53)	59±23 (65)
Physician's GDA	46±8 (45)	36±14 (34)*	31±10 (36)*	—	33±18 (28)*	42±19 (43)†	48±15 (48)†
SWS (mL/min)	0.43±0.25 (0.39)	0.47±0.39 (0.34)	0.50±0.31 (0.56)	—	0.41±0.33 (0.24)	0.38±0.26 (0.32)	0.31±0.22 (0.28)†
UWS (mL/min)	0.17±0.17 (0.12)	0.16±0.13 (0.15)	0.14±0.15 (0.08)	—	0.16±0.15 (0.10)	0.14±0.14 (0.10)	0.15±0.14 (0.11)
Parotid saliva, stimulated (mL/min)	0.16±0.19 (0.08)	0.13±0.12 (0.10)	0.15±0.13 (0.13)	—	0.11±0.11 (0.07)	0.11±0.07 (0.12)	0.09±0.06 (0.07)
Schirmer (mm/5 min)	9.8±6.7 (9.5)	10.4±8.8 (6.0)	12.4±11.1 (7.5)	—	8.9±8.5 (5.0)	9.6±8.2 (6.5)	8.3±10.9 (1.0)
TBUT (s)	8.1±1.9 (8.0)	8.0±2.3 (9.0)	8.1±2.7 (9.0)	—	8.0±2.4 (10.0)	7.5±2.9 (8.0)	6.7±3.0 (7.0)†
Rheumatoid factor (kIU/L)	89±94 (43)	72±73 (45)*	57±62 (35)*	56±63 (31)*	56±63 (28)*	82±113 (31)†	87±103 (36)†
IgG (g/L)	21.5±7.3 (20.2)	19±6.2 (17.1)*	19.1±8.3 (15.5)*	18.2±7.5 (16.5)*	18.2±7.2 (16.5)*	20.6±9.6 (17.2)†	21.1±10.3 (18.6)†

Generalised estimating equations were used to analyse variables over time within subjects during treatment (weeks 0–24) and off treatment (weeks 24–48). Values are presented as mean±SD (median).

*p<0.05 compared with baseline.

†p<0.05 compared with week 24.

ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI, EULAR Sjögren's Syndrome Patients Reported Index; GDA, global disease activity scale; pSS, primary Sjögren's syndrome; SWS, stimulated whole salivary flow rate; TBUT, tear breakup time test; UWS, unstimulated whole salivary flow rate.

levels dropped, fatigue diminished and patients experienced improved HR-QoL. Salivary and lacrimal gland function did not change during treatment. No SAEs occurred; neither did patients withdraw from the study due to AEs. Safety results in this trial were comparable with those found in rheumatoid arthritis patients.^{14 15}

Abatacept treatment resulted in a significant decrease in ESSDAI and ESSPRI. For ESSDAI, most improvement was found in the articular, biological, constitutional and glandular domains and for ESSPRI in pain and fatigue. Although we did not specifically include patients with high levels of systemic involvement or symptoms, our inclusion criteria resulted in a

Figure 1 Change over time in pSS patients treated with abatacept. Generalised estimating equations were used to analyse variables over time within subjects during treatment (weeks 0–24) and off treatment (weeks 24–48). (A) ESSDAI, (B) ESSPRI, (C) physician's GDA, (D) patient's GDA, (E) stimulated whole salivary flow, (F) tear breakup time, (G) rheumatoid factor and (H) IgG. Box-and-whisker plots (Tukey); boxes=medians with IQRs; +=means; whiskers=1.5 times the interquartile distances; •=outliers. *p<0.05. GDA, global disease activity; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI, EULAR Sjögren's Syndrome Patients Reported Index; pSS, primary Sjögren's syndrome.

Clinical and epidemiological research

patient cohort with rather high ESSDAI and ESSPRI baseline values.⁷

No change in salivary and lacrimal function was found during treatment, while a small decrease was observed post-treatment. Therefore, abatacept treatment may have a minor beneficial effect on preservation of salivary and lacrimal gland function, but has a stronger effect on systemic manifestations during this limited observation period.

Thus far, the utility of abatacept in pSS has been investigated in an open-label study in 11 pSS patients by Adler and coworkers.¹⁶ Patients were treated following the same dosing regimen as our patients. In contrast to our study, none of their patients suffered from extraglandular disease and evaluation took place at baseline and 4 weeks after the last infusion (week 28), making comparisons difficult. Overall, their study demonstrated beneficial effects of abatacept treatment, namely, a slight increase in SWS (Saxon's test: from 1.61 g/2 min (baseline) to 1.74 g/2 min (week 28)), cellular changes and reduced inflammation in labial salivary glands. The increase in SWS is probably clinically not relevant since a change in SWS < 25% can be explained by inter-individual variation.¹⁷ Beneficial effects on patients' symptoms were also described by Adler and coworkers, although no standardised description of the clinical effects of abatacept was given, for example, evaluation of disease activity (ESSDAI and/or ESSPRI), fatigue or HR-QoL.¹⁶

In conclusion, in this open-label proof of concept study, abatacept treatment was effective, safe and well tolerated in active and early pSS patients. Abatacept treatment resulted in improved disease activity, laboratory parameters, fatigue and HR-QoL. No change was found in salivary and lacrimal function. The results of our study support the concept that T cells play an important role in the pathophysiology of pSS. These promising results warrant confirmation in placebo-controlled RCTs.

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Contributors PMM: literature search, figures, study design, patient recruitment, data collection, data analysis, data interpretation, writing; AV: study design, data collection, data analysis, data interpretation and writing; FGMK: study design, data analysis, data interpretation and writing; FKLS: study design, data collection, data interpretation and writing; NSS-K: data collection, data interpretation and writing; WHA: data collection, data analysis and writing; JB-K and EB: patient recruitment, data collection and writing; SA: study design, figures, data analysis, data interpretation and writing; HB: literature search, study design, patient recruitment, data collection, data interpretation and writing.

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Competing interests None.

Patient consent Obtained.

Ethics approval Institutional Review Board of the University Medical Center Groningen (METc2009.371).

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