ARD Online First, published on September 14, 2012 as 10.1136/annrheumdis-2012-201915

EXTENDED REPORT

Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in ankylosing spondylitis

Ejaz Pathan,[1] Sonya Abraham,[2] Elizabeth Van Rossen,[3] Robin Withrington,[3] Andrew Keat,[4] Peter J Charles,[1] Erin Paterson,[1] Muslima Chowdhury,[1] Catherine McClinton,[5] Peter C Taylor[5]

[1]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Kennedy Institute of Rheumatology, University of Oxford, London, UK
[2]Faculty of Medicine, Imperial College London, London, UK
[3]Department of Physiotherapy, Kent and Canterbury Hospital, Canterbury, Kent, UK
[4]Department of Rheumatology, Northwick Park Hospital, Harrow, UK
[5]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Kennedy Institute of Rheumatology, University of Oxford, Botnar Research Centre, Oxford, UK

Correspondence to
Professor Peter C Taylor, Kennedy Institute of Rheumatology, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Botnar Research Centre, Windmill Road, Headington, Oxford OX3 7LD, UK;
peter.taylor@kennedy.ox.ac.uk

Accepted 14 August 2012

ABSTRACT

Objectives To evaluate the efficacy and safety of an oral phosphodiesterase 4 inhibitor, apremilast, in treatment of ankylosing spondylitis (AS) by monitoring symptoms and signs in a pilot study including exploratory investigation of effects of PDE4 inhibition on blood biomarkers of bone biology.

Methods In this double-blind, placebo-controlled, single-centre, Phase II study, patients with symptomatic AS with active disease on MRI were randomised to apremilast 30 mg BID or placebo over 12 weeks. Bath Indices were monitored serially. Patients were followed for 4 weeks after stopping medication. Bone biomarkers were assessed at baseline and day 85.

Results 38 subjects were randomised and 36 subjects completed the study. Although the primary end-point (change in BASDAI at week 12) was not met, apremilast was associated with numerically greater improvement from baseline for all clinical assessments compared with placebo with mean change in BASDAI (-1.59 ± 1.48 vs -0.77 ± 1.47), BASFI (-1.74 ± 1.91 vs -0.28 ± 1.61) and BASMI (-0.51 ± 1.02 vs -0.21 ± 0.67); however, differences did not achieve statistical significance. The clinical indices returned to baseline values by 4 weeks after cessation of apremilast. Six apremilast patients (35.3%) vs 3 placebo (15.8%) achieved ASAS20 responses ($p=0.25$). There were statistically significant decreases in serum RANKL and RANKL:osteoprotegrin ratio and plasma sclerostin but no significant changes in serum DKK-1, bone alkaline phosphatase, TRAP5b, MMP3, osteoprotegrin, or osteocalcin.

Conclusions Although a small pilot study, these results suggest that apremilast may be effective and well tolerated in AS and modulates biomarkers of bone biology. These data support further research of apremilast in axial inflammation.

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory arthritis affecting the spine with or without involvement of peripheral joints. Historically, the mainstay of AS treatment was physiotherapy and non-steroidal anti-inflammatory drugs (NSAIDs). Although NSAIDs may provide symptomatic relief,[1] they are not always efficacious and often poorly tolerated.[2] Traditional disease-modifying anti-rheumatic drugs (DMARDs) such as sulphasalazine and methotrexate are ineffective in axial AS[3 4] and not recommended treatments under EULAR guidance for AS management.[5 6]

Pharmacological management of AS advanced with anti-TNF therapy. Clinical trials have shown that 50–70% of AS anti-tumour necrosis factor (anti-TNF) treated patients have a ≥20% improvement in disease activity scores by 24 weeks.[7–9] Furthermore, switching between biologics within the class of TNF inhibitors is also effective.[10] However, TNF blockade does not prevent radiographic ankylosis over 2 years,[11–13] although a recent study suggests that longer-term treatment (8 years) may reduce radiographic progression.[14] Despite generally favourable safety, the risk of serious infection remains and anti-TNF therapy should only be used with caution in certain patient groups. Furthermore, the expense of treatment may restrict use. Therefore, a major unmet need exists for alternative and symptomatically effective oral therapies in AS.

Phosphodiesterase 4 (PDE4) is a major phosphodiesterase expressed in leukocytes and keratinocytes, where it hydrolyses cyclic AMP (cAMP) into AMP, leading to production of pro-inflammatory cytokines such as TNFα, IL-23, IL-17, and interferon-γ, and suppression of anti-inflammatory cytokines such as IL-10.[15–18] Inhibitors of PDE4 cause accumulation of intracellular cAMP, which activates protein kinase A and other downstream effectors, suppressing pro-inflammatory cytokine transcription and other cellular responses such as neutrophil degranulation, chemotaxis and adhesion to endothelial cells. Furthermore, PDE4 inhibition upregulates anti-inflammatory mediators such as IL-10 through the cAMP response element-binding transcription factor.[17 19 20]

Apremilast is an orally available, small molecule specific PDE4 inhibitor which, in vitro, inhibits spontaneous release of TNFα from human rheumatoid synovial membrane cultures and lipopolysaccharide-induced TNF production from peripheral blood mononuclear cells (PBMCs). It also decreases TNFα and IL-23 mRNA levels in PBMCs from healthy human donors.[21] Apremilast significantly suppresses arthritis in rodent models[22] and has demonstrated efficacy in phase II trials of psoriasis[23] and psoriatic arthritis[24] with acceptable safety. Phase III studies for these conditions are now ongoing.

Given that cytokines influenced by PDE4 play an important role in spondyloarthritis, there is a rationale to explore apremilast use in this condition and we report here the findings of the first clinical trial of apremilast in patients with AS.

The aims of this pilot study were to evaluate the efficacy and safety of apremilast in patients with AS and to explore the effect of apremilast on biomarkers of bone biology. We also assessed the effects of apremilast on MRI imaging of the sacroiliac joints and spine from baseline to 12 weeks and this will be reported separately.

PATIENTS AND METHODS

Study design

This was a single-centre, randomised, double-blind, placebo-controlled, Phase II, investigator-led, pilot study carried out at the Kennedy Clinical Trials Unit (Clinicaltrials.gov number NCT00944658) and sponsored by Imperial College London. It was conducted in accordance with good clinical practice and received ethics committee approval from The Hammersmith Hospital Research Ethics Committee. Each patient provided written informed consent.

The study involved a 12-week, double-blind, placebo-controlled period followed by a 4-week follow-up for safety and clinical assessments. Patients were randomised 1:1 to receive apremilast 30 mg twice daily or placebo in a double-blind fashion. An unblinded pharmacist allocated patients to receive either placebo or active drug according to a randomisation code generated by Celgene. All other study personnel remained blinded to treatment until the end of the double-blind period. Patients were started on apremilast 10 mg twice daily or placebo and the dose was titrated by 20 mg every 2 days until the maximum dose of 30 mg twice daily was achieved on day 5. Apremilast/placebo was then given daily until day 85 (week 12). Patients were allowed to continue stable doses of NSAIDs but were not allowed DMARDs within 8 weeks of randomisation or corticosteroids in oral/parenteral form within 4 weeks of randomisation.

Patients

Key inclusion criteria included modified New York criteria for AS, disease duration greater than 2 years, symptoms of back pain and stiffness confirmed with a score of greater than or equal to 1 on questions 2 and 5 of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI; spinal pain and stiffness) and presence of active bone oedema either in the spine or sacroiliac joints confirmed by MRI. Patients with prior treatment with TNF inhibitors were permitted to enrol.

Patients were excluded if there were abnormalities on routine blood tests other than a raised erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), contraindications to MRI scanning, or positive tuberculosis testing (Mantoux and TB Elispot).

Evaluation of efficacy

The primary end point was the mean change in BASDAI score at week 12 compared with baseline. Additional efficacy assessments included changes in function using the Bath Ankylosing Spondylitis Functional Index (BASFI) and improvement in spinal mobility using the Bath Ankylosing Spondylitis Metrology Index (BASMI). The Bath Ankylosing Spondylitis Global Score (BAS-G) and night time pain scores were also recorded. The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire was used to assess improvement in the quality of life. The Ankylosing Spondylitis Activity Score 20 (ASAS20) and ASAS40 responses were calculated. All assessments were carried out at baseline (day1) and days 8, 15, 29, 56 and 85 (week 12) and were repeated at the end of the safety follow-up period (day 113). Post hoc analyses of AS disease activity score (ASDAS) changes were undertaken.

Laboratory biomarkers

Routine biochemistry, including CRP and haematology with ESR, were performed at all patient visits. Additional blood samples were centrifuged at 1200 g for 15 min within 2 h of phlebotomy and stored at −80°C. The following commercially available ELISA were used: osteocalcin, tartarate-resistant acid phosphatase (TRAP5b), osteoprotegrin (OPG) and bone alkaline phosphatase (BAP (MicroVue Bone Health, Quidel Corporation, California, USA)), matrix metalloproteinase 3 (MMP3 (Quantikine, R&D Systems, Abingdon, UK)) and human serum receptor activator of NF-κB ligand (sRANKL (Peprotech Inc, New Jersey, USA)). Commercially available DuoSet ELISA development system (R&D Systems) was used to measure total DKK-1 levels in serum. A sandwich ELISA protocol was developed using R&D Systems' recombinant human sclerostin, biotinylated anti-human sclerostin antibody (1:500 dilution) and monoclonal anti-human sclerostin antibody (2 μg/ml) to measure sclerostin levels in plasma.

Statistical methods

Sample size estimation

This was an exploratory study conducted without prior knowledge of effect size of apremilast in AS. The sample size was chosen based on feasibility and on the basis that for an effect size similar to that of anti-TNF, a sample size of 18 patients in each arm would have 80% power to detect differences between groups at a 95% level of significance.

The primary objective was to evaluate the efficacy of apremilast. Analysis of covariance was used to assess differences between treatment and placebo arms for various clinical outcome measures. Baseline values were considered as covariates to nullify any differences between groups.

Analyses on biomarkers were purely exploratory hence a simpler evaluation of unpaired t-tests (ANOVA) or non-parametric Mann-Whitney as appropriate. No adjustment for baseline values were explicitly made; however, the endpoint evaluated was the percentage change from baseline. A p value <0.05 was considered significant.

RESULTS

Patient demographics and baseline characteristics

Fifty-five patients were screened (six failing to demonstrate bone oedema on MRI) and 38 were enrolled into this study. With the exception of two patients (both receiving apremilast), all others completed the study. The two withdrawals discontinued treatment within 1 week of commencing due to non-serious adverse events and were included in the safety population but not in the efficacy analysis. Hence, the efficacy population consisted of 17 patients on apremilast and 19 on placebo.

Patient demographics and baseline characteristics in each group are shown in table 1. The study population was predominantly Caucasian and male (M : F=8 : 1). The mean age was 42.95 years (range 27–67 years) and disease duration 19.5 ±11.01 years (range 2–44 years). The majority of patients (33/36) were on stable doses of NSAIDs while the remaining did not take any concomitant NSAID therapy during the trial period. Three subjects had received prior anti-TNF therapy (placebo, 2; apremilast, 1).

Table 1 Baseline patient characteristics

	Placebo* (n=19)	Apremilast* (n=17)	p Value (ANCOVA)
Age (years)	39.21 (13.3)	44.88 (11.1)	0.17
Disease duration (years)	18.39 (10.17)	20.88 (12.32)	0.51
BASDAI	4.36 (1.757)	4.79 (2.161)	0.52
BASFI	3.49 (2.208)	4.55 (2.429)	0.178
BASMI	3.16 (1.598)	4.48 (1.963)	0.03
BAS-G	4.13 (2.329)	4.33 (2.850)	0.82
Night pain	4.03 (2.524)	4.25 (2.940)	0.81
FACIT-F	110.04 (26.147)	107.75 (25.716)	0.79
CRP (mg/dl)	6.24 (2.56)	11.37 (12.12)	0.43

*Data are mean (SD).
ANCOVA, analysis of covariance; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue.

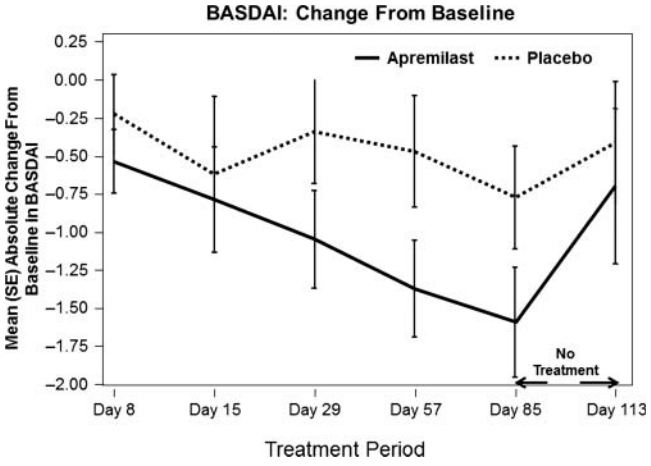

Figure 1 Mean absolute change in BASDAI over 12 weeks in ankylosing spondylitis patients receiving apremilast (n=17) or placebo (n=19).

Patients assigned to apremilast had higher BASDAI, BASFI and BASMI scores at baseline compared with the placebo arm. The difference in the BASMI baseline scores was statistically significant (p=0.03). This was corrected for by using baseline values as a covariate in the statistical analysis. None of the p values for the treatment by baseline effect were significant (p values not shown). Hence, there was a comparable difference in clinical outcome measures in patients with higher or lower values at baseline.

Clinical response

Apremilast was associated with numerically larger improvements than placebo at week 12 in BASDAI (−1.59±1.48 vs −0.77±1.47), BASFI (−1.74±1.91 vs −0.28±1.61) and BASMI (−0.51±1.02 vs −0.21±0.67), although differences did not achieve statistical significance (table 2). The magnitude of improvement from baseline in the apremilast group increased over the treatment period and did not appear to reach a maximum by week 12. These improvements in all indices were lost by 4 weeks after cessation of therapy (figure 1). Six patients (35.3%) in the apremilast groups versus three (15.8%) in the placebo group achieved an ASAS20 response (p=0.25). Similarly, four patients (23.5%) in the apremilast group versus one patient (5.3%) in the placebo group achieved an ASAS40 response (p=0.17). ASAS 5/6 responses were achieved by three patients in the apremilast group versus one in the placebo group. A post hoc analysis of mean (SD) change in ASDAS showed a reduction of 0.46(0.66) in the apremilast group versus 0.15(0.71) in the placebo group (p=0.35 by Mann-Whitney). ASDAS improvements greater than or equal to 1.1 were observed in 4/17 apremilast patients and 1/19 placebo patients.

Table 2 Mean change from baseline in clinical parameters at week 12

	Placebo* (n=19)	Apremilast* (n=17)	p Value (ANCOVA)
BASDAI	−0.77 (1.47)	−1.59 (1.48)	0.139
BASFI	−0.28 (1.61)	−1.74 (1.91)	0.108 (RANK ANCOVA)
BAS-G	−0.17 (2.83)	−1.36 (2.35)	0.166
BASMI	−0.21 (0.67)	−0.51 (1.02)	0.617
FACIT-F	5.07 (13.44)	9.38 (12.79)	0.358
Night pain	−0.23 (2.75)	−0.81 (3.01)	0.587

*Data are mean change (SD).
ANCOVA, analysis of covariance; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue.

Laboratory biomarkers

Percentage changes from baseline in bone biomarkers in each study group are shown in table 3. There were no significant differences in baseline bone biomarker parameters between the treatment groups. There was a significant reduction in RANKL (p=0.04) and RANKL : OPG ratios (p=0.008) in the apremilast group, but not in OPG levels which remained relatively unchanged. RANKL levels were below the detectable range at both time points in a third of the patients. There was significant decrease in plasma sclerostin levels (p=0.02) and a trend towards reduction in levels of DKK-1 (p=0.18).

In a post hoc analysis that classified treated patients as responders or non-responders, with response being defined as a decrease in BASDAI by ≥1 unit, a statistically significant fall in sclerostin was only observed in the apremilast-treated responder population (figure 2).

Table 3 Mean percentage change from baseline in bone biomarkers

Biomarker	Apremilast* (n=17)	Placebo* (n=19)	p Value
Serum RANKL (pmol/l)	−14.7±6.0	3.6±5.47	0.04†
Serum OPG (pmol/l)	−2.01±4.4	−7.2±4.3	0.4
RANKL:OPG	−12.6±6.4	15.4±7.4	0.008†
Serum DKK-1 (pg/ml)	−11.7±11.1	8.1±9.7	0.18
Plasma sclerostin (pg/ml)	−14.3±5.5	18.7±11.3	0.02
Serum BAP (U/l)	2.6±2.4	−6.5±5.1	0.12
Serum osteocalcin (ng/ml)	13.5±5.5	0.48±3.9	0.058
Serum MMP3 (ng/ml)	−0.08±5.9	7.5±8.4	0.92
Serum TRAP5b (U/l)	7.6±6.5	−2.7±6.3	0.26
Serum CRP (mg/l)	32.6±22.3	28.99±22.7	0.72
ESR (mm/h)	−2.32±8.75	7.34±10.12	0.25
Serum IgA (mg/dl)	0.69±3.0	1.1±2.6	0.91

*Data are mean±SE (%).
†Excludes one outlier that had RANKL levels below recordable range at baseline.
BAP, bone alkaline phosphatase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MMP3, matrix metalloproteinase 3; OPG, osteoprotegrin; RANKL, human serum receptor activator of NF-κB ligand.

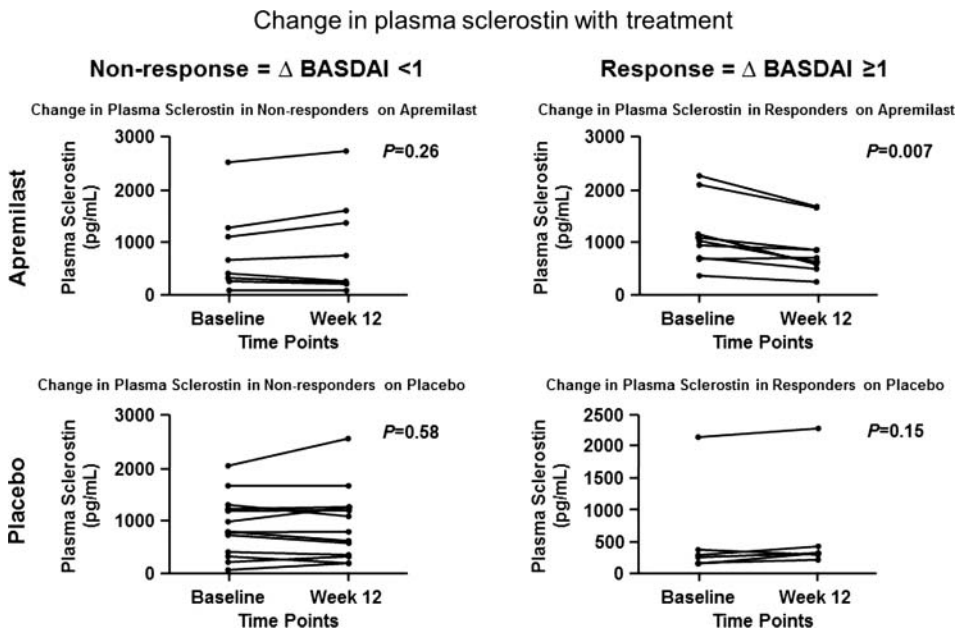

Figure 2 Study patients were classified as responders or non-responders with response being defined as a decrease in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) by at least one unit. Individual patient change in plasma sclerostin levels over 12 weeks is depicted depending on BASDAI response. A statistically significant fall in sclerostin was only observed in the apremilast-treated responder population.

There was a rise in osteocalcin levels in the apremilast group approaching statistical significance (p=0.058). There were no significant changes in CRP between treatment and placebo groups. At baseline, 8/17 apremilast patients had CRP greater than 5. Four of these patients exhibited decreases in CRP with rebound on stopping medication. At baseline, 8/19 placebo patients had CRP greater than 5 of which all but two showed little change. Of these two, one patient demonstrated a rise in CRP from 5 to 17 corresponding to an increase in disease activity and the other showed an increase from 7.4 to 30 corresponding to an upper respiratory tract infection.

Safety data

The incidence of adverse events was similar in the two treatment arms at 17/19 (94.7%) in the apremilast and 18/19 (89.5%) in the placebo groups (table 4). The majority (68.4%) of all adverse events were classified as 'mild' and no serious adverse events were observed. Two apremilast patients withdrew from the study after two to three doses of medication. The first discontinued due to diarrhoea, which settled after stopping medication. The second patient developed poor concentration and felt dazed after three doses with resolution on discontinuing treatment. Compared with placebo, apremilast patients reported a higher incidence of headaches (26.3% vs 42.1%) and loose stools (10.5% vs 26.3%). Two apremilast patients developed palpitations. One of these had sinus tachycardia and continued treatment with spontaneous resolution of symptoms. The other had frequent ventricular ectopics which resolved following medication withdrawal on study completion.

DISCUSSION

This exploratory pilot study is the first trial to investigate the effect of a PDE4 inhibitor, apremilast in AS. Although the primary endpoint was not met, Bath indices showed trends towards responses over a 12 week treatment period. As expected, the improvements in BASDAI, BASFI, and BAS-G were more marked compared with the change in BASMI, which may have been due to higher baseline BASMI scores in the apremilast group, as well as BASMI scores being generally more resistant to change over short periods. It is noteworthy that the magnitude of reduction in disease activity continued to increase in sequential measurements over 12 weeks, suggesting that the maximal clinical response may not have been reached by that time point. Cessation of medication led to

Table 4 Summary of treatment-emergent adverse events reported by two or more patients

	Placebo* (n=19)					Apremilast* (n=19)				
Coded term	**Any severity**	**Mild**	**Moderate**	**Severe**	**Missing**	**Any severity**	**Mild**	**Moderate**	**Severe**	**Missing**
Patients with AEs	17 (89.5)	13 (68.4)	3 (15.8)	0	1 (5.3)	18 (94.7)	13 (68.4)	4 (21.1)	0	1 (5.3)
Headache	5 (26.3)	5 (26.3)	0	0	0	8 (42.1)	7 (36.8)	1 (5.3)	0	0
URTI	6 (31.6)	6 (31.6)	0	0	0	6 (31.6)	5 (26.3)	0	0	1 (5.3)
Loose stools	2 (10.5)	2 (10.5)	0	0	0	5 (26.3)	5 (26.3)	0	0	0
Nausea	3 (15.8)	3 (15.8)	0	0	0	3 (15.8)	2 (10.5)	1 (5.3)	0	0
Diarrhoea	2 (10.5)	2 (10.5)	0	0	0	2 (10.5)	1 (5.3)	1 (5.3)	0	0
Flatulence	0	0	0	0	0	2 (10.5)	2 (10.5)	0	0	0
Raised serum amylase	0	0	0	0	0	2 (10.5)	2 (10.5)	0	0	0

*Data are n (%).
AEs, adverse events; URTI, upper respiratory tract infection.

rapid loss of improvement in Bath indices. This observation may reflect patient bias. However, loss of response in apremilast-treated patients was of greater magnitude than placebo patients, suggesting a possible symptomatic benefit of apremilast and supporting the view that further studies are warranted in AS. Similarly, at 12 weeks the proportions of patients achieving ASAS20 (35% vs 16%) and ASAS40 (23.5 vs 5.3%), although greater in the apremilast group, were not statistically distinct from placebo.

This study suggested that apremilast was well tolerated in the majority of patients. The apremilast dose titration regimen over the first 5 days of treatment was designed to optimise tolerability. Commonly observed adverse events were generally mild and consistent with those reported for other phosphodiesterase inhibitors and previous reports of apremilast,[25 26] including nausea, diarrhoea/loose stools, and headaches. No severe or serious adverse events were reported. There was no significant increase in infection risk blood dyscrasias or abnormalities of liver function in the apremilast group. Hence, from this small, short study, apremilast appears to have an acceptable safety profile although long-term studies will be required to better characterise this.

Patients with AS may exhibit concurrent effects of bone resorption (eg, vertebral osteopenia) and formation (eg, ligamentous ossification). It is therefore interesting to note that our study suggests that apremilast may modulate certain biomarkers of bone biology. Most published reports have studied bone biomarkers in AS after at least 24 weeks of treatment so we did not anticipate any statistically significant changes over the 12 weeks of our study. This was largely true, except for serum RANKL and plasma sclerostin both of which showed significant reduction with apremilast treatment.

The binding of RANK to RANKL promotes osteoclast differentiation. RANKL inhibition in arthritis models inhibits bone erosion[27] and denosumab, an inhibitor of RANKL, has efficacy in osteoporosis.[28] In AS, the RANKL:OPG ratio is increased and associated with reduced bone mineral density and radiological findings of active inflammation.[29] Hence, successful treatment might be associated with a reduction in this ratio and this is in keeping with our findings. However, levels of TRAP5b, a marker of osteoclastic activity, did not show a corresponding fall in patients receiving apremilast. This might be related to changes in osteoblast and osteoclast populations. For example, PDE4 inhibition increases PGE2-induced cAMP production and RANKL mRNA expression in murine osteoblasts in a manner directly proportional to osteoclast formation in co-cultures of bone marrow cells and calvarial osteoblasts.[30]

Previous studies in AS reported low sclerostin levels to correlate with formation of new syndesmophytes over 2 years.[31] Further, a recent report suggests that serum sclerostin levels rise, but do not normalise, after 6 months of anti-TNF therapy.[32] It is not currently known whether low sclerostin expression in AS has a causal relationship to syndesmophyte formation or whether it is a response to it. In post-hoc analyses, we observed significant reductions in plasma sclerostin in patients responding to 12 weeks of apremilast. The clinical significance of this is uncertain.

DKK-1 is an inhibitory molecule regulating the Wnt pathway which controls osteoblastogenesis. Blocking DKK-1 prevents inflammatory bone loss in hTNFtg mice by stimulating osteoblast function[33] but also promotes ankylosis of sacroiliac joints in the same model.[34] In AS patients, anti-TNF therapy is reported to increase levels of DKK-1 without evidence of increased Wnt signalling, suggesting that DKK-1 is dysfunctional in AS.[34] In the present study, there was a trend towards DKK-1 decrease on apremilast therapy. We also observed trends towards increases in osteocalcin and BAP in the apremilast group suggestive of osteoblastic activity, consistent with the changes observed in sclerostin and DDK-1 levels. However, the longer term correlates of these findings are uncertain with respect to bone density or syndesmophyte development. Larger, long-term studies with apremilast measuring both bone density and imaging progression would be required to answer this question.

This pilot study has several limitations. Most notably it was likely underpowered to detect a significant benefit of apremilast in AS patients because no information on an effect size was available to aid in the study design. While the randomisation process included one unblinded pharmacist, this individual did not disclose any information to investigators or patients, making bias unlikely. The long disease duration (~20 years) of enrolled patients may have diminished the possibility to demonstrate symptomatic improvement. Nonetheless, all subjects had symptomatically active AS and evidence of disease activity on MRI. A further limitation was the short treatment duration which may not have permitted the maximum therapeutic effect of apremilast to be reached, a suggestion consistent with the incremental improvements in BASDAI and BASFI during the treatment period. The relatively short nature of our study, together with the differential and largely unknown long-term effects of certain bone biomarkers, makes interpretation of the observed biomarker changes difficult. Any conclusions on the impact of these changes in bone biomarkers should therefore be made with extreme caution and further longer term studies with appropriate endpoints are required to fully understand their clinical implications.

To summarise, although a small pilot study, these data suggest that apremilast may be effective in AS. Given the current lack of effective oral DMARDs in AS, our findings support the conduct of a suitably powered study of longer duration to further investigate the role apremilast in axial inflammation and the management of AS.

Acknowledgements The authors would like to thank Ms Leslie Hastings and Ms Amy Fox for their assistance with nursing matters during the course of this clinical study. The authors would also like to thank Dr Andrew Freiden and Ms Annette Winter for assistance with data monitoring. Ms Winter also provided administrative support.

Contributors PCT, EP, SA: conception and design of the study; PCT, EP, PC: analysis and interpretation of the data; PCT, EP: drafting of the article; PCT, EP, SA, EVR, RW, AK, PC, EP, MC, CM: critical revision of the article for important intellectual content; PCT, SA, EP, RW, AK: final approval of the article; AK, RW, EVR, PCT, SA, CM: provision of patients; EP, CM, PC, ErinP, MC: collection and assembly of data.

Funding The study was funded by an unrestricted grant from Celgene Corporation.

Competing interests PCT has received research grant support from Celgene Corporation and has been an invited advisor to Celgene. EP, SA, EVR, RW, AK, PC, EP, MC and CM declare no conflicts of interest.

Ethics approval Hammersmith and Queen Charlotte's & Chelsea Research Ethics Committee (now known as NRES Committee London—West London).

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **van der Heijde D,** Baraf HS, Ramos-Remus C, *et al*. Evaluation of the efficacy of etoricoxib in ankylosing spondylitis: results of a fifty-two-week, randomized, controlled study. *Arthritis Rheum* 2005;**52**:1205–15.
2. **Dougados M,** Gueguen A, Nakache JP, *et al*. Ankylosing spondylitis: what is the optimum duration of a clinical study? A one year versus a 6 weeks non-steroidal anti-inflammatory drug trial. *Rheumatology (Oxford)* 1999;**38**:235–44.
3. **Braun J,** Zochling J, Baraliakos X, *et al*. Efficacy of sulfasalazine in patients with inflammatory back pain due to undifferentiated spondyloarthritis and early ankylosing

spondylitis: a multicentre randomised controlled trial. *Ann Rheum Dis* 2006;**65**:1147–53.
4. **Haibel H,** Brandt HC, Song IH, *et al*. No efficacy of subcutaneous methotrexate in active ankylosing spondylitis: a 16-week open-label trial. *Ann Rheum Dis* 2007;**66**:419–21.
5. **Braun J,** van den Berg R, Baraliakos X, *et al*. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2011;**70**:896–904.
6. **Zochling J,** van der Heijde D, Burgos-Vargas R, *et al*. ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2006;**65**:442–52.
7. **Brandt J,** Haibel H, Cornely D, *et al*. Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor alpha monoclonal antibody infliximab. *Arthritis Rheum* 2000;**43**:1346–52.
8. **Brandt J,** Haibel H, Sieper J, *et al*. Infliximab treatment of severe ankylosing spondylitis: one-year followup. *Arthritis Rheum* 2001;**44**:2936–7.
9. **Brandt J,** Khariouzov A, Listing J, *et al*. Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. *Arthritis Rheum* 2003;**48**:1667–75.
10. **Lie E,** van der Heijde D, Uhlig T, *et al*. Effectiveness of switching between TNF inhibitors in ankylosing spondylitis: data from the NOR-DMARD register. *Ann Rheum Dis* 2011;**70**:157–63.
11. **van der Heijde D,** Landewe R, Einstein S, *et al*. Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. *Arthritis Rheum* 2008;**58**:1324–31.
12. **van der Heijde D,** Landewe R, Baraliakos X, *et al*. Radiographic findings following two years of infliximab therapy in patients with ankylosing spondylitis. *Arthritis Rheum* 2008;**58**:3063–70.
13. **van der Heijde D,** Salonen D, Weissman BN, *et al*. Assessment of radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab for up to 2 years. *Arthritis Res Ther* 2009;**11**:R127.
14. **Baraliakos X,** Haibel H, Listing J, *et al*. Radiographic progression in ankylosing spondylitis results after up to 8 years of infliximab treatment. *Arthritis Rheum* 2011;**63**(Suppl 10):546.
15. **Boniface K,** Bak-Jensen KS, Li Y, *et al*. Prostaglandin E2 regulates Th17 cell differentiation and function through cyclic AMP and EP2/EP4 receptor signaling. *J Exp Med* 2009;**206**:535–48.
16. **Claveau D,** Chen SL, O'Keefe S, *et al*. Preferential inhibition of T helper 1, but not T helper 2, cytokines in vitro by L-826,141 [4-[2-(3,4-Bisdifluromethoxyphenyl)-2-[4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan- 2-yl)-phenyl]-ethyl]3-methylpyridine-1-oxide], a potent and selective phosphodiesterase 4 inhibitor. *J Pharmacol Exp Ther* 2004;**310**:752–60.
17. **Seldon PM,** Barnes PJ, Giembycz MA. Interleukin-10 does not mediate the inhibitory effect of PDE-4 inhibitors and other cAMP-elevating drugs on lipopolysaccharide-induced tumors necrosis factor-alpha generation from human peripheral blood monocytes. *Cell Biochem Biophys* 1998;**29**:179–201.
18. **Li X,** Murray F, Koide N, *et al*. Divergent requirement for Galphas and cAMP in the differentiation and inflammatory profile of distinct mouse Th subsets. *J Clin Invest* 2012;**122**:963–73.
19. **Liu J,** Chen M, Wang X. Calcitonin gene-related peptide inhibits lipopolysaccharide-induced interleukin-12 release from mouse peritoneal macrophages, mediated by the cAMP pathway. *Immunology* 2000;**101**:61–7.
20. **Persson E,** Voznesensky OS, Huang YF, *et al*. Increased expression of interleukin-6 by vasoactive intestinal peptide is associated with regulation of CREB, AP-1 and C/EBP, but not NF-kappaB, in mouse calvarial osteoblasts. *Bone* 2005;**37**:513–29.
21. **Schafer PH,** Parton A, Gandhi AK, *et al*. Apremilast, a cAMP phosphodiesterase-4 inhibitor, demonstrates anti-inflammatory activity in vitro and in a model of psoriasis. *Br J Pharmacol* 2010;**159**:842–55.
22. **McCann FE,** Palfreeman AC, Andrews M, *et al*. Apremilast, a novel PDE4 inhibitor, inhibits spontaneous production of tumour necrosis factor-alpha from human rheumatoid synovial cells and ameliorates experimental arthritis. *Arthritis Res Ther* 2010;**12**:R107.
23. **Papp K,** Cather J, Rosoph L, *et al*. Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial. *Lancet* 2012;**380**:738–46.
24. **Schett G,** Wollenhaupt J, Papp K, *et al*. Oral apremilast is effective in the treatment of subjects with active moderate to severe psoriatic arthritis: results of a multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum* (Epub ahead of print 21 June 2012). doi:10.1002/art.34580.
25. **Schett G,** Wollenhaupt J, Papp K, *et al*. Apremilast is active in the treatment of psoriatic arthritis (PsA) [abstract]. *Arthritis Rheum* 2009;**60**(Suppl 10):1258.
26. **Schett GA,** Hu A, Stevens R. Oral apremilast is effective with and without concomitant methotrexate therapy in the treatment of subjects with active psoriatic arthritis [abstract 780]. *Arthritis Rheum* 2011;**63**(10 Suppl):S306–7.
27. **Schett G,** Hayer S, Zwerina J, *et al*. Mechanisms of disease: the link between RANKL and arthritic bone disease. *Nat Clin Pract Rheumatol* 2005;**1**:47–54.
28. **Cummings SR,** San MJ, McClung MR, *et al*. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009;**361**:756–65.
29. **Kim HR,** Lee SH, Kim HY. Elevated serum levels of soluble receptor activator of nuclear factors-kappaB ligand (sRANKL) and reduced bone mineral density in patients with ankylosing spondylitis (AS). *Rheumatology (Oxford)* 2006;**45**:1197–200.
30. **Noh AL,** Yang M, Lee JM, *et al*. Phosphodiesterase 3 and 4 negatively regulate receptor activator of nuclear factor-kappaB ligand-mediated osteoclast formation by prostaglandin E2. *Biol Pharm Bull* 2009;**32**:1844–8.
31. **Appel H,** Ruiz-Heiland G, Listing J, *et al*. Altered skeletal expression of sclerostin and its link to radiographic progression in ankylosing spondylitis. *Arthritis Rheum* 2009;**60**:3257–62.
32. **Saad CGS,** Ribeiro ACM, Moraes JCB, *et al*. Sclerostin as a marker of bone formation in ankylosing spondylitis under anti-TNF therapy: a 12-month longitudinal analysis [abstract 1647]. *Arthritis Rheum* 2011;**63**(Suppl 10):S644.
33. **Heiland GR,** Zwerina K, Baum W, *et al*. Neutralisation of Dkk-1 protects from systemic bone loss during inflammation and reduces sclerostin expression. *Ann Rheum Dis* 2010;**69**:2152–9.
34. **Uderhardt S,** Diarra D, Katzenbeisser J, *et al*. Blockade of Dickkopf (DKK)-1 induces fusion of sacroiliac joints. *Ann Rheum Dis* 2010;**69**:592–7.
35. **Daoussis D,** Liossis SN, Solomou EE, *et al*. Evidence that Dkk-1 is dysfunctional in ankylosing spondylitis. *Arthritis Rheum* 2010;**62**:150–8.

Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in ankylosing spondylitis

Ejaz Pathan, Sonya Abraham, Elizabeth Van Rossen, Robin Withrington, Andrew Keat, Peter J Charles, Erin Paterson, Muslima Chowdhury, Catherine McClinton and Peter C Taylor

Ann Rheum Dis published online September 14, 2012