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### Apremilast for the treatment of active psoriatic arthritis: a single-centre real-life experience

#### Rheumatology key message

- Real-life experience of apremilast in PsA suggests enhanced efficacy in early disease.

SIR, Apremilast (Otezla; Celgene, Summit, NJ, USA) is a small-molecule phosphodiesterase-4 inhibitor that offers a novel oral therapeutic option for patients with psoriasis and PsA. Recent randomized controlled trials (RCTs) show that apremilast is effective in both psoriasis and PsA [1–6], however, there is still a paucity of real-life data in unselected patients.

We performed, at our tertiary centre, a retrospective analysis of the effectiveness and tolerability of apremilast at a standard dose of 30 mg twice a day in subjects with PsA treated in a dedicated outpatient clinic following a zero cost scheme prior to National Institute for Health and Care Excellence approval in the UK.

All subjects fulfilled classification criteria for PsA [7] and had active disease according to the treating clinician. In addition, all subjects had previously been exposed to adequate trials of DMARDs. Ethical approval was not required, as this report was an audit of standard practice and service evaluation.

As part of our local clinic algorithms, subjects were assessed at baseline and every 6 months (s.d. 3). Clinical assessments at each visit included tender (0–78) and swollen (0–76) joint count and CRP levels. When patient and physician global assessments on a 5-point Likert scale were available on clinical notes review, PsA response criteria were also calculated [8].

Subjects were classified as responders and non-responders based on the overall physician judgement of clinical status (yes/no), specifically, the absence of peripheral arthritis, enthesitis and dactylitis on clinical examination; or improvement of clinical signs at physical examination and concurrent patient's reported improvement of symptoms as per PsA response criteria. Response was defined based on the last available follow-up assessment as compared with the baseline evaluation.

Binomial variables were expressed as number and percentage and continuous variables as median (range) or mean (s.d.) as appropriate. Comparisons between baseline and follow-up measurements were performed using Wilcoxon matched pairs signed-rank test. Significant differences between responders and non-responders were defined as those at a level of  $P < 0.05$  by unpaired  $t$  test or

Fisher's or  $\chi^2$  test. Statistical analysis was carried out using GraphPad Prism version 7.0 (GraphPad Software, La Jolla, CA, USA).

A total of 71 patients [ $n = 33$  (46.5%) male] with a mean follow-up of 172.6 days (s.d. 105.5) were identified and included in this report. Clinical characteristics are summarized in Table 1. Of the 71 patients started on apremilast, 51 had at least a 6 months (s.d. 3) of follow-up assessment. Based on overall clinician judgement, 31 of 51 (60.8%) patients were classified as responders and 20 (39.2%) as non-responders. In patients in which joint count was recorded at the baseline and at the follow-up assessment ( $n = 22$ ), there was a statistically significant improvement of tender ( $P = 0.004$ ) and swollen ( $P = 0.003$ ) joint counts. In patients with abnormal CRP levels at baseline, measurements slightly decreased at follow-up ( $P = 0.04$ ). Of note, responders had a shorter disease duration compared with non-responders [5.23 (s.d. 4.46) vs 9.15 (6.8) years;  $P = 0.016$ ] and had a lower exposure to previous biologic DMARDs ( $P = 0.0055$ ) and conventional or synthetic DMARDs, although this latter difference did not reach statistical significance ( $P > 0.05$ ). No other significant differences were found between the two groups.

A total of 28 (39.4%) subjects required drug discontinuation after a mean period of 129.7 days (s.d. 77.7) due to a lack of efficacy and/or side effects. Overall, 27 (38%) patients developed one or more side effects (Table 1). The most common side effects were gastrointestinal (GI) symptoms (19/71), including nausea (9/71), vomiting (3/71), diarrhoea (13/71) and abdominal pain with loss of appetite (1/71). Two patients experienced depression (2.8%), of which one had associated suicidal ideation and concomitant headache and GI symptoms that required drug withdrawal in week 8.

To our knowledge, this is the first real-life report of the use of apremilast in unselected PsA patients. Previously published RCTs have shown that apremilast is effective in patients with PsA and psoriasis, with an acceptable safety profile. In patients with PsA treated with apremilast 30 mg twice a day, the 20% improvement in ACR criteria response ranged between 32.1 and 41% at week 16 in three different phase 3 RCTs [4–6]. Despite using different response criteria, our data from an unselected tertiary centre population confirm these results. The main limitations of our report are the small numbers treated and the amount of missing data that reflects a real population observation, which is due in part to the use of paper-based assessments in our hospital.

An important observation however, and despite the low numbers, is that clinical response appeared to be enhanced in the subset of patients with shorter disease duration, suggesting that apremilast may be better placed earlier on in the treatment algorithm for PsA, although this

**TABLE 1** Baseline clinical characteristics of 71 PsA patients treated with apremilast

Male, <i>n</i> (%)	33 (46.5)
Age, mean (s.d.), years	51 (13.2)
PsA disease duration, mean (s.d.), years	7.7 (6.4)
Peripheral involvement (all polyarticular), <i>n</i> (%)	71 (100)
Axial involvement, <i>n</i> (%)	22 (31)
Psoriasis, <i>n</i> (%)	59 (83.1)
Nail involvement, <i>n</i> (%)	20 (44.4)
Enteseal/dactylitis involvement, <i>n</i> (%)	38 (60.3)
CRP baseline, median (range), mg/l	7.1 (5–115)
Tender joint count, median (range)	7 (0–40)
Swollen joint count, median (range)	3 (0–16)
Patient's disease activity (1–5), median (range)	4 (1–5)
Physician's disease activity (1–5), median (range)	3 (1–5)
Current cDMARDS, <i>n</i> (%)	
MTX	18 (25)
SZ	1 (1.4)
HCQ	2 (2.8)
LEF	1 (1.4)
Combination (MTX + SZ, MTX + HCQ)	2 (2.8)
Current bDMARDS, <i>n</i> (%)	
Certolizumab	2 (2.8)
Golimumab	2 (2.8)
Ustekinumab	2 (2.8)
Adalimumab	1 (1.4)
Etanercept	1 (1.4)
Secukinumab	1 (1.4)
Tocilizumab	1 (1.4)
Previous cDMARDS, <i>n</i> (%)	67 (94.4)
Previous bDMARDS, <i>n</i> (%)	40 (56.3)
Contraindication to bDMARDS, <i>n</i> (%)	10 (14.1)
Apremilast discontinuation, <i>n</i> (%)	28 (39.4)
Ineffective	11 (15.5)
Side effects	27 (38)
GI symptoms	19
General malaise	2
Headache	8
Depression, suicidal ideation	2, 1
Time to discontinuation, days	
Mean (s.d.)	129.7 (77.7)
Median (range)	132 (21–313)
Time of follow-up, days	
Mean (s.d.)	172.6 (105.5)
Median (range)	153 (21–519)

Percentage in parenthesis is calculated based on the number of patients with the specific feature among the total patients with the available data on clinical notes review. bDMARDS: biologic DMARDS; cDMARDS: conventional DMARDS.

observation will need to be confirmed with larger numbers.

In conclusion, our data provide real-life evidence of the short-term efficacy of apremilast in the treatment of active PsA and suggest that this may be enhanced in earlier disease stages. Apremilast represents a valuable additional oral synthetic molecule for the treatment of PsA. Larger observational cohort studies with health economic

evaluations will help confirm the placing of apremilast in the treatment algorithm for PsA.

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### An unexpected response to rituximab in a patient with rheumatoid arthritis

#### Rheumatology key message

- Permanent blockade of CD19<sup>+</sup> CD20<sup>+</sup> B cell generation in rheumatoid arthritis is associated with long-term remission.

SIR, Rituximab, a chimeric mAb that selectively targets CD20<sup>+</sup> B cells, induces clinical remission in most seropositive patients with RA. However, patients inevitably relapse following infusions, mostly within the next 6–12 months [1]. We report herein the case of a patient with a 9-year history of sustained biologic-free clinical remission, along with persistent peripheral B cell depletion, after three iterative rituximab courses.

Prior to the first rituximab cure in 2006, the 54-year-old patient had been suffering from a severely active RA since 1992, along with pulmonary fibrosis, having not responded to conventional therapy. Etanercept was initiated in 2004 though discontinued in 2005, owing to worsening of the pulmonary fibrosis. In March 2006, two infusions of rituximab 1000 mg were administered to the patient with a 2-week interval. At this time, his disease was clinically and serologically very active (Fig. 1A and B). In the months after treatment, a significant clinical improvement was observed, with the disease remaining stable for 9 months then requiring a second rituximab course (2 × 1000 mg, 2 weeks apart). Once again, disease relapse occurred 1 year thereafter, requiring the patient to be re-treated with rituximab (2 × 1000 mg, 2 weeks apart). Since this second rituximab treatment delivered in 2008, the patient has not experienced any clinical relapse, the disease remaining quiescent without any biologic treatment given. During the 9-year follow-up, peripheral CD19<sup>+</sup> B cells were undetectable (Fig. 1C) and levels of both anti-CCP antibodies and immunoglobulins G declined

(Fig. 1B and D) yet the decline in anti-CCP antibodies occurred at a more rapid rate. Despite these immunological abnormalities, the patient has not experienced any severe infection since the last rituximab cure over the 9-year follow-up.

To our knowledge, this case report is the biologic-free complete clinical remission of the longest duration documented after introducing biologic therapy in a patient with very advanced disease. Whether such sustained remission occurs more commonly after rituximab compared with other treatments is still unknown. However, identifying persistent remission is probably easier with rituximab, which is typically administered only during relapses, unlike other biotherapies administered at regular intervals, even in the absence of flare, thus rendering remission cases more difficult to identify. This case report nicely illustrates the critical involvement of B cells in disease progression, with these cells acting directly via the secretion of pathogenic autoantibodies and/or indirectly via the modulation of autoreactive T cells [2]. Interestingly, several aspects of this case merit further discussion. Firstly, our observation challenges the concept that biologic-free remission is unlikely to occur in patients with long-standing RA. According to the current paradigm, namely the window of opportunity concept, several RA patients may achieve biologic-free remission following early therapeutic intervention. This observation is based on the hypothesis that autoimmunity is not fully established during the early disease phase. As a result, long-lasting disease is supposedly associated with irreversible autoimmunity, presumed to be incompatible with long term biologic-free remission [3]. The corollary of this concept is that inducing long-term remission in advanced RA stages would necessitate a purge of autoimmune cells, an undemonstrated hypothesis to date. Secondly, it appears rather surprising that long-term B cell depletion is so well tolerated by our patient, given that he has never required immunoglobulin replacement therapy, unlike other patients with persistent post-rituximab B cell dysfunction [4, 5]. Despite B cell depletion, the patient has likely maintained the level of total immunoglobulins G, which has proven sufficiently high to protect him against infectious agents [6]. This maintenance of protective humoral immunity might be explained by the contribution of the recently described CD19<sup>−</sup> subset of plasma cells that contribute to long-lived protection against infection and do not require replenishment from CD20<sup>+</sup> B cells [7, 8]. It is thus tempting to speculate that the CD19<sup>−</sup> long-lived plasma cell compartment of our patient contains the historical record of B cell responses mounted early in life, notably against pathogens, while being almost devoid of plasma cells activated later in life such as autoimmune plasma cells. Given this scenario, autoimmune plasma cells could be primarily restricted to the CD19<sup>+</sup> plasma cell compartment that requires replenishment from CD20<sup>+</sup> B cells. Permanent blockade of such cell generation by a hitherto unknown mechanism, as observed in our patient, may account for the unexpected long-term remission. Decrypting the mechanisms of medication-