decrease medical care cost and increase treatment options,[3] extrapolation of clinical data from other indications has sparked an intense scientific debate on the interchangeability between originator and biosimilar in real life, and recently reports on the efficacy and safety of the biosimilar SB4 in plaque-type psoriasis have been published.[4,5] The aim of our single-centre, observational, retrospective real-life study was to investigate the etanercept biosimilar SB4 in patients affected by plaque-type psoriasis and PsA.

We evaluated 40 patients (21 men, 19 women; mean age 55·10 years, range 19·89–79·15 years) receiving the etanercept biosimilar SB4 between 21 October 2016 and 31 March 2017 at the Department of Dermatology, University of Rome Tor Vergata. The following data were available at baseline: age, sex, previous treatments, Psoriasis Area and Severity Index (PASI) and, for patients with PsA, visual analogue scale (VAS) for pain (pain-VAS), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), tender joint count (TJC) and swollen joint count (SJC). PASI, pain-VAS, ESR, CRP, TJC and SJC were recorded at each visit. Based on the collected data, we calculated the Disease Activity Score for 28 joints using a formula with ESR as variable (DAS28-ESR). Fourteen patients (35%) had plaque-type psoriasis (mean PASI at baseline 9·61) and 26 (65%) had PsA (mean PASI 4·69, mean DAS28-ESR 5·45). All patients had been treated previously with systemic conventional and biologic treatments. In particular, 10 patients (25%) had previously received etanercept originator. These 10 patients had been treated with a 24-week intermittent regimen, which was interrupted once clinical resolution was considered achieved by the clinician. They did not receive any other treatment between ending the etanercept originator and starting the etanercept biosimilar; mean exposure to etanercept originator was 50·4 weeks (range 24–96 weeks) and mean washout period from originator to biosimilar was 12·1 weeks (range 8–24 weeks). Statistical analysis was performed using software (GraphPad Software, Inc., La Jolla, CA, U.S.A.) and comparisons between correlated groups were performed using paired *t*-test. $P < 0·05$ was considered significant.

At week 24, mean PASI had improved significantly in the plaque psoriasis and PsA cohorts ($P < 0·001$ for both) (Fig. 1a). For patients with PsA, improvement in severity scores during the treatment is summarized in Figure 1b. All scores achieved a statistically significant improvement, with the exception of SJC, which improved markedly but not significantly. We performed a subanalysis of the patients previously exposed to etanercept originator, and observed no significant differences in PASI change or DAS28-ESR/pain-VAS improvement between these patients and etanercept-naïve patients.

No serious adverse events were observed or reported. One patient experienced an episode of injection site reaction that did not require treatment interruption. Two patients discontinued treatment; one decided to leave Italy and the other wanted abdominal plastic surgery.

Despite the limitations of our study (low sample size, limited follow-up time), our results suggest that etanercept biosimilar is an effective treatment for patients with psoriasis even if they were previously exposed to originator. This observation could be of interest when possible price differences between originator and biosimilar are considered. In particular, in our experience, the cost saving achieved by using the biosimilar instead of the originator is 61·58% and 62·55% for the 50 mg and 25 mg vial, respectively. The achieved saving allowed us to guarantee the continuity of etanercept-treated patients' care and gave us the opportunity to allocate patients to innovative but more expensive agents with a marginal increase in our annual budget.

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CD11b$^+$ cells markedly express the itch cytokine interleukin-31 in polymorphic light eruption

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Dear Editor, Itch is one of the cardinal symptoms of polymorphic light eruption (PLE), the most common form of photodermatosis known to be mediated immunologically.[1–3] Indeed, itch often precedes the skin lesions or may even be the only symptom in PLE,[4] and is sometimes aggravated to a burning sensation. There have been reports of a variant

called PLE sine eruption, with intense pruritus on sun-exposed areas without any visible skin changes.[4] However, the underlying cause and cellular mechanisms of itch in PLE are not known. Interleukin (IL)-31 is a novel cytokine of the IL-6 family, also described as a 'pruritogenic cytokine' owing to its link between the immune and neuronal systems to induce itch.[5] IL-31 is expressed by a variety of inflammatory cells.[5] It binds to the IL-31 receptor alpha complex (IL-31RA), and mediates inflammatory itch by forming a functional receptor through coupling to oncostatin M receptor (OSMR)β.[6]

We examined IL-31, IL-31RA and OSMR expression by immunohistochemistry and immunofluorescence on archived formalin-fixed, paraffin embedded samples obtained from our tissue bank, which were reported in a previous study.[7] The samples comprised lesional skin of 12 women and one man (age range 16–76 years) with photoprovoked PLE (eight had undergone UVA testing, three UVB testing, one UVB phototherapy and one natural sunlight exposure, with PLE occurring in all within 1–3 days after exposure). In addition we analysed samples from eight people (one woman, seven men; age range 6–63 years) with subacute to chronic atopic dermatitis (AD) and eight (seven women, one man; age range 31–74) years with chronic plaque psoriasis. Healthy-appearing skin samples from tumour-adjacent sites obtained by surgical excision of lesions such as naevi and nonmelanoma skin cancers of 10 patients (five women, five men; age range 51–87 years) were used as control. The investigations were in accordance with protocols approved by the Ethics Committee of Medical University of Graz, Graz, Austria (18-068 ex 06/07 and 25-293 ex 12/13) and the guidelines of the Declaration of Helsinki Principles.

Following heat-induced antigen retrieval, staining was performed with peroxidise/3-amino-9-ethylcarbazol (AEC) (REAL™ Detection system; Dako, Glostrup, Denmark), using antibodies directed against IL-31 (1 : 200, #GTX85642; GeneTex, Irvine, CA, USA), IL-31RA (1 : 200, #ab113498; Abcam, Cambridge UK), and OSMR (1 : 20, #10982-1-AP, Proteintech, Rosemont, IL, USA). Expression levels (mean ±

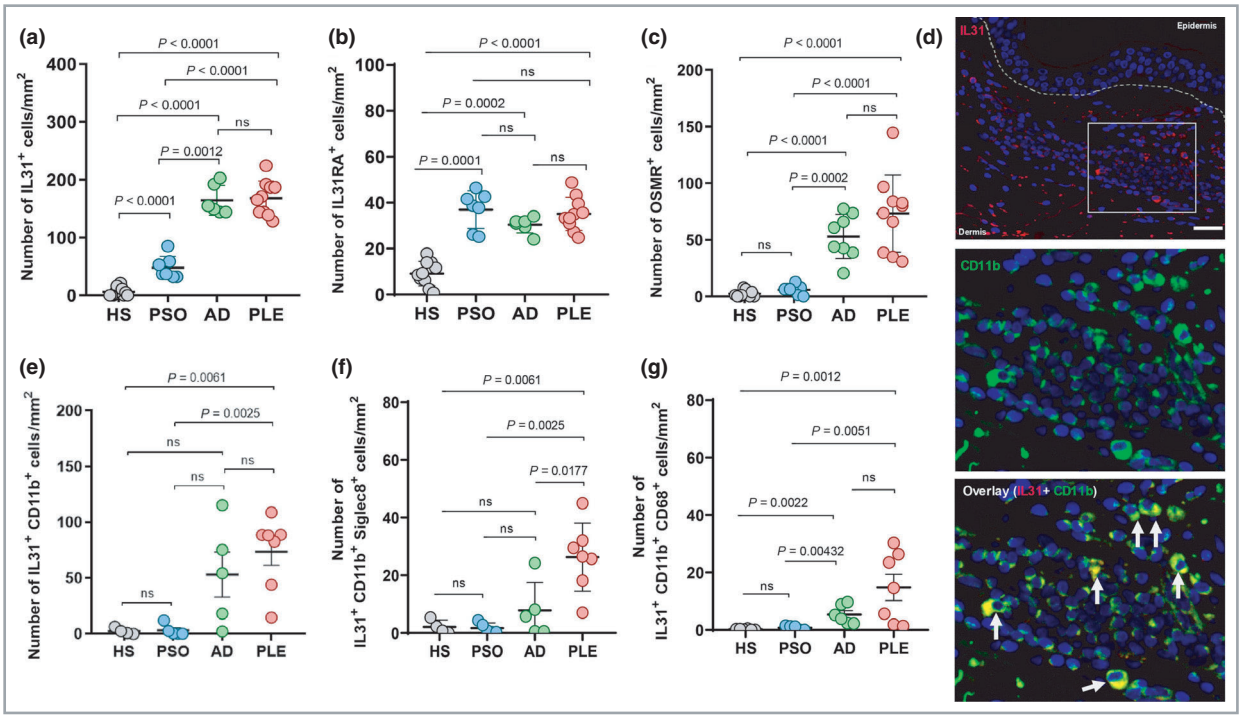

Fig. 1. The majority of interleukin (IL)-31 expression in polymorphic light eruption (PLE) is by $CD11b^+$ cells. Quantitative analysis of immunohistochemical staining showing the number of (a) interleukin (IL)31^+ cells; (b) IL-31 receptor alpha complex $(IL31RA)^+$ cells; and (c) oncostatin M receptor $(OSMR)^+$ cells in different diseases. Visual analysis (a–c) was performed by counting positively stained cells in five of the most densely infiltrated microscopic fields randomly selected from the same section, at a magnification of × 40. (d) Representative images of double staining showing high numbers of $CD11b^+$ cells expressing IL31 in PLE. (e–g) Quantitative analysis showing the number of (e) IL-31-expressing $CD11b^+$, (f) IL31 expressing $CD11b^+$ $Siglec8^+$ (eosinophils); and (g) $CD11b^+$ $CD68^+$ cells (macrophages). Automated analysis for immunofluorescence (e–g) was performed using TissueQuest image analysis software v6·0 (TissueGnostics GmbH, Vienna, Austria). Briefly, nuclei were assessed by 4,6-diamidino-2-phenylindole mean intensity and area measurement, while cell surface and intracellular markers were detected inside and around nuclear staining, respectively. Number of positive cells/mm² was calculated and used for statistical analysis. Data are presented as mean ± SD. P values were determined by Mann–Whitney test. (f) All P values except one [atopic dermatitis (AD) vs PLE] remained significant after Bonferroni correction, setting significance to $P \leq 0{\cdot}0083$; ns, not significant. Scale bar, 50 μm.

SD) of IL-31, IL-31 RA and OSMR in lesional skin of PLE (168·0 ± 29·8, 35·1 ± 7·2 and 73·2 ± 33·9 cells/mm^2, respectively) were similar to those in AD (164·4 ± 26·0, 30·3 ± 3·4 and 52·9 ± 19·5 cells/mm^2) and higher than in healthy skin (6·3 ± 7·4, 9·1 ± 5·0 and 2·4 ± 2·8 cells/mm^2) (Fig. 1a–c). In psoriatic skin, overall expression of IL-31 (48·0 ± 19·4 cells/mm^2) and OSMR (5·9 ± 3·9 cells/mm^2) was lower compared with PLE, while IL-31RA (36·9 ± 8·2 cells/mm^2) was expressed at similar levels. High numbers of IL-31$^+$, IL-31RA$^+$ and OSMR$^+$ cells were observed in polymorphonuclear leucocyte infiltrations in the dermis and in blood vessels (mostly in PLE lesions) (data not shown). There was no expression of IL-31 in the epidermis (Fig 1d).

To identify the cellular sources of IL-31 in the different disease conditions, we performed multicolour staining using conjugated monoclonal antibodies against IL-31 (1:30, clone: 1D10B31, #659603), CD68 (1:20, clone: Y1/82A, #333810), Siglec8 (1:20, clone: 7C9, #347106) (all Biolegend, San Diego, CA, USA), CD11b (1:20, clone: Bear1, #IM0530; Beckmann Coulter, Brea, CA, SA), and 4,6-diamidino-2-phenylindole nuclear marker (Roche Applied Sciences; Indianapolis, IN, USA). Double staining indicated that the major source of IL-31 in PLE was mainly CD11b$^+$ cells (73·8± 32·5 cells/mm^2) (Fig. 1d, e). Triple staining indicated that a substantial portion of IL-31$^+$ CD11b$^+$ cells were also positive for Siglec8 (eosinophilic marker) (Fig. 1f) or CD68 (macrophage marker) (Fig. 1g). The numbers of those cells were significantly higher in PLE lesions compared with healthy or psoriatic skin (Fig. 1e–g).

A previous study showed CD11b$^+$ cells in skin of people with PLE and enhanced infiltration of these cells upon UV exposure in lesional skin, and found that most of these CD11b$^+$ cells were CD68$^+$ macrophage-like cells.[1] Furthermore, PLE lesions are sometimes infiltrated with eosinophils.[4] In our study, we observed elevated numbers of macrophages and eosinophils expressing IL-31 in PLE lesions (Fig. 1f, g), in levels nearly similar to AD.[6]

IL-31 is known to be induced by exposure to UV radiation, and its potential mediators including human beta-defensins (HBDs) and LL-37.[6] We have previously reported increased HBD-2 and LL-37 in PLE lesions.[7] Certain antimicrobial peptides can augment the production of IL-31 through a positive loop response and thus could contribute to the development of the itchy lesions in PLE.[6] Interestingly, macrophages that were stimulated by microbial elements such as staphylococcal exotoxins [staphylococcal enterotoxin B (SEB), alpha-toxin] were able to significantly upregulate IL-31RA.[6] Microbial elements are hypothesized to be involved in the pathogenesis of PLE.[8] Furthermore, macrophages and eosinophils treated with SEB and IL-31 can secrete pro-inflammatory cytokines such as IL-1β.[6] In this regard, Lembo *et al.* have shown increased expression of IL-1 family members in PLE.[2]

Although this study has limitations such as overall small sample size and imperfect age and sex matching, its findings may open new avenues for the development of novel treatment strategies in PLE, targeting IL-31. Indeed, anti-IL-31 blockade has been designed for treating itch and the monoclonal anti-IL-31 receptor antibody nemolizumab has been successfully used to neutralize the itch in patients with moderate-to-severe atopic dermatitis.[6]

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