De novo onset of arthritis in patients previously treated with efalizumab: an observational case series

Sirs,

Efalizumab has been shown to be beneficial in the treatment of patients with moderate to severe psoriasis (1). Marketing authorisation for efalizumab was suspended in February 2009 because its use is associated to an increased risk of progressive multifocal leukoencephalopathy (PML) (2, 3). Then, efalizumab had its Europe wide recall in June 2009. Despite its effectiveness in psoriasis, efalizumab has not been shown to be effective on psoriatic arthritis (PsA) (4). We report a case-patient report of psoriatic arthritis that appeared after the discontinuation of efalizumab.

Since April 2009 we have observed 11 cases in our Rheumatology Clinic with suspected acute peripheral entheso-arthritis that appeared in psoriatic patients after the discontinuation of efalizumab. At presentation all patients were assuming topical treatments for psoriasis.

All patients fulfilled the CASPAR criteria (5). After stopping efalizumab, all patients were closely monitored for infections and neurological symptoms for 2 months, with negative results. Clinical and laboratory characteristics of the patients are summarised in Table I. Median age at the onset of arthritis was 40 years (IQR 30.5–40.5). A poli-entheso-arthritis, usually asymmetric, mostly involving the ankles (n=7, 64%), wrists (n=6, 55%), knees (n=5, 45%) and entheses (n=10, 91%), especially at the Achilles tendon, were the most common symptoms.

The median time lag between the stopping of efalizumab and the onset of psoriatic arthritis was 13 weeks (IQR 12.5–15), whereas the median efalizumab treatment was 8 months (IQR 4–9.5).

A comparison of the PASI at the beginning of efalizumab treatment, at its end, and at the onset of osteo-articular complaints revealed that all the patients had had a good response to efalizumab, but that the onset of rheumatologic symptoms was associated to psoriasis recrudescence (median PASI score 21 before efalizumab *versus* 4.3 on the suspension of efalizumab and 22.7 at the onset of arthritis).

We are describing a case-patient series of *de novo* psoriatic entheso-arthritis in subjects previously treated with efalizumab.

The limited knowledge of the safety profile of efalizumab, and generally of all biologicals, at the time of their approval, underlines the need for pharmacovigilance (6). The safety management of biologicals in the postapproval real world-setting can lead to the identification of important safety problems. Whether active surveillance or data-mining methods are used, finding potential drug-safety problems requires skilful observation by clinicians who are sensitized to the possibility of drug-related adverse events and aware of the need to report them (7).

The effects of efalizumab on the immune system last for about 8 to 12 weeks, therefore we argue that in our case series, the onset of arthritis could be considered as a delayed side effect of efalizumab.

Efalizumab, in fact, has shown to inhibit the interaction of LFA-1 with ICAM-1, and thus, to limit T cells activation and migration processes. Likewise, it is tempting to speculate that the T lymphocytes involved in the pathogenesis of psoriasis could also be pathogenetic for articular disease (8). Alternatively, it is also possible that the suspension of efalizumab has led to a "rebound" effect with an increased expression of pro-inflammatory cytokines such as TNF-α. In conclusion, although causality assessment remains complicated because of concomitant drugs and the lack of a strong temporal relationship between the event and drug therapy or its discontinuation, our observation should raise the consciousness to monitorise psoriatic patients who had received efalizumab for the possibility of the occurrence of a *de novo* entheso-arthritis too. From our observation is not possible to draw any epidemiological conclusion because most of the patients came from other districts.

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Competing interests: none declared.

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Table I. Clinical and immunological characteristics of our case series.

Patient	Age*	Sex	Efalizumab treatment (months)	Time lag (weeks¥)	Axial involvement	Peripheric arthritis	Enthesitis[9]	Dactylitis[10]	PASI score*	Psoriatic nail dystrophy	ANA	RF	Anti-CCP	HLA-B27
1	50	M	4	10	no	left wrist, left knee, ankles	yes	yes	23.4	yes	–	–	–	+
2	32	F	8	9	no	right ankle, left knee, wrists	yes	no	12,.4	no	–	–	–	–
3	18	M	10	13	no	right shoulder, left PIP, MCPs	yes	no	12.5	yes	–	–	–	+
4	27	M	2	15	no	ankles, knees, left wrist	yes	yes	30.9	no	–	–	–	–
5	40	F	16	14	no	left hip, wrists	yes	yes	9.6	yes	–	–	–	+
6	40	M	3	13	no	knees, ankles	yes	yes	25.3	no	–	–	–	+
7	36	M	5	16	no	PIPs, DIPs	yes	no	18.4	yes	–	–	–	+
8	44	M	9	12	no	ankles, PIPs, right shoulder	yes	yes	26.1	yes	–	–	–	–
9	29	F	8	13	no	left wrist, left ankle, right PIPs	yes	no	9.8	yes	–	–	–	–
10	41	F	11	15	no	ankles, knees	yes	no	24.3	no	–	–	–	+
11	40	F	4	20	no	wrists, PIPs, DIPs	no	no	22.7	yes	–	–	–	+

*at the onset of arthritis; ¥ time between stop of efalizumab and onset of psoriatic arthritis.
ANA: antinuclear antibody; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide; PIP: proximal interphalangeal; DIP: distal interphalangeal; MCP: metacarpophalangeal.