where, despite extensive investigation, an underlying aetiology is not found. Drug-induced eosinophilia is a diagnosis of exclusion where a temporal relationship exists between drug initiation, development of eosinophilia and eosinophilia resolution with drug cessation. Certain rheumatological medications, such as SSZ, allopurinol and ciclosporin, are known to be associated with drug reaction with eosinophilia.

Limited case reports exist involving infliximab and adalimumab in both RA and PsA patients, highlighting an association between anti-TNF-α therapy and hypereosinophilia [2, 3]. It has been postulated that this reaction occurs as a result of an exaggerated Th2 response to anti-TNF-α therapy. Etanercept and adalimumab have been reported to cause an eosinophilic cellulitis (Wells' syndrome) at the site of s.c. injection [4, 5], and certolizumab is reported to cause peripheral eosinophilia in 10 in 1000 patients [3].

Hypereosinophilia in this case was associated with an eosinophilic infiltrate into the epithelial layer of the gastrointestinal tract, resulting in the patient experiencing severe epigastric pain that required hospitalization. In this case, the eosinophil count rose steadily over the first 3 months (Fig. 1) and was already significantly raised 1 month after the first infusion. We would therefore recommend that a full blood count be performed monthly for the first 3 months. If the eosinophil count is seen to rise, then we would recommend withdrawal of further treatment with tocilizimab in order to prevent end-organ damage.

Rheumatology key message

- Early detection of hypereosinophilia with tocilizumab treatment in RA may prevent end-organ damage.

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Paradoxical psoriatic arthritis in a patient with psoriasis treated with ustekinumab

SIR, Psoriasis and PsA share common pathophysiological mechanisms. The mutual role of Th17 cells is supported by the therapeutic efficacy of ustekinumab, an IL-12/23 mAb, in PsO and PsA [1]. Reports of paradoxical PsA in patients treated with ustekinumab are very sparse. We report disabling polyarthritis during ustekinumab monotherapy in a patient with severe plaque psoriasis.

An obese (BMI 32) 46-year-old man with severe psoriasis and no history of PsA was treated with numerous therapies, mostly ineffective. Subsequently, ustekinumab (90 mg) was introduced. At week 15 the patient developed a cough and severe myalgia; 1 week later he developed fever (37.8°C) and pain in the left hip, although no abnormality was detected by radiography. He denied symptoms of urethritis or diarrhoea. Two days later the patient developed migratory arthritis, involving the knees, shoulders, wrists and entire second digit of the left hand. This outbreak was followed by spontaneous resolution of the psoriasis. Acute-phase reactants were elevated. Ustekinumab was suspended and methylprednisolone was introduced; he became afebrile and mobile. As methylprednisolone was tapered, joint pain and swellings reappeared. We then introduced MTX, and after a few months, LEF.

The possible causal relationship between our patient's new-onset PsA (with dactylitis and elevated acute-phase reactants) and ustekinumab can be supported by the longer lag time from psoriasis onset to PsA diagnosis than described in the literature (10 years) [1]. Furthermore, as our patient has been treated principally with acitretin and topical therapies, and only briefly with MTX, the possibility of a pre-existing subclinical joint disease masked by therapy is minimal. As arthritis reappeared after CS tapering, reactive arthritis and drug hypersensitivity were also excluded. The same paradoxical reaction has been described elsewhere (see Table 1) [2–4].

Table 1 Our patient and patients from other studies with paradoxical PsA after ustekinumab

Study	PsA	M/F	Age	Psoriasis, years	UST dose, mg	UST efficacy	Time to flare	Previous biologic	Arthritis type	Laboratory findings	Stop UST	Current therapy
[2]	–	M	38	18	90	+	3 days	ETA	Abrupt polyarthritis	Normal	+	ETA
[2]	–	M	43	20	45	+	15 weeks	–	PIP left, right fourth digit	Normal	+	ADA
[3]	+	M	40	NR	90	+	1 month	ADA, ETA	PsA	NR	+	ETA
[3]	–	M	50	NR	45	+	5 months	ETA, ADA	Migratory arthritis	NR	+	ADA + MTX
[3]	+	M	60	NR	45	+	5 months	ETA, ADA	Polyarthritis	NR	–	UST + NSAID
[3]	–	M	40	NR	45	+	3 months	ETA	Migratory arthritis	NR	–	UST + NSAID
[4]	–	F	65	31	90	+	28 months	ADA, ETA	Dactylitis, erosions	Elevated CRP	+	SSZ + GOL
[4]	–	F	49	42	45	+	22 months	–	Enthesitis, dactylitis, fasciitis	–	+	PsA worsened on ETA, improved on ADA
[4]	+	M	50	>40	90	+	4 months	ADA, ETA	Synovitis, enthesitis, dacylitis	–	+	ETA
[4]	–	F	69	18	90	±	15 months	ADA, ETA	Enthesitis, dactylitis	RTG +, CRP↑	+	GOL failed, INF
[4]	–	F	57	7	45	+	8 months	ADA, ETA	Synovitis, enthesitis	–	+	GOL failed, INF
[4]	+	M	65	60	90	+	12 months	–	Enthesitis, synovitis	RTG +, CRP↑	–	Psoriasis worsened and PsA unimproved on ETA; UST restarted psoriasis improved, PsA worsened
[4]	–	F	55	14	90	+	19 months	ADA, ETA	Synovitis	–	–	UST + MTX
Our patient	–	M	46	>20	90	–	4 months	–	Migratory arthritis	CRP ↑, ESR↑, RF ↑, ANA –ANCA –	+	MTX + LEF

ADA: adalimumab; ETA: etanercept; F: female; GOL: golimumab; INF: infliximab; M: male; NR: not reported; RTG: radiological images; UST: ustekinumab.

Although PsA occurs just as frequently in both sexes [1], from this small series review it appears that paradoxical joint inflammation (PJI) affects mostly males (9 of 14 cases). Ten of the 14 patients were previously treated with biologics, most frequently etanercept. The latency period varies from 3 days to 5 months [2, 3] to 8–28 months [4]. The majority of patients (10 of 14) had no history of PsA.

Our patient, and two more, developed migratory arthritis (within the first 5 months), and one patient developed an abrupt polyarthritis. Migratory arthritis is a rare manifestation of PsA, and the relatively high prevalence in this small case series may indicate a change in clinical presentation of PsA to a more acute one. Similarly, pustular lesions predominated (>50%) as a paradoxical skin reaction after anti-TNF therapy, while in the classic psoriatic patients they represent only 1.7% of cases [5]. Eight patients, including ours, were treated with 90 mg of ustekinumab. The negative impact of obesity on the efficacy of ustekinumab has recently been elaborated [6]. Ruiz *et al.* [6] stated that the probability of a favourable response appears to be lower in patients weighing >100 kg and treated with 90 mg of ustekinumab, as well as in patients in which anti-TNF-α therapy has failed [6].

It is possible that inside the ustekinumab-associated PJI there are two subgroups: the first appears early (<5 months), often with migratory arthritis, as a result of changes in cytokine balance, which causes a switch from skin psoriasis to articular psoriasis (as in our patient). The second subgroup develops later, in patients with subclinical PsA, which progresses into clinical PsA as a result of lower efficacy of ustekinumab on the joint inflammation [4, 7].

We need more data to estimate the relevance of previous anti-TNF, especially etanercept, therapy in the development of ustekinumab-associated PJI. Etanercept as a fusion protein acts differently from other anti-TNFs. It blocks IL-23 p40 subunit production very early [8], but final disease resolution depends on down-modulation of Th1 cells, which, in the case of etanercept, happens late, as IFN-γ is not decreased until week 12 and STAT-1 until after several months of treatment [8].

It is possible that this cytokine imbalance, occurring after administration of anti-TNF, especially etanercept, or in patients not previously treated with anti-TNF, but with high BMI, as a consequence of a lower efficacy of ustekinumab on the joints than on the skin, may trigger or unmask PsA. PsA seems to need higher doses of ustekinumab than the skin lesions [1]. Further studies are needed to evaluate whether obese male patients with severe psoriasis, especially those previously treated with anti-TNFs, require

higher doses of ustekinumab or additional MTX to prevent aggravation of or new-onset PsA.

Rheumatology key message

- Patients with a high BMI or those previously treated with anti-TNFs more often develop ustekinumab-induced PsA.

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Comment on: Intravenous neridronate in the treatment of acute painful knee osteoarthritis: a randomized controlled study

Sir, We read the article by Varenna *et al*. [1] with great interest. They reported that, compared with placebo, i.v. infusion of neridronate, an amino-bisphosphonate, provided clinically relevant pain benefit and functional improvement in patients with acute knee pain (<3 months duration) suffering from knee OA with MRI scan showing bone marrow oedema [1]. This would be good news in view of our currently unsatisfactory armamentarium for OA [2]. However, we would like to express some reservations about this study.

First, the authors wrote that the statistical analysis was performed according to the intention-to-treat principle. However, they reported data of outcome measures for completers only, suggesting that a per-protocol analysis was actually conducted. If that is so, the results of their study may be biased.

Second, neridronate appeared to be at least as efficacious as any current pharmacological treatment for OA [2]. Based on changes in pain measured by visual analogue scale (0–100 mm) from baseline to day 60, the primary outcome measure, the effect size (ES) of neridronate may be estimated at 1.2 (95% CI 0.6, 1.7), which corresponds to a surprisingly large effect. Using WOMAC pain subscale scores, the ES for pain relief, albeit lower (0.8, 95% CI 0.2, 1.3), is still clinically relevant. As a matter of interest, the corresponding ES of oral NSAIDs was estimated at 0.4–0.5 [2].

Finally, we wonder whether bisphosphonates might be a promising therapeutic option for the management of symptomatic OA. The systematic review by Davis *et al*. [3] led to the conclusion that 'there is little evidence that bisphosphonates are effective in the treatment of OA pain' [3]. According to the meta-analysis of the two largest controlled trials of risedronate (at a dose of up to 15 mg/day) in knee OA, no statistically significant improvements in WOMAC (total, pain subscale and function subscale) outcomes were observed compared with placebo [3]. Similarly, oral alendronate (70 mg weekly) failed to show any clinical benefit over placebo in patients with knee OA [3]. Conversely, a single infusion of 5 mg of zoledronic acid was reported be effective, compared with placebo, in relieving pain after 6 months, but not after 3 or 12 months, in the per-protocol population