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Incidence of serious gastrointestinal events among tildrakizumab-treated patients with psoriasis

Dear Editor

Psoriasis and inflammatory bowel disease (IBD) are chronic inflammatory diseases with shared genetic susceptibility and immunologic aspects, mediated by the interleukin (IL)-23/IL-17 axis.[1] Biologic therapies targeted against IL-17A and IL-17 receptor A have been associated with exacerbation of IBD both in clinical trials[2–4] and real-world data.[5] As IL-17 and IL-23 inhibitors act on the same inflammatory pathway, it is important to evaluate the effect of IL-23 inhibitors on IBD. Here, we examined the incidence of serious gastrointestinal (GI) disorders, specifically cases of IBD, including Crohn's disease and ulcerative colitis, reported during a phase 2b (P05495, NCT01225731) and 2 phase 3 (reSURFACE 1, NCT01722331; reSURFACE 2, NCT01729754) trials of tildrakizumab, an anti-IL-23p19 monoclonal antibody.[6,7] The trials included patients aged ≥18 years with moderate to severe chronic plaque psoriasis (body surface area involvement ≥10%, Physician's Global Assessment score ≥3, and Psoriasis Area and Severity Index score ≥12). Patients were randomized to receive subcutaneous placebo, tildrakizumab 100 mg or tildrakizumab 200 mg at Week 0, Week 4 and every 12 weeks thereafter. Full study details and results were published previously.[6,7] This post hoc analysis was based on data from all patients with exposure to placebo, tildrakizumab 100 mg or tildrakizumab 200 mg at any time during the base study period. All adverse events (AEs) were reviewed; exposure-adjusted incidence rates (number of events/100 patient-years) of serious GI AEs and cases of new onset or exacerbations of pre-existing IBD were compared across treatment groups.

The analysis included 1911 patients from the three clinical trials, with a total exposure of 1927.19 patient-years for tildrakizumab and 218.86 patient-years for placebo. Across treatment groups, patients had similar pre-existing medical conditions (Table 1) and 15–19% of patients had pre-existing GI disorders (Table 1). The incidence of pre-existing IBD was low (family history was not recorded). In total, seven patients had a history of IBD: three patients had ulcerative colitis, 1 in each of the tildrakizumab and placebo groups; two patients had Crohn's disease, both from the tildrakizumab 200-mg group; and two patients had IBD (unclassified), both from the tildrakizumab 100-mg group. Serious GI AEs were infrequent and observed in one patient (0.46/100 patient-years) who received placebo, eight patients (0.80/100 patient-years) who received tildrakizumab 100 mg and four patients (0.43/100 patient-years) who received tildrakizumab 200 mg. There were no new cases of IBD or exacerbation of pre-existing IBD during the study. A summary of serious GI AEs is shown in Table 2. No individual event occurred in more than one patient across the treatment groups.

This analysis suggests that the IL-23 inhibitor tildrakizumab does not induce or worsen IBD in patients with psoriasis. In contrast, clinical trials of IL-17 and IL-17 receptor A inhibitors showed occasional new cases and exacerbation of IBD in patients with psoriasis[2] and in patients with Crohn's disease.[3,4] The differential effects might be explained by IL-23-independent production of IL-17A and the protective effect of IL-17A in the presence of epithelial injury, demonstrated in a preclinical

Table 1 Summary of pre-existing medical conditions*

Medical history	PBO (*N* = 357)	TIL 100 mg (*N* = 705)	TIL 200 mg (*N* = 708)	TIL total (*N* = 1413)
Patients with ≥1 condition	357 (100)	705 (100)	708 (100)	1413 (100)
Blood and lymphatic disorders	7 (2.0)	12 (1.7)	17 (2.4)	29 (2.1)
Cardiac disorders	29 (8.1)	43 (6.1)	41 (5.8)	84 (5.9)
Congenital, familial and genetic disorders	5 (1.4)	15 (2.1)	11 (1.6)	26 (1.8)
Endocrine disorders	26 (7.3)	30 (4.3)	47 (6.6)	77 (5.4)
GI disorders	69 (19.3)	128 (18.2)	103 (14.5)	231 (16.3)
Hepatobiliary disorders	16 (4.5)	33 (4.7)	27 (3.8)	60 (4.2)
Immune system disorders	58 (16.2)	146 (20.7)	148 (20.9)	294 (20.8)
Nervous system disorders	55 (15.4)	84 (11.9)	99 (14.0)	183 (13.0)
Pregnancy, puerperium and perinatal conditions	1 (0.3)	2 (0.3)	3 (0.4)	5 (0.4)
Renal and urinary disorders	17 (4.8)	33 (4.7)	36 (5.1)	69 (4.9)
Respiratory, thoracic and mediastinal disorders	44 (12.3)	90 (12.8)	80 (11.3)	170 (12.0)

Data in table are *n* (%) for conditions in which incidence was >0% in 1 or more treatment groups.
*All patients randomized and based on part 1 treatment assignment from P05495 (phase 2b), reSURFACE 1 (phase 3) and reSURFACE 2 (phase 3) trials.
GI, gastrointestinal; PBO, placebo; TIL, tildrakizumab.

Table 2 Summary of Serious GI AEs*

Serious GI AEs	PBO (*N* = 588)	TIL 100 mg (*N* = 1083)	TIL 200 mg (*N* = 1041)	TIL Total (*N* = 1911)
Patients with serious GI AEs	1 (0.46)	8 (0.80)	4 (0.43)	12 (0.62)
Abdominal hernia	0	0	1 (0.11)	1 (0.05)
Abdominal pain	0	1 (0.10)	0	1 (0.05)
Upper abdominal pain	0	0	1 (0.11)	1 (0.05)
Constipation	0	1 (0.10)	0	1 (0.05)
Diverticulum	0	1 (0.10)	0	1 (0.05)
Dyspepsia	0	1 (0.10)	0	1 (0.05)
Food poisoning	1 (0.46)	0	0	0
Gastritis	0	1 (0.10)	0	1 (0.05)
Thrombosed haemorrhoids	0	1 (0.10)	0	1 (0.05)
Oesophageal polyp	0	1 (0.10)	0	1 (0.05)
Pancreatitis	0	1 (0.10)	0	1 (0.05)
Acute pancreatitis	0	0	1 (0.11)	1 (0.05)
Salivary gland enlargement	0	0	1 (0.11)	1 (0.05)

Data in table are *n* (*n*/100 PY).
*Based on data from all patients with exposure to tildrakizumab 100 mg or 200 mg at any time during the study period (up to 64 weeks).
AE, adverse event; GI, gastrointestinal; PBO, placebo; PY, patient-years; TIL, tildrakizumab.

model.[8] These mechanistic hypotheses are validated by the positive results obtained with ustekinumab (IL-12/23 inhibitor) and risankizumab (IL-23 inhibitor) in clinical trials in patients with Crohn's disease.[9,10] Additional data on tildrakizumab from further clinical trials, clinical use and postmarketing surveillance are required to confirm the trial findings.

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Switching from a fumaric acid ester mixture to dimethylfumarate monotherapy in psoriasis

Editor

Psoriasis is a chronic inflammatory skin disorder with a significant disease burden. Whilst numerous treatments exist, development of effective and affordable therapies offering good patient outcomes remains desirable.

A mixture of fumaric acid esters (FAE) is commonly prescribed for oral treatment of moderate-to-severe plaque psoriasis in Germany. In other European countries (UK, Ireland, Italy and the Netherlands, among others), FAE have been imported or compounded by local pharmacies. Current international guidelines recommend FAE for the short- and long-term management of psoriasis.[1] Although the original formulation (Fumaderm®) contains a mixture of FAE, the main active ingredient is dimethylfumarate (DMF), an anti-inflammatory and immune-modulating agent with proven efficacy in psoriasis.[2] The monoethylfumarate salts within the FAE formulation have shown much lower biological activity both *in vitro* and *in vivo*.[3–5]

Dimethylfumarate (Skilarence®) was approved for use as monotherapy for the treatment of plaque psoriasis in June 2017. Its pivotal study was a phase III, double-blind, randomized, placebo-controlled, non-inferiority trial (BRIDGE, ClinicalTrials.gov NCT01726933), comparing the efficacy and safety of DMF versus the FAE mixture in patients with moderate-to-severe plaque psoriasis.[6] At week 16, DMF was superior to placebo ($P < 0.001$) and non-inferior to the FAE mixture ($P < 0.001$) in achieving Psoriasis Area and Severity Index 75, and superior to placebo in the percentage of patients who achieved 'clear' or 'almost clear' in the Physician's Global Assessment ($P < 0.001$). DMF also showed comparable results to the FAE mixture in quality of life improvement. Importantly, at a comparable dose, the safety profile of DMF was like that of the FAE mixture.[6]

So far, FAE have demonstrated a favourable long-term safety profile and good drug survival over time, alongside good levels of patient acceptability and satisfaction with treatment. Considering all preclinical and clinical evidence, it is reasonable to conceive that single-compound therapy with DMF will achieve comparable efficacy results, and at least similar tolerability, in patients with moderate-to-severe plaque psoriasis who undergo a straightforward 1 : 1 switch in terms of dosing.

In this context, phasing out of previous FAE treatment is not required, and treatment response will not be affected by the timing of the switch. This assumption is largely because DMF, the active ingredient in both formulations, is administered at identical doses in each tablet (30 or 120 mg). Benefits of switching include treatment with a therapy that is now licensed across Europe and requires less frequent monitoring (quarterly, rather than monthly) in patients with lymphocyte counts >1000/mL.[7,8] Whilst monitoring after DMF administration is still recommended, as for all other anti-psoriatic therapies, less frequent monitoring remains clinically meaningful as it reduces treatment burden for both patients and physicians, whilst still ensuring an appropriate safety margin.

Switching from the FAE mixture to DMF is common in clinical practice. For example, in the Netherlands, both the FAE mixture and DMF have been available alongside each other for some time and switching from the FAE mixture to DMF is feasible without loss of efficacy or side-effects. In addition, recently published results from a German prospective study in 40 patients who switched from the FAE mixture to an equivalent dose of DMF confirmed that a direct treatment switch is possible. Moreover, this study demonstrated that a direct switch offered the same clinical relief and did not require a washout period between therapies.[9] In summary, as clinical experience of switching grows, evidence indicates that switching to DMF is both feasible and effective.

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