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Tocilizumab-induced mucosal ulcers in a patient with relapsing polychondritis: An adverse drug reaction?

Dear Editor,

We have read with interest, the article by Deroux et al. [1], describing the use of tocilizumab (TCZ) in refractory Behçet's disease (BD), in which four female patients were treated successfully without any adverse event. In particular, mucocutaneous lesions responded well to TCZ administration.

In addition to the letter to Editor written by Emmi et al. [2], the mucocutaneous paradoxical effect of TCZ is well reported in other diseases, such as rheumatoid arthritis and ankylosing spondylitis, and in different portions of the gastrointestinal tract, involving oral mucosa as well as small and large intestine [3,4]. In this regard we report herein a patient affected by relapsing polychondritis (RP) resistant to corticosteroid treatment that developed recurrent mucosal ulcers after the second infusion of TCZ.

B.F. is a 46-year-old-man in which RP was diagnosed in 2009 for the presence of recurrent auricular and nasal chondritis, dry cough, hoarseness, pain at proximal trachea and larynx, and a non-erosive peripheral arthritis involving both hands and wrists and the left knee. Acute phase reactants resulted highly elevated and both rheumatoid factor and anti-citrullinated protein antibody were negative. The patient had never suffered from mucosal ulceration. The patient was at first treated with repeated bolus corticosteroids and intramuscular methotrexate 15 mg/weekly, with a weak control of the symptomatology. For this reason, in 2010 he started a therapy with infliximab (350 mg every 8 weeks, augmented to 350 mg every 5 weeks) till June 2015, when the drug was suspended for loss of efficacy and reappearance of the symptomatology above mentioned. TCZ was started at a dose of 8 mg/kg every 4 weeks in August, with a good initial response. Since the second infusion, the patients started suffering from recurrent major oral ulcers (Fig.); ulcers swabs twice demonstrated the absence of Herpes viruses. An empirical 1-week treatment with valaciclovir 1000 mg/tid did not ameliorate the ulcers. Due to the persistence of oral ulcerations and, since the 13th infusion, the onset of peripheral arthritis involving both hands, the shoulders and the hips, TCZ was suspended and ulcers progressively disappeared during the following 15 days.

In addition to the conflicting data about TCZ efficacy in mucocutaneous manifestations of BD patients well summarized by Emmi and colleagues and already reported by Diamantopoulos [5], this biological agent seems to be associated independently with gastrointestinal ulceration, and mouth ulcerations are reported as common adverse reactions in TCZ data sheet. In fact, several trials (STREAM, TOWARD, SATORI, SAMURAI, and OPTION) reported a variable percentage ranging from 2% to 11.5% of "oral ulcerations" and "stomatitis" in patients treated with TCZ, without any clinical description or correlation with infections [6–10] (Table). In addition to this, TCZ was associated with gastrointestinal perforation and Iwasa et al. [3] speculated that this condition may be preceded by mucosal ulceration. The mechanism is not clear, but it is probably mediated by inhibiting STAT3, which promotes injury and impaired regeneration of intestinal epithelium [11]. For this reason, TCZ-related mucosal ulcers seem to be a general adverse effect more than an exacerbation of mucocutaneous involvement as it can happen in BD. Ad hoc

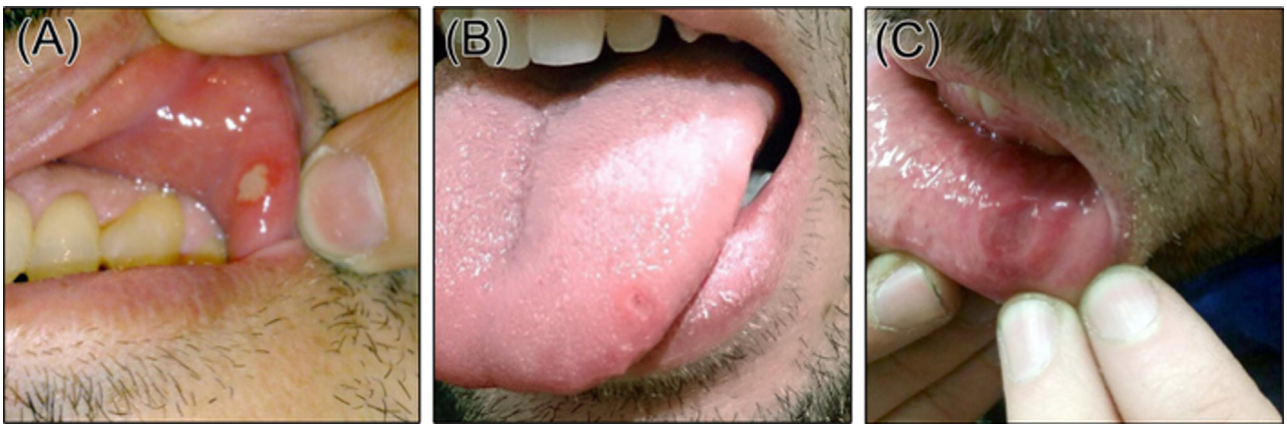

Fig. Major oral ulcers involving the oral mucosa (A), the tongue (B) and the lower lip (C).

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Table
Reported rates of tocilizumab-related stomatitis and/or oral ulcerations during some clinical trials

Study	Patients	Drugs	Stomatitis/oral ulcers
STREAM [5]	54	Placebo	3.7%
	54	TCZ 4 mg	5.6%
	53	TCZ 8mg	7.3%
TOWARD [6]	414	Placebo + DMARD	Mouth ulceration 1%/stomatitis 0%
	802	TCZ 8 mg + DMARD	Mouth ulceration 2%/stomatitis 1%
SATORI [7]	61	MTX 8 mg	0%
	66	TCZ 8 mg	11.5%
SAMURAI [8]	148	DMARD	9.0%
	158	TCZ 8 mg	5.7%
OPTION [9]	204	Placebo	0.5%
	212	TCZ 4 mg	2%
	206	TCZ 8 mg	2%

clinical studies are needed to clarify the linkage between mucosal ulceration and TCZ administration.

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