SEVERE BITTER TASTE ASSOCIATED WITH APREMILAST.

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Sir,

Apremilast, which is currently licensed for the treatment of psoriasis and psoriatic arthritis is a small-molecule inhibitor of phosphodiesterase-4 (PDE-4), an enzyme responsible for the breakdown of cyclic adenosine monophosphate (cAMP) (Torres, 2018).

An 83-year-old male with psoriasis and psoriatic arthritis was referred to our Department of Dermatology with severe plaques and dactylitis of the second finger of his right hand. He was overweight (body mass index 29.4 kg/m^2), had a Psoriasis Area Severity Index (PASI) of 11, and complained of a drastic reduction in his quality of life (Dermatology Life Quality Index [DLQI] 23).

As his medical history included a myocardial infarction and bladder cancer respectively two and three years earlier, biological treatment was absolutely contraindicated, and he failed to respond to narrow-band ultraviolet B (NB-UVB) plus methotrexate, the only remaining on-label systemic treatment was with apremilast, a PDE-4 inhibitor. After precisely following the induction (10mg/day at day 1, 10+10mg/day at day 2, 10+20mg/day at day 3, 20+20mg

at day 4, 20+30 mg at day 5, after 30+30mg/daily) and maintenance (30+30 mg/daily, after day 5) treatment protocol, optimal psoriasis was achieved in four weeks, supported by a PASI of 1 and a DLQI of 3.

However, after eight weeks of follow-up, he complained of relapse marked by a PASI of 6 and the sudden onset of a severe bitter taste in his mouth, which occurred at the same time as a loss of appetite and a 2 kg weight loss. He had no previous history of taste dysfunction, occupational exposure to substances causing taste dysfunction, or any drugs traditionally associated with dysgeusia, and so an extensive oral and dental evaluation was made in order to rule out local causes. The main structures of the oral cavity (soft tissues, periodontal bone and teeth) were clinically assessed, and magnetic resonance imaging was used to exclude any cranial nerve or structural brain disease.

As the bitter taste appeared acutely and persisted in the absence of any food or drink, a diagnosis of phantogeusia was made, apremilast was stopped, and topical therapy with calcipotriol monohydrate/betamethasone dipropionate was added for three weeks. As the bitter taste resolved after the discontinuation of apremilast and re-appeared when the drug was re-administered, the Naranjo algorithm was used to assess whether it was an adverse drug reaction.

Although apremilast has never been associated with taste dysfunction, drug-related changes in taste are frequent and often underestimated in clinical trials (Garcia-Doval, 2012). Many drugs can affect a patient’s taste, especially those that modify ion channels or cyclic nucleosides such as cGMP, cAMP and inositol phosphate (Naik, 2010). As an inhibitor of PDE-4, apremilast

increases cAMP levels, and high intracellular levels of cAMP in type II taste cells of the tongue, prevents depolarisation and, consequently, message delivery (see Figure 1). A bitter taste may be a result of the hyperactivation of bitter taste receptors such as T2R or the decreased activation of sweet taste receptors such as T1R2/T1R3, and analysis of the regulatory dynamics of cAMP-related signalling suggests that apremilast acted on our patient's T1R2/T1R3 receptors. The medical implications of this may be detrimental in the case of a diabetic patient ingesting excess sugar in order to suppress the bitter taste caused by medication, but taste perception is also involved in the neuronal pathways modulating the digestion, absorption, and storage of nutrients (Naik, 2010), and a dysfunction in taste perception can decrease a patient's quality of life by altering appetite, body weight, and psychological health (DuBois, 2016) or also be an accompanying symptom of burning mouth syndrome (Kolkka-Palomaa, 2015).

In conclusion, it would be worth investigating this side effect further as it may greatly affect the compliance of patients being treated for chronic diseases such as psoriasis.

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Figure legend :

Physiologically, a sweet taste ligand stimulates the G protein-coupled receptor (GPCR) which, via trimeric G proteins, activates phospholipase C isoform b2 (PLCb2) and phosphodiesterase (PDE)-4. In particular, Gα activates PDE-4, which opens cyclic-AMP (cAMP) and, by decreasing cAMP levels, inhibits protein kinase A (PKA). PLCb2, which is activated by G$\beta\gamma$, catalyses the hydrolysis of phosphatidyl inositol 4,5 biphosphate to the second messenger inositol 1,4,5-triphosphate (IP3), which determines the release of Ca2+ from the endoplasmic reticulum via the inositol 1,4,5-trisphosphate receptor (IP3R) channel and consequently allows cell depolarisation and message delivery.

By inhibiting PDE-4, apremilast (in red) increases intracellular cAMP levels and activates PKA which, by phosphorylating IP3R, prevents the release of

Ca2+, gustatory cell depolarisation, and the delivery of the sweet taste message.