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Clinical healing of erosive oral lichen planus with tildrakizumab implicates the interleukin-23/interleukin-17 pathway in the pathogenesis of lichen planus

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TITLE: Clinical healing of erosive oral lichen planus with tildrakizumab implicates the interleukin-23/interleukin-17 pathway in the pathogenesis of lichen planus

Running Title: Tildrakizumab in oral lichen planus

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CONFLICT OF INTEREST: Professor Rodney Sinclair was a Principal Investigator in Sun Pharma Global FZE Phase 3 Clinical Trial evaluating the efficacy and safety of tildrakizumab in moderate-to-severe Chronic Plaque Psoriasis.

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MANUSCRIPT:

We report on a 59-year-old lady with a nine-month history of biopsy-proven, severe erosive oral lichen planus (OLP) that was refractory to multiple treatments, who experienced significant clinical improvement after three doses of the anti-interleukin-23 (IL-23) monoclonal antibody tildrakizumab. The patient had a history of well-controlled Type 2 diabetes mellitus. She was not on any oral hypoglycaemic agents or antihypertensive medications.

Examination of the oral cavity revealed active disease with reticular striations and severe erosions of the gums, palate and buccal mucosa (Figure 1). The lesions were bilateral and symmetric. Clinically the lesions were consistent with the Modified WHO criteria and the American Academy of Oral and Maxillofacial Pathology criteria for the diagnosis of lichen planus (LP)[1,2]. There was no evidence of LP on examination of the skin, genitals, scalp or nails. Histology of an active lesion in the buccal mucosa revealed acanthosis and a band of lichenoid inflammation, with linear basement membrane staining for fibrinogen evident on immunofluorescence.

At first presentation, treatment was commenced with isotretinoin 20mg weekly, cyclosporine 50mg twice daily, topical nystatin and topical clobetasol dipropionate 0.05% in an orabase

vehicle. After 6 weeks, there was minimal improvement and the dose of isotretinoin was increased to 5mg daily and cyclosporine to 100mg twice daily. Two months later there was no further symptomatic improvement and she had ongoing active disease with erosions of the gums, palate and buccal mucosa. She was unable to tolerate whole food, and was required to puree all food to enable her to swallow.

Screening investigations, including viral hepatitis serology and QuantiFERON-TB Gold, were negative. Following Therapeutic Goods Administration (TGA) special-access scheme approval for off-label use, tildrakizumab 100mg was injected subcutaneously at week 0 and at week 4. The patient was reviewed at week 16 and at this point had experienced some symptomatic improvement. Isotretinoin and cyclosporine were ceased at week 16 and the third dose of tildrakizumab was administered. The patient was reviewed again at week 24 and her OLP had significantly improved. She was able to eat whole food again and could tolerate everything apart from very spicy curry. Examination revealed complete healing of her erosions, with residual fine reticular striations (Figure 2). There were no adverse effects. Figure 3 illustrates the time course of clinical events and treatments.

OLP is a chronic T-cell mediated inflammatory disease that affects mucous membranes of the buccal mucosa, palate, gums and tongue[3]. Cytotoxic CD8+ T cells trigger apoptosis of keratinocytes in the oral epithelium. The exact pathogenesis is not fully elucidated[3]. OLP affects 1-2% of the population and occurs more frequently in women[3]. OLP is considered a pre-malignant inflammatory dermatosis. A subset of patients with OLP will develop oral squamous cell carcinoma[4]. Malignant transformation is most common in patients with the erosive subtype of OLP[4]. The risk of malignant transformation in this group has been reported as 1.7%[4].

Treatment options for OLP include topical and intralesional corticosteroids and topical calcineurin inhibitors[5]. Severe or persistent disease can be managed with isotretinoin, systemic corticosteroids or other systemic immunosuppressive medications. There are no randomized controlled trials or expert consensus guidelines to guide treatment of OLP.

There is limited literature surrounding the use of biologic therapies for LP. Successful treatment of oral and cutaneous LP with adalimumab has previously been reported[6].

Secukinumab and the infliximab biosimilar CT-P13 have been reported to induce LP in patients who are being treated with biologic therapies for psoriasis[7,8].

Tildrakizumab is a fully humanized monoclonal antibody that inhibits the p19 subunit of IL-23 and is approved by the TGA, Food and Drug Administration (FDA) and European Medicines Agency (EMA) for use in patients with moderate to severe psoriasis[9]. The IL-23/IL-17 axis plays a key role in the pathogenesis of many chronic inflammatory diseases and overexpression of IL-23 and IL-17 in OLP lesions compared to normal oral mucosal tissue using polymerase chain reaction (PCR) has been described[10]. The profound clinical response seen in this patient further implicates the IL-23/IL-17 pathway in the pathogenesis of OLP and suggests that tildrakizumab may be a potential treatment option for OLP, although larger studies are needed to support these findings.

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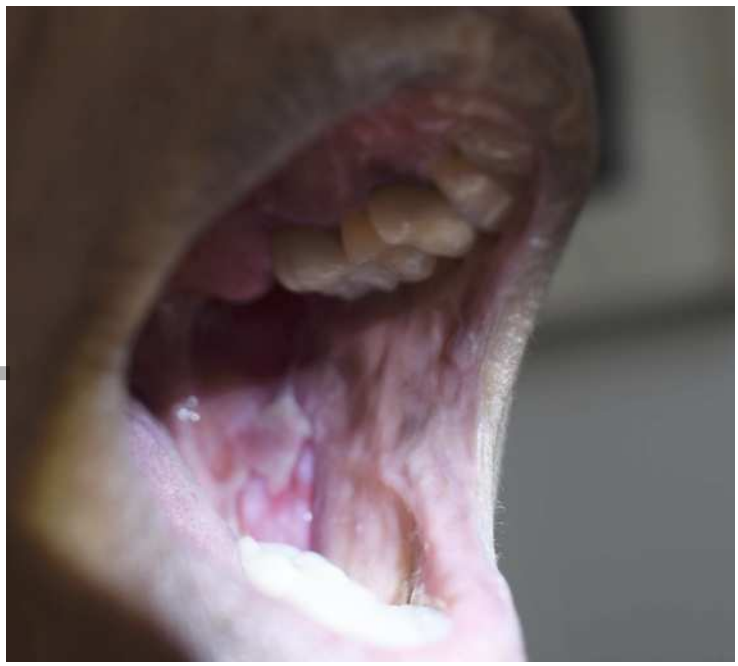
FIGURE LEGENDS

Figure 1: Reticular striations and severe erosions of the buccal mucosa prior to treatment with tildrakizumab

Figure 2: After three doses of tildrakizumab, erosions and erythema had resolved although faint reticular striations were still evident

Figure 3: Timeline depicting clinical events and treatments in this case



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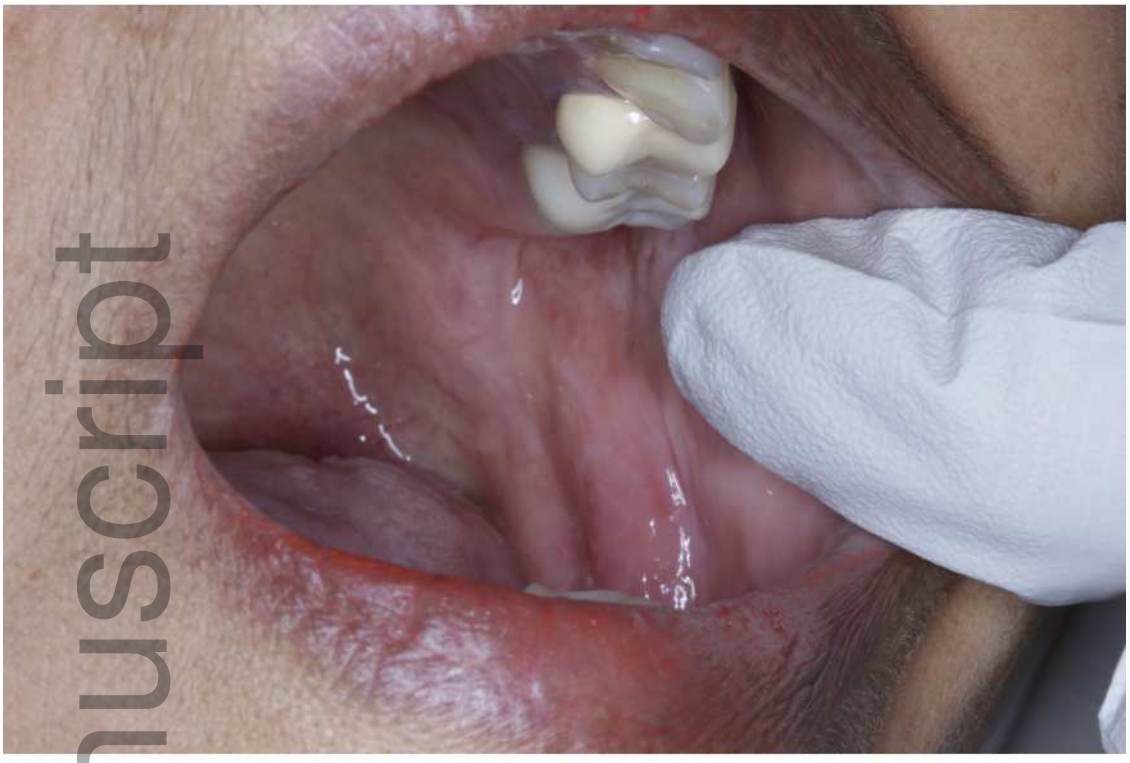

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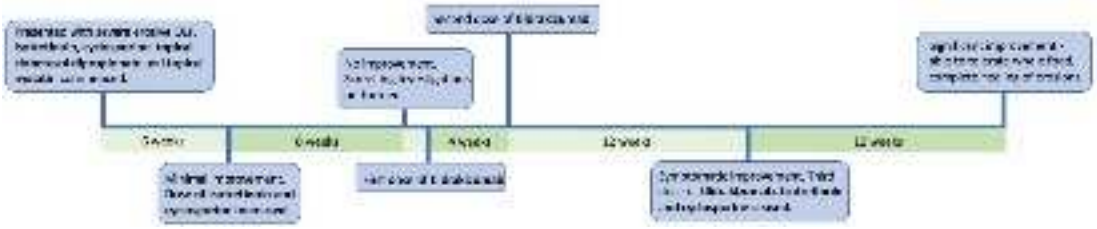

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