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PLENARY ABSTRACT

Biological response modifiers in inflammatory oral mucosal disease

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Introduction

Biological response modifiers are immunomodulatory agents which inhibit molecular pathways involved in the inflammatory process, targeting various stages of T and B cell activation and function, or block proinflammatory cytokines, including tumour necrosis factor-alpha (TNF-α), which promote increased leukocyte recruitment to sites of mucosal inflammation. These processes are central to the pathogenesis of aphthous ulceration, oral lichen planus (OLP), and vesiculo-bullous disorders such as pemphigus vulgaris (PV) and mucous membrane pemphigoid (MMP). As such, inhibition of these processes would seem an obvious therapeutic strategy.

Immunomodulatory agents used in oral mucosal disease may be categorised as those having general activity in inhibiting proinflammatory cytokine activity (including TNF-α) and others with a more specific action, often referred to as 'biologics'. The former include thalidomide, pentoxifylline, and calcineurin inhibitors such as ciclosporin; these have been available and used for many years with varied reports of efficacy, and merit discussion. More recently, biologics with a more focused mode of action have been developed, many of which are monoclonal antibodies (Smith *et al*., 2009). These include infliximab, etanercept, adalimumab, rituximab, and alefacept. Their success in clinical practice where a substantial evidence base exists has led to an increasing number of reports of efficacy in oral mucosal disease now published (O'Neill, 2008, 2010). This overview highlights the present status of biological response modifiers in oral disease, with some commentary on general guidance on such use, and mention of any future additional agents and conditions which may be trialed.

TNF-α inhibitors

These agents may be considered as those having anti-TNF- α activity as part of a more general immunomodulatory activity (thalidomide and pentoxifylline), and more specific agents which target TNF- α directly (infliximab, etanercept and adalimumab).

Thalidomide

Use of thalidomide is now an established, although cautionary therapy in a variety of immunologically driven disease including oral mucosal disease (Wu *et al*, 2005). Indeed of all agents discussed here, the greatest body of published data exists for thalidomide, with many randomised controlled trials (RCTs), uncontrolled studies, and case-series reporting its efficacy; in particular for aphthous ulceration including that seen in HIV infection, Behçet's disease (BD) and recurrent aphthous stomatitis (RAS) (Wu *et al*., 2005; Bruce and Rogers, 2007; Hello *et al*., 2010). Use is also reported for severe treatment-resistant disease OLP and MMP (Bruce and Rogers, 2007). For these, less data is available, although substantial improvement in OLP with thalidomide has been reported in a case-series with long-term follow-up (Torti *et al*., 2007). Nevertheless, the well recognised teratogenicity restricts its use and other adverse effects, notably peripheral neuropathy, can lead to discontinuation in a significant minority of patients (Wu *et al*., 2005; Hello *et al*, 2010). In addition, not all patients may respond. As such, although effective in inducing aphthous ulcer resolution (but not ulcer recurrence), thalidomide is advocated only where all other treatment options have failed, and where patients are considered suitable to receive thalidomide.

Pentoxifylline

Pentoxifylline has similar effects on TNF- α as thalidomide, but with little immunosuppressive activity and has a far less adverse-effect profile, along with fewer prescribing restrictions when used as systemic therapy (Bruce and Rogers, 2007). Use in RAS has been the subject of small uncontrolled studies and one RCT in which only 11 patients completed treatment (Thornhill *et al*., 2007). Across all studies, the limited (and conflicting) data suggests that, in RAS, pentoxifylline may be beneficial in inducing ulcer resolution and remission, but such benefits are of borderline significance at best and of short-term duration (Thornhill *et al*., 2007; Bruce and Rogers, 2007). The single RCT which investigated its use in OLP found no benefit (Wongwatana *et al*., 2005).

Infliximab

Infliximab has been used in the management of aphthous stomatitis presenting as part of BD and also in various oral manifestations of Crohn's disease (CD). In BD, where oral (and genital ulceration) is the major disease component, reports describe the adjunctive use of infliximab to induce resolution mucosal aphthosis in patients where conventional systemic therapies had failed; with a total of 4 patients reported. In CD reports exist of rapid response to infliximab in aphthous ulceration (4 patients), and in cases of primary orofacial CD, pyostomatitis vegetans, and overt fistulising disease (O'Neill, 2008, 2010).

Etanercept

Etanercept has some efficacy in treating aphthous ulcers, including those associated with BD, and in MMP (O'Neill, 2008, 2010). One RCT involving 40 patients with predominantly mucocutaneous BD compared etanercept vs. placebo over 4 weeks. Although etanercept had little effect upon genital ulceration, a significant rapid improvement in oral ulceration was noted in 8 patients (40%), with complete remission of oral ulcers after 4 weeks. Similar effects have also been reported as individual case reports for 5 patients. Response is also reported for RAS (one patient), and in 4 patients with MMP (O'Neill, 2008, 2010).

Adalimumab

Reports of the use of adalimumab are limited. Two reports describe its use in the treatment of 2 patients with RAS unresponsive to a variety of agents, where rapid improvements with complete remission were reported (O'Neill, 2008, 2010).

The evidence base for TNF-α antagonists as a group in treating oral disease remains weak, with only one RCT (for which only short-term data is available). Follow-up data is reported in individual case reports or as part of a small case-series, involving a total of 23 patients (O'Neill, 2008, 2010). In many of these, their use resulted in disease resolution and often reduced recurrence of further disease flares. Furthermore, prior to TNF- α blockade, many patients were refractory to, or intolerant of conventional systemic immunosuppressive therapy, resulting in significant morbidity and reduced quality of life. It should be noted that most cases involve aphthous ulceration either in RAS or as a component of BD, or CD. In RAS, of those patients previously refractory or intolerant to a range of therapies (including thalidomide and ciclosporin), all responded to a TNF-antagonist. In these, a TNF-α blocker was often the sole therapy, while in others a clinically significant reduction in concomitant immunosuppressant dosage was achieved. Most responses observed were rapid within 4 weeks and often sooner, although delayed responses and the need to switch to an alternative TNF- α antagonist are also reported (O'Neill, 2008, 2010).

Although TNF-α antagonists as a class are generally considered safe, adverse effects and toxicities are well recognized. The existence and strength of an association between use of biologics and increased risk of malignancy remains uncertain, with the current data and its interpretation with respect to psoriasis recently reported (Smith *et al.*, 2009). In this context, reports of the development of significant oral mucosal pathology exist, following use of TNF-α antagonists rheumatoid arthritis. These include the development of severe oral epithelial dysplasia observed whilst receiving adalimumab, and more recently the development of oral squamous carcinoma in a patient receiving etanercept. Although no direct causal relationship was shown, these cases highlight the importance of careful assessment and follow-up of all patients receiving biologics, as emphasised in current guidelines (Smith *et al*., 2009). Given the recognised association between OLP and oral squamous carcinoma (Lodi *et al*., 2005), particular caution should be considered regarding the use of TNF-α blockers in OLP.

Other agents

Other biological agents may act directly on and modulate B and T lymphocyte function. These include the rituximab and alefacept. Calcineurin inhibitors are macrolide-class immunomodulators derived from fungi/yeasts and include ciclosporin, tacrolimus and pimecrolimus. By binding cytoplasmic proteins to Inhibition of calcineurin activation, they inhibit its downstream effect in promoting cytokine release (including IL-2, interferon -γ and TNF-α) by T cells.

Rituximab

Rituximab is a well-recognised, if unlicensed, treatment for auto-immune blistering mucocutaneous disease. A number of case-series describing its use in treatment-refractory oral disease have been reported, involving a total of 7 patients, where efficacy has allowed dose reduction of co-existing immunosuppressive therapy (Schmidt *et al*., 2007, O'Neill, 2010). It should be noted that significant adverse effects are reported in clinical use in mucosal disease so particular caution is recommended (Schmidt *et al*., 2007).

Alefacept

While chiefly used in the US for the treatment of psoriasis, some reports exist for alefacept in the treatment of OLP (O'Neill, 2008, 2010). These include 4 patients with oral and cutaneous or vulval LP where treatment led to significant improvement (as

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measured by improved disease and mucosal pain scores). However little follow-up data is available.

Calcineurin inhibitors

Of available agents, only ciclosporin has been used as systemic therapy either as an intermittent agent, in lower doses as combination therapy, or in rotational or sequential regimens, typically in patients with severe aphthous ulceration. Longer term use is limited by treatment related nephrotoxicity and increased risk of malignancy, with treatment discontinuation common. Less toxicity is associated with topical use although the data for this is limited (Al Johani *et al*., 2009). Greater efficacy is reported for topical tacrolimus and pimecrolimus, as recently reviewed by Al Johani *et al*. (2009). Used topically, systemic adverse effects are reduced, although prescribing caution remains (Bruce and Rogers, 2007). A variety of oral mucosal disease may respond, including OLP, PV, and BMMP. In particular, tacrolimus is effective in treating OLP unresponsive to topical corticosteroids so reducing the need for systemic therapy (Al Johani *et al*., 2009). However, although effective in inducing disease resolution, treatment discontinuation often results in recurrence of active disease, with maintenance therapy often required (Bruce and Rogers, 2007).

Creating an evidence base, other potential agents and ongoing clinical trials

Of the agents discussed, the strongest evidence base is for thalidomide, having been validated in RCTs for inducing ulcer resolution in patients with HIV infection and BD (Wu *et al*., 2005), and also in longer-term follow-up studies in RAS (Hello *et al*., 2010). The evidence for other agents and mucosal conditions is less compelling, being the subject of small and often contradictory RCT efficacy outcomes (Thornhill *et al*., 2007; Wongwatana *et al*., 2005; Bruce and Rogers, 2007), retrospective case series or individual case reports (O'Neill, 2008, 2010). The paucity of RCTs for systemic agents in oral mucosal disease such as RAS and OLP is well recognised, as is the small number of patients recruited (Lodi *et al*., 2005; Bruce and Rogers, 2007), which in part may reflect the number of patients failing to respond to more conservative (often topical) therapies. Few ongoing studies exist. Of those currently on US National Institutes of Health clinical trials register (http://clinicaltrials.gov), etanercept is the subject of two separate RCTs in lichen planus including OLP, while another study (albeit with a prolonged recruitment phase) is investigating its role in reducing chemotherapy-related mucositis in patients undergoing haematopoietic stem-cell transplantation. These may provide greater support for TNF-α antagonists. It is also likely that further cases of TNF-α blockers may be reported, and, that more recently developed agents e.g. ustekinumab, which targets interleukins-12 and -23 and is already being used for conditions e.g. psoriasis may also be used. Although to date, no reports of TNF-α antagonists use in HIV-associated aphthosis exist, limited experience in other conditions suggests that these are safe when used cautiously in HIV infection (Domm *et al*., 2008). These may have a potential role in such patients with severe disease who merit but are refractory or intolerant to thalidomide.

Rationale for use of systemic immunomodulatory agents

For most oral mucosal disease, including RAS and OLP, many patients respond to first-line treatments such as topical corticosteroids, and only patients with severe or resistant disease would merit alternative systemic agents. In clinical practice treatment strategies usually involve use of available therapies in a step-wise approach (Bruce and Rogers, 2007; Lodi *et al*., 2005; Torti *et al*., 2007). As such, of the agents discussed here, perhaps topical calineurin inhibitors would be used as a second-line therapy, if topical corticosteroids were ineffective (Bruce and Rogers, 2007). Use of pentoxifylline could be considered in patients with RAS resistant to such therapies, but may not be beneficial in OLP (Thornhill *et al*., 2007; Bruce and Rogers, 2007, Wongwatana *et al*., 2005). It is perhaps more difficult to position the systemic TNF-α inhibitors (thalidomide, ciclosporin, and specific antagonists) and other biologics within such a ''therapeutic ladder''. Both thalidomide and ciclosporin have some established efficacy but adverse effects and prescribing restrictions are such that use is only available in select patients, and not all patients may respond (O'Neill, 2008, 2010); use would seem appropriate only after other systemic therapies (e.g. short course corticosteroids, methotrexate, dapsone, colchicine) have failed. This treatment-point would also seem to be appropriate for consideration of specific biologic therapy as an alternative, although cost and limited evidence remains a deterrent. Of course the great majority of patients with inflammatory oral mucosal disease would not require such therapy, which in part explains the lack of available evidence. However, as reported, such alternative therapies are required for a small subset of patients (O'Neill, 2008; Hello *et al*, 2010). If considered, what is essential is that use is in agreement with best available guidance, preferably in consultation with clinicians experienced in their use (Wu *et al*., 2005; Smith *et al*., 2009; O'Neill, 2010).

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Conflicts of Interest

The author declares no conflict of interest.

References

Al Johani KA, Hegarty AM, Porter SR, Fedele S (2009). Calcineurin inhibitors in oral medicine. *J Am Acad Dermatol* **61:** 829–840.

Bruce A, Rogers RS III (2007). New and old therapeutics for oral ulcerations. *Arch Dermatol* **143:** 519–523.

Domm S, Cinatl J, Mrowietz U (2008). The impact of treatment with tumour necrosis factor-alpha antagonists on the course of chronic viral infections: a review of the literature. *Br J Dermatol* **159:** 1217–1228.

Hello M, Barbarot S, Bastuji-Garin S, Revuz J, Chosidow O (2010). Use of thalidomide for severe recurrent aphthous stomatitis: a multicenter cohort analysis. *Medicine (Baltimore)* **89:** 176–182.

Lodi G, Scully C, Carrozzo M, Griffiths M, Sugerman PB, Thongprasom K (2005). Current controversies in oral lichen planus: report of an international consensus meeting. Part 2. Clinical management and malignant transformation. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **100:** 164–78.

O'Neill ID (2008). Off-label use of biologicals in the management of inflammatory oral mucosal disease. *J Oral Pathol Med* **37:** 575–581.

O'Neill I (2010). Guidance on the use of biological agents in the treatment of oral mucosal disease. *Br J Dermatol* **162:** 1410–1411.

Schmidt E, Seitz CS, Benoit S, Bröcker EB, Goebeler M (2007). Rituximab in autoimmune bullous diseases: mixed responses and adverse effects. *Br J Dermatol* **156:** 352–356.

Smith CH, Anstey AV, Barker JN, Burden AD, Chalmers RJ, Chandler DA, Finlay AY, Griffiths CE, Jackson K, McHugh NJ, McKenna KE, Reynolds NJ, Ormerod AD, Chair of Guideline Group. (2009). British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. *Br J Dermatol* **161:** 987–1019.

Thornhill MH, Baccaglini L, Theaker E, Pemberton MN (2007). A randomized, doubleblind, placebo-controlled trial of pentoxifylline for the treatment of recurrent aphthous stomatitis. *Arch Dermatol* **143:** 463–470.

Torti DC, Jorizzo JL, McCarty MA (2007). Oral lichen planus: a case series with emphasis on therapy. *Arch Dermatol* **143:** 511–515.

Wongwatana S, Leao JC, Scully C, Porter S (2005). Oxpentifylline is not effective for symptomatic oral lichen planus. *J Oral Pathol Med* **34:** 106–108.

Wu JJ, Huang DB, Pang KR, Hsu S, Tyring SK (2005). Thalidomide: dermatological indications, mechanisms of action and side-effects. *Br J Dermatol* **153:** 254–273.