Calcineurin inhibitors in oral medicine

Khalid A. Al Johani, BDS, MSc,[a] Anne M. Hegarty, MSc, MFD RCSI, MBBS,[b] Stephen R. Porter, PhD, MD, FDSRCS, FDSRCSE,[a] and Stefano Fedele, DDS, PhD[a]
London, United Kingdom

Topically applied calcineurin inhibitors have been suggested to be of some benefit in the treatment of immunologically mediated oral mucosal disorders, particularly oral lichen planus. This article reviews the current evidence of the efficacy and safety of topical calcineurin inhibitor agents in the management of different oral conditions. Current evidence suggests that topical tacrolimus and pimecrolimus may be of benefit (at least in the short term) in the treatment of immunologically mediated oral mucosal disease, especially oral lichen planus that has not responded to topical corticosteroids. Both tacrolimus and pimecrolimus are minimally absorbed through the oral mucosa and give rise to few clinically significant local or systemic adverse side effects. There is little evidence to indicate that topical cyclosporine is more effective than topical corticosteroids for the treatment of immunologically mediated oral mucosal disease. Currently, there is no objective evidence suggesting that topical tacrolimus or pimecrolimus increase the risk of oral malignancy associated with oral lichen planus. There is a need for well-designed randomized controlled trials to establish the precise efficacy of topical calcineurin inhibitors for the treatment of immunologically mediated oral mucosal disease. (J Am Acad Dermatol 2009;61:829-40.)

Key words: calcineurin inhibitors; cyclosporine; mucous membrane pemphigoid; oral cancer; oral lichen planus; orofacial granulomatosis; pemphigus vulgaris; pimecrolimus; tacrolimus.

Calcineurin inhibitors are microbially derived immunosuppressive that have been primarily used in transplant medicine and in the treatment of immune-mediated diseases. The principle agents are tacrolimus, pimecrolimus, and cyclosporine. Calcineurin inhibitors bind to different cytoplasmic proteins of T lymphocytes (cyclosporine to cyclophilin; tacrolimus and pimecrolimus to FK506-binding protein) to form complexes that in turn inhibit calcineurin leading to suppression of transcription and production of many cytokines. Calcineurin inhibitors have been suggested to be of clinical benefit in the management of some immunologically mediated oral mucosal disorders. However, there is much debate about their long-term efficacy and safety and their advantage with respect to conventional therapies. The current article reviews current knowledge regarding the management of oral mucosal diseases with this group of agents. The aim is to help clinicians to decide when to use calcineurin inhibitors, which agent is most appropriate, and how to balance risk and benefit.

Abbreviations used:

AD:	atopic dermatitis
FDA:	Food and Drug Administration
GvHD:	graft-versus-host disease
IL:	interleukin
MMP:	mucous membrane pemphigoid
OFG:	orofacial granulomatosis
OLP:	oral lichen planus
SCC:	squamous cell carcinoma

METHODS

MEDLINE (1966-December 2008), EMBASE (1980-December 2008), and the *Cochrane Database of Systematic Reviews* were searched using different combinations of the following key terms: "calcineurin inhibitors," "tacrolimus," "pimecrolimus," "cyclosporine," "ciclosporin," "oral medicine," "oral mucosal diseases," "oral lichen planus" (OLP), "graft-versus-host disease" (GvHD), "mucous membrane pemphigoid" (MMP), "pemphigus vulgaris," "paraneoplastic pemphigus," "orofacial granulomatosis" (OFG), and

From Oral Medicine, University College London (UCL) Eastman Dental Institute,[a] and Eastman Dental Hospital University, College London Hospital Trust (UCLHT).[b]

This work was undertaken at UCL/UCLHT, which received a proportion of funding from the Department of Health's National Institute for Health Research Biomedical Research Center funding scheme. Dr. Al-Johani received sponsorship from the King Abdulaziz University, Saudi Arabia.

Conflicts of interest: None declared.

Reprint requests: Khalid A. Al-Johani, BDS, MSc, Oral Medicine, UCL Eastman Dental Institute, 256 Gray's Inn Rd, London WC1X 8LD United Kingdom. E-mail: K.aljohani@eastman.ucl.ac.uk.

0190-9622/$36.00

© 2009 by the American Academy of Dermatology, Inc.

doi:10.1016/j.jaad.2009.03.012

"oral Crohn disease." The abstracts of the articles were retrieved to exclude irrelevant studies and the references hand searched for relevant articles that had not appeared in the main search. A few non-English-language abstracts were included so as to include all the relevant articles reporting adverse side effects of calcineurin inhibitors in the management of oral diseases. Moreover, US Food and Drug Administration (FDA) reports on potential carcinogenic effects of topical tacrolimus and pimecrolimus were included.

CAPSULE SUMMARY:

- Topical application of calcineurin inhibitors, in particular tacrolimus, may be of some clinical benefit with no major adverse effects in the management of immunologically mediated oral mucosal diseases.
- Topical tacrolimus and pimecrolimus can be as effective as topical corticosteroids, and can be used as a second-line therapy, in patients who do not respond to topical corticosteroids.
- There is little evidence to support the use of topical cyclosporine in the management of oral mucosal diseases.
- There is no objective evidence supporting an increased risk of oral malignancy in association with the use of topical tacrolimus or pimecrolimus.

Mechanism of action of the calcineurin inhibitors

In the normal immune response, antigens presented by the major histocompatibility complex to the T-cell receptor cause an elevation of intracytoplasmic calcium that binds to calmodulin, leading to the activation of calcineurin. The free calcium also leads to synthesis of the nuclear factor of activated T cells. Calcineurin (a protein phosphatase) dephosphorylates the cytoplasmic subunit of nuclear factor of activated T cells that eventually binds to the nuclear subunit.[1] This cytoplasmic—nuclear subunit of nuclear factor of activated T cells complex facilitates transcription of many cytokines including interleukin (IL)-2, IL-3, IL-4, tumor necrosis factor-α, interferon-γ, transforming growth factor-β, and granulocyte-macrophage colony-stimulatory factor. Calcineurin inhibitors interfere with this pathway by inhibiting cytosolic calcineurin function hence resulting in suppression of the generation of proinflammatory cytokines.[1-4] Tacrolimus (FK506) and pimecrolimus bind to intracellular FK506-binding protein whereas cyclosporine binds to cytosolic cyclophillin.[5] These intracellular complexes eventually bind to calcineurin, inhibiting its phosphatase activity. Tacrolimus also inhibits histamine release and the de novo synthesis of prostaglandin D2 from mast cells activated by IgE,[6] whereas pimecrolimus can inhibit mast cell cytokine, serotonin, and beta-hexosaminidase release.[2,4]

Tacrolimus

Tacrolimus is a macrolide immunosuppressant derived from *Streptomyces tsukubaensis*. It is a relatively selective inhibitor of calcineurin and was initially developed as a systemic agent to lessen allograft rejection. Formulated for topical application in the management of atopic dermatitis (AD), it was approved in 2000 by the US FDA to be used in moderate to severe AD for patients older than 2 years. Topical tacrolimus has proven to be of benefit in the treatment of other disorders including cutaneous psoriasis, contact allergy, corticosteroid-induced rosacea, pyoderma gangrenosum, alopecia areata, mucocutaneous lichen planus, and GvHD.[1,7-11] Topical tacrolimus is available in different concentrations (0.03%, 0.1%). Systemic tacrolimus is substantially less expensive and 10 to 100 times more potent than cyclosporine,[12,13] even though relative potency of topical preparations has never been evaluated.

With regard to the management of oral mucosal diseases, topical tacrolimus has been reported to be effective in the treatment of symptomatic OLP[13-22] and desquamative gingivitis.[23] Topical tacrolimus has also been reported to be effective in the management of oral mucosal lesions of GvHD,[24-26] MMP,[27-29] pemphigus vulgaris of the lip,[30] and the oral ulceration and labial enlargement of OFG and oral Crohn disease.[31,32]

Oral lichen planus. T-cell activation is central to the pathogenesis of lichen planus (OLP),[33] hence logically a blockage of calcineurin function might be expected to lessen the severity of such disease. There are now numerous reports of the efficacy of tacrolimus in the management of OLP. Effectiveness has been assessed via open-label prospective studies,[13,16,22] randomized trials,[34,35] retrospective studies,[19,36] case series,[17,18] and described in several case reports.[15,20,21] (Table I). Initial studies focused on patients with symptomatic OLP that had not responded to topical corticosteroids or who were at risk of adverse side effects from corticosteroids. Rozycki et al[18] reported retrospectively 13 patients with OLP who had received topical tacrolimus for a mean duration of 6.5 months. Eleven patients had either complete resolution or partial improvement of painful oral mucosal lesions within 4 weeks from the start of the treatment although two patients showed no response. Both 0.1% and 0.3% concentrations of tacrolimus were able to induce complete healing of

Download English Version:

https://daneshyari.com/en/article/3209059

Download Persian Version:

https://daneshyari.com/article/3209059

Daneshyari.com