Published in final edited form as:

Oral Surg Oral Med Oral Pathol Oral Radiol. 2013 April ; 115(4): e26–e30. doi:10.1016/j.oooo.2012.07.487.

Topical Tacrolimus with Custom Trays in the Treatment of Severe Oral cGVHD Refractory to a Potent Topical Steroid Therapy: A Case Report

Ronald S. Brown, DDS, MS^a, Dean Edwards, DDS^b, Tracey Walsh-Chocolaad, PharmD^c, and Richard W. Childs, MD^d

^aProfessor, Department of Oral Diagnostic Services, Howard University College of Dentistry, Clinical Associate Professor, Department of Otolaryngology, Georgetown University Medical Center, Washington, DC, Volunteer, NHLBI/NIH, Hematology Branch, Bethesda, MD

^bClinical Staff Dentist, NIDCR/NIH, Bethesda, MD (formerly Dr. Dean Aria)

^cClinical Pharmacy Specialist, Hematology Branch, NHLBI/NIH, Bethesda, MD

^dTenured Senior Investigator, Deputy Clinical Director, Hematology Branch, NHLBI/NIH, Bethesda, MD

Abstract

Background—The authors present a case demonstrating the success of topical tacrolimus (TAC) therapy with custom trays in the treatment of oral chronic graft versus host disease (cGVHD). The 41 year-old male patient initially responded to topical steroid therapy (clobetasol propionate 0.05% ointment) applied both topically and with flexible carrier trays, but later became refractory to this potent topical agent. Topical TAC therapy with flexible carrier trays and systemic prednisone therapy was initiated.

Results—The patient responded favorably with the change to topical TAC therapy with custom trays (and oral prednisone). His oral cGVHD lesions resolved within a period of four weeks. The improvement has remained stable at 14 month follow-up.

Clinical Implications—This is the first case reported with regard to the successful resolution of steroid recalcitrant cGVHD successfully treated with topical TAC with custom trays.

Keywords

Tacrolimus; allogeneic bone marrow stem cell transplant; oral chronic graft versus host disease

Topical tacrolimus (TAC) has demonstrated success in the treatment of both oral chronic graft-versus-host disease (cGVHD) and immunologically mediated oral mucosal diseases such as oral lichen planus. Topical TAC has demonstrated success in situations where potent topical steroid medications were insufficient to control immune related vesiculoerosive oral mucosal disorders.¹⁻⁵ TAC is a lactone immunosuppressive calcineurin inhibitor drug that

© 2012 Mosby, Inc. All rights reserved.

Corresponding author: Dr. Ronald S. Brown, rbrown@howard.edu; 202-364-9400, fax 703-528-2496, Howard University College of Dentistry, 600 W Street, NW, Room 406, Washington, DC 20059.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

was first discovered in a soil fungus in 1984 (although produced by a type of bacterium *Streptomyces tsukubaensis*). Systemic TAC was first approved by the U.S. Food and Drug Administration (FDA) in 1994 for the prevention of graft rejection in allogeneic liver transplantation. Tacrolimus reduces interleukin-2 (IL-2) production by T-cells, and subsequent T-cell activation. It is believed to bind to an intracellular protein called FKBP-12, which further complexes with calcium, calmodulin, and calcineurin. The resulting complex inhibits the phosphatase activity of calcineurin, thereby inhibiting both T-lymphocyte signal transduction and IL-2 transcription resulting in immunosuppression equal to or superior to that of cyclosporine.⁶⁻⁹

cGVHD including oral cGVHD is a relatively common and serious complication following allogeneic hematopoietic cell transplantation (HSCT). cGVHD may involve a number of organs including the integumentary system, gastrointestinal tract, and liver. Oral cGVHD develops in thirty to seventy percent of patients surviving more than 100 days after transplantation. Oral findings include lichenoid changes, erythema, xerostomia, dysphagia, erosion, ulceration, and superficial mucocoeles often resulting in oral pain. Oral cGVHD is a vesiculoerosive condition of the oral mucosa that clinically and histopathologically resembles oral autoimmune disease such as oral lichen planus (OLP). Histopathologic changes of oral cGVHD are notable for dyskeratotic (apoptotic) keratinocytes with adjacent lymphocytic and subepithelial mononuclear infiltrates.¹⁰ With regard to cGVHD, alloreactive donor T-lymphocytes target epithelial cells leading to inflammation and apoptosis with subsequent tissue disease. Despite a variety of available prophylaxis regimens, and the utilization of immunosuppressive and immuno-modulatory therapies, cGVHD is currently the leading cause of non-relapse treatment-related mortality in patients surviving beyond two years after allogeneic HSCT.^{10,11} Approximately half of the affected patients have 3 or more involved organs, and treatment typically requires systemic immunosuppressive medications for approximately 2 to 3 years. cGVHD is associated with a reduced risk of leukemia or relapse of other blood element-related cancers (i.e., GVHD illustrates an antibody challenge by the engrafted immune system, which tends to demonstrate a change in chimerism that will positively result in a graft versus cancer effect). However, cGVHD remains a major cause of late death following HSCT. The morbidity and mortality associated with cGVHD is multifactorial and occurs as a consequence of organ dysfunction, by cGVHD-associated immunodeficiency (intrinsic to the disease process), and immune suppressive medications used to treat this condition.¹²

We present a case in which a patient with severe oral cGVHD unresponsive to clobetasol propionate, a potent topical steroid, responded favorably to topical TAC therapy.

CASE REPORT

After signing informed consent, a 41 year-old African-American patient with a diagnosis of myelodysplastic syndrome (MDS) underwent a reduced intensity allogeneic HSCT at the National Heart Lung Blood Institute of the National Institute of Health (NHLBI/NIH) on July 30, 2008, using peripheral blood stem cells mobilized from his HLA identical sibling following high dose filgrastim.

The patient presented with oral discomfort and inflammation, in June 2009, which was subsequently diagnosed as oral GVHD. His oral condition was successfully managed with topical dexamethasone rinse (0.5 mg/ 5 ml in a swish and spit twice daily regimen), and topical clobetasol propionate (0.05% ointment twice daily). During this period of time, the patient's therapeutic regimens also included cyclosporine (CSA, 150 mg, a. m. dose and 175 mg, p. m. dose), budesonide (3 mg twice daily), dexamethasone (0.5 mg/ 5 ml in a swish and spit twice daily regimen), clotrimazole (10 mg oral topical troches, twice a day),

valacyclovir (500 mg twice daily), sulfamethoxazole and trimethoprim (160 mg and 800 mg once daily), omeprazole (20 mg daily, amlodipine (10 mg daily), lisinopril (20 mg daily), Magnesium Oxide (800 mg twice daily), and Insulin R (12 units subcutaneously three times daily). During flares of cGVHD, prednisone was initiated at 20 mg daily for three days and tapered over the next four days down to 10 mg daily.

However, by the middle of August, he developed presumed cGVHD of the GI tract and his oral cGVHD recurred. He was subsequently instructed to increase the dexamethasone swish and spit oral solution to a four times daily and oral budesonide (3 mg twice daily) was added for the gastrointestinal (GI) tract cGVHD. In September of 2009, a gingival biopsy was performed which revealed only non-specific inflammation. His cGVHD of the GI tract gradually improved and the budesonide was decreased to once daily dosing by February of 2010. Due to persistent gingival inflammation, the oral mucosal biopsy was repeated, which revealed histopathological features consistent with a diagnosis of oral cGVHD. The CSA dose was increased to 200 mg twice daily. In October of 2010, CSA was decreased to 125 mg BID and budesonide (3 mg) was decreased to once daily.

The patient's oral cGVHD was associated with oral burning and intolerance to spicy foods. The facial marginal gingiva was noted for erythema consistent with cGVHD. A regimen of clobetasol propionate 0.05% ointment applied with the flexible custom trays was added to the treatment regimen. The patient's oral erythema and symptoms gradually resolved after three months.

By January of 2011, the patient's oral cGVHD severely deteriorated despite the continued use of topical clobetasol propionate with custom trays, and swish and spit dexamethasone solution (Fig. 1). The oral mucosal biopsy was repeated. The biopsy again revealed histopathological changes consistent with cGVHD including dyskeratotic keratinocytes, with adjacent lymphocyte and subepithelial mononuclear infiltrate and multi-nucleated giant cells (Fig. 2). The dental clinic fabricated new custom trays and clinicians prescribed topical 0.1% tacrolimus ointment for twice a day therapy at the beginning of February. The patient also used the dexamethasone rinse and spit regimen, along with oral prednisone (20 mg once daily) and continued CSA. The CSA dose was decreased to 150 mg twice daily due to higher serum levels than desired in mid-February. After four weeks of topical TAC application, the patient's symptoms were eliminated and the clinical appearance was within normal limits (Fig. 3). The patient (on his own) discontinued systemic prednisone in the beginning of March without a taper. The CSA dose was decreased to 125 mg twice daily and the budesonide was decreased to one daily 3 mg dose. The improved condition has remained stable at 14-month follow-up. During this time period, the patient has had some minor flares, which successfully responded to the topical TAC in custom trays regimen.

Discussion

Topical TAC has demonstrated success in the treatment of immune-mediated, oral vesiculoerosive mucosal conditions refractory to topical steroid therapy.¹³⁻¹⁵ Topical TAC tacrolimus and pimecrolimus have been successfully utilized in the treatment of oral cGVHD refractory to topical steroid therapy.^{3-5,15,16} Our patient had a dramatic improvement in his oral cGVHD following topical TAC (and oral prednisone) despite the failure of systemic CSA, clobetasol propionate, and dexamethasone elixir therapies to control mucosal disease. This observation suggests that the tissue levels of this calcineurin inhibitor when delivered directly to the gingiva were higher than those obtainable with oral systemic CSA, and that topical tacrolimus therapy was more potent compared to clobetasol propionate and dexamethasone elixir. Furthermore, a non-steroid immunosuppressive drug is preferable over high dose systemic steroids which are associated with problematic steroid

side-effects such as gastritis, diabetes, steroid-induced insomnia, fluid retention, opportunistic infection, psychosis, cataract formation and osteoporosis and topical TAC therapy possibly resulted in greater efficacy and decreased disease duration compared to oral prednisone alone and possibly allowed for a reduced dose and duration of systemic steroid therapy.

Albert et al.,³ reported that topical TAC therapy in children (five with chronic oral GVHD and one with acute GVHD) was very well tolerated and that none of the subjects in their study developed secondary infections often associated with steroid administration. Systemic absorption of topical TAC following application to mucosal membranes has been noted to be low in most patients, even when used in combination with certain azole antifungal medications that are strong inhibitors of cytochrome P450 3A4, the liver enzyme responsible for TAC biotransformation.^{2,5,11,17} It is important to keep in mind that the mouth has considerably less surface area compared to the skin. Therefore, the use of topical TAC for dermatologic immune-related lesions such as cGVHD of the skin might be associated with higher degrees of systemic absorption. Although, Siegfried et al.,¹⁸ reported high systemic absorption in a group of patients treated for Netherton syndrome, a pediatric dermatitis condition.

Nineteen cases of secondary malignancies have been reported with the use of topical TAC since its FDA approval in November 2004. These reports are through voluntary surveillance programs. The actual number of patients treated with tacrolimus is unknown, therefore, the true incidence of secondary malignancies associated with the drug cannot be determined from this data. However, 3.2 million prescriptions were written for topical TAC from January 2001 to August 2004, so the risk appears to be very low. Of the 19 reported cases of malignancy, nine were lymphoma, and ten were cutaneous tumors including seven at the site of topical application.¹⁹ Mattsson et al.,²⁰ reported a case of squamous cell carcinoma in a patient previously treated for OLP with topical TAC. Certainly, cutaneous and mucosal immune-related and autoimmune conditions such as lichen planus have been documented to undergo malignant transformation regardless of the use of immunosuppressive calcineurin inhibitor drugs. Therefore, the argument can be made that it is possible that the malignant transformation may have occurred without the medication. Remitz and Reitamo²¹ and Reitamo et al.,²² reported that topical TAC therapy is both safe and efficacious, with no increased risk of infections or cancer known to be associated with clinical studies with up to a four-year follow-up period. The FDA has approved topical TAC with a black box warning regarding oncogenic potential. There are rare cases of malignancies reported associated with TAC, but a direct causal association has not been established.¹⁹⁻²²

Elad et al.,¹ reported that topical TAC has been successful in the management of such immune-related disorders as oral lichenoid reactions, oral cGVHD, pemphigoid/pemphigus, Crohn's disease, desquamative gingivitis, and pyostomatitis vegetans. Mawardi et al.,¹¹ reported that combined oral dexamethasone (swish and spit) and topical TAC therapy resulted in improvement of objective and subjective outcomes in the majority of BMT patients with oral cGVHD. Most of the patients included in the study were treated with systemic immunosuppressants, and most regimens were stable or tapered during the study period, strongly suggesting a direct topical effect of the combined topical immunosuppressive agents. Mawardi et al.,¹¹ reported that their patients were likely to have more severe/refractory oral cGVHD compared with all the patients from their center who developed oral cGVHD during the study period. Mawardi et al.,¹¹ noted that previous reports³⁻⁵ related to the success of TAC in the treatment of oral cGVHD with commercially available ointments in contrast to a TAC rinse formulation used in their study which was designed for easier application. Because of the difficulty of application of an ointment onto oral mucosal surfaces, we decided to utilize a tray/carrier delivery system, a technique which

has a record of success with regard to ease of application and efficacy.^{11, 12} As topical steroid and immunosuppressive therapeutics are manufactured primarily for dermatologic therapies, these medications may be problematic for the treatment of oral lesions. Therefore, previous case reports regarding topical steroid refractory oral cGVHD and successful therapy with topical TAC are somewhat problematic. Oral medicine clinicians have devised specific techniques to enhance therapeutic efficacy such as compounding with orabase, and the utilization of elixirs, rinses, and tray carriers.^{11,12,23} In the case presented, the patient's oral cGVHD condition became unresponsive to tray therapy with topical clobetasol and then responded dramatically to tray therapy with topical TAC. To our knowledge, this is the first case to demonstrate such. Future topical drug efficacy studies will need to be designed to compare elixirs to one another, and topicals to one another utilizing similar therapeutic formats. The literature revealed only limited cases reports related to the treatment of topical steroid unresponsive oral GVHD which were successfully treated with topical TAC. Fricain et al.,⁴ and Eckhardt et al.,⁵ both reported three such cases and Rojas et al.,²⁴ reported one such case, and there are no reported cases that utilized flexible custom trays.

The medical management of patients undergoing allogeneic HSCT is complex and requires regular supervision. Our patient required close monitoring, and the need for frequent adjustments in the doses of several of his medications. While we acknowledge the patient was receiving other systemic as well as topical immunosuppressive therapies at the time of resolution of his oral cGVHD, his cGVHD symptoms flared despite those medications, leading us to conclude that the initiation of topical TAC accounted for the dramatic improvement in his oral cGVHD symptoms. However, we can not exclude the possibility that other immunosuppressive therapies played a role in his improvement.

In conclusion, we report a single case of topical steroid- and CSA-refractory oral cGVHD that responded dramatically to the addition of topical TAC with the assistance of fabricated applicator trays.

REFERENCES

1. Elad S, Epstein JB, Yarom N, et al. Topical immunomodulators for management of oral mucosal condition, a systematic review; part I: calcineurin inhibitors. *Expert Opin Emerg Drugs*. 2010; 15:713–26. [PubMed: 21091397]
2. Al Johani KA, Hegarty AM, Porter SR, Fedele S. Calcineurin inhibitors in oral medicine. *J Am Acad Dermatol*. 2009; 61:829–40. [PubMed: 19836643]
3. Albert MH, Becker B, Schuster FR, Klein V, Adam K, Nienhoff C, et al. Oral graft vs. host disease in children - treatment with topical tacrolimus ointment. *Pediatr Transplant*. 2007; 11:306–11. [PubMed: 17430488]
4. Eckardt A, Starke O, Stadler M, Reuter C, Hertenstein B. Severe oral chronic graft-versus host disease following allogeneic bone marrow transplantation: highly effective treatment with topical tacrolimus. *Oral Oncol*. 2004; 40:811–4. [PubMed: 15288836]
5. Fricain JC, Sibaud V, Swetyenga N, Tabrizi R, Campana F, Taieb A. Long-term efficacy of topical tacrolimus on oral lesions of chronic graft-versus-host disease. *Br J Dermatol*. 2007; 156:588–90. [PubMed: 17300261]
6. Taylor AL, Watson CJ, Bradley JA. Immunosuppressive agents in solid organ transplantation: Mechanisms of action and therapeutic efficacy. *Crit Rev Oncol Hematol*. 2005; 56:23–46. [PubMed: 16039869]
7. Pritchard D. Sourcing a chemical succession for cyclosporin from parasites and human pathogens. *Drug Discov Today*. 2005; 10:688–91. [PubMed: 15896681]
8. Henenway CS, Heitman J. Calcineurin, Structure, function, and inhibition. *Cell Biochem Biophys*. 1999; 30:115–51. [PubMed: 10099825]

9. Liu J, Farmer J, Lane W, Friedman J, Weissman I, Schreiber S. Calcineurin is a common target of cyclophilin-cyclosporin A and FKBP-FK506 complexes. *Cell*. 1991; 66:807–15. [PubMed: 1715244]
10. Immanguli MM, Alevizos I, Brown R, Pavletic SZ, Atkinson JC. Oral graft-versus-host disease. *Oral Diseases*. 2008; 14:396–412. [PubMed: 18593456]
11. Mawardi H, Stevenson K, Gokani B, Soiffer R, Treister N. Combined topical dexamethasone/tacrolimus therapy for management of oral chronic GVHD. *Bone Marrow Transpl*. 2010; 45:1062–7.
12. Gonzalez-Moles MA, Ruiz-Avila I, Rodriguez-Archilla A, Morales-Garcia P, Mesa-Aguado F, Bascones-Martinez A, et al. Treatment of severe erosive gingival lesions by topical application of clobetasol propionate in custom trays. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2003; 95:688–92. [PubMed: 12789149]
13. Crincoli V, Di Bisceglie MB, Scivetti M, Lucchese A, Tecco S, Festa F. Oral lichen planus: update on etiopathogenesis, diagnosis and treatment. *Immunopharmacol Immunotoxicol*. 2011; 33:11–20. [PubMed: 20604639]
14. Riano Arguelles A, Martino Gorbea R, Iglesias Zamora ME, Garatea Crelgo J. Topic tacrolimus, alternative treatment for oral erosive lichen planus resistant to steroids: a case report. *Med Oral Patol Oral Cir Bucal*. 2006; 11:E462–6. [PubMed: 17072247]
15. Lopez-Jornet P, Camacho-Alonso F, Salazar-Sanchez N. Topical tacrolimus and pimecrolimus in the treatment of oral lichen planus: an update. *J Oral Pathol Med*. 2010; 39:201–5. [PubMed: 19943858]
16. Sanchez AR, Sheridan PJ, Rogers RS. Successful treatment of oral lichen planus-like chronic graft-versus-host disease with topical tacrolimus: A case report. *J Periodontol*. 2004; 75:613–9.
17. Dodds-Ashley E. Management of drug and food interactions with azole antifungal agents in transplant recipients. *Pharmacotherapy*. 2010; 30:842–54. [PubMed: 20653361]
18. Siegfried AA, Silverman R, Williams ML, Elias PM, Szabo SK, Korman NJ. Significant absorption of topical tacrolimus in 3 patients with Netherton syndrome. *Arch Dermatol*. 2001; 137:747–50. [PubMed: 11405764]
19. Patel TS, Greer SC, Skinner RB Jr. Cancer Concerns with Topical Immunomodulators in atopic dermatitis: overview of data and recommendations to clinicians. *Atopic Dermatitis. Am J Clin Dermatol*. 2007; 8:189–94. [PubMed: 17645374]
20. Mattsson U, Magnusson B, Jontell M. Squamous cell carcinoma in a patient with oral lichen planus treated with topical application of tacrolimus. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2010; 110:e19–25. [PubMed: 20610291]
21. Remitz A, Reitamo S. Long-term safety of tacrolimus ointment in atopic dermatitis. *Expert Opin Drug Saf*. 2009; 8:501–6. [PubMed: 19435404]
22. Reitamo S, Wollenberg A, Schop E, Perrot JL, Marks R, Ruzicka T, et al. The European Tacrolimus Ointment Study Group. Safety and efficacy of 1 year of tacrolimus ointment monotherapy in adults with atopic dermatitis. *Arch Dermatol*. 2000; 135:999–1006. [PubMed: 10926735]
23. Lozada-Nur F, Miranda C, Maliksi R. Double-blind clinical trial of 0.05% clobetasol propionate ointment in orabase and 0.05% fluocinonide ointment in orabase in the treatment of patients with oral vesiculoerosive diseases. *Oral Surg Oral Med Oral Pathol*. 1994; 77:598–604. [PubMed: 8065723]
24. Rojas AG, Govzalez GN, Venables GC, Araos HD. Graft versus host disease with oral involvement: report of one case. *Rev Med Chil*. 2008; 136:1570–3. [PubMed: 19350175]

Figure 1.
Severe oral chronic graft versus host disease recalcitrant to clobetasol propionate therapy with flexible custom trays.

Figure 2. Photomicrograph of oral mucosa demonstrating inflammatory infiltration consistent with graft versus host disease, (hematoxylin-eosin staining, original magnification x 200).

Figure 3.
Healthy mucosal appearance after one month's therapy with topical tacrolimus with flexible custom trays.