

Management of recurrent aphthous stomatitis-current trends & perspective

Akhilanand Chaurasia^{1,*}, Akansha Vatsa²

¹Assistant Professor, ²Resident, Dept. of Oral Medicine & Radiology, Faculty of Dental Sciences, King George's Medical University, Lucknow, Uttar Pradesh, India

***Corresponding Author:**

Email: chaurasiaakhilanand49@gmail.com

Abstract

Recurring oral ulcers are among most common oral disease encountered by oral physicians in day to day practice. Recurrent aphthous stomatitis (RAS) is a common disorder characterized by recurring ulcers confined to the oral mucosa with no other signs of systemic diseases. It affects approximately 20% of general population. Clinically it is classified as minor ulcers, major ulcers and herpetiform ulcers. This article insights the current trends in management of this commonly occurring disease.

Keywords: Recurrent Aphthous Stomatitis, Oral ulcers, Etanercept, Autoimmune diseases.

Introduction

Aphthous word is derived from the greek word *aptha* meaning "eruption" or "ulcer". Recurrent is the word added to name because of the nature of disease, occurring repeatedly in oral cavity at intervals. The etiology behind this disease is still unclear. Cell mediated immune response plays pivotal role in immunopathogenesis of aphthous ulcer.¹ There are at least 4 episodes of the disease per year.² Prevalence is found to be higher in developed countries irrespective of age, race or geographic distribution.³

Sometimes it is related to systemic diseases like Crohn's disease and Behcet's disease, adversely influencing the quality of life of patients.⁴ Certain HLA findings in some patients strengthens role of genetic predisposition.⁵ Some patients report of prodromal burning sensation 2 hrs to 2 days before the appearance of ulcer.⁶ Some predisposing factors are associated with RAS like trauma, vitamin deficiencies, stress, hormonal influences, immunologic parameters and microbial load.^{6,7}

Initiation of cascade of inflammatory cytokines against oral mucosa triggered by predisposing factors results in activation of T-lymphocytes and leukocyte chemotaxis.⁸ Production of cytokines like interferon-alpha (INF- α), interleukin-2, interleukin-12 and tumor necrosis factor-alpha (TNF- α) from T-helper cells further contributes to the immune response. Some evidences of presence of auto-antibodies against oral mucosa are also found.⁹

Current trends in management of RAS

Clinical appearance of RAS is as single or multiple painful shallow round ulcers with pseudomembranous centre and erythematous margin. RAS has 3 subtypes; recurrent aphthous major, minor and herpetiform. It mostly involves non keratinizing oral mucosa like buccal mucosa, labial mucosa and tongue.^{1,6} Till today it is difficult to catch whether a similar pathogenesis exists between RAS associated with other systemic

disease and RAS unassociated with any systemic disease.¹⁰ A study by Ozyurt K et al., reveals that the serum interferon gamma, alpha-enolase levels, interleukin-1, interleukin-13, interleukin-18 were found to be in increased concentration in patients with Behcet's disease as well as RAS in comparison to healthy controls.^{10,11} There is no specific diagnostic test. The main basis of diagnosis is a meticulous patient history and gross clinical examination. Family history also plays a vital role. While examining the patient we must give concern to the size, number, location and frequency of ulcers. To have an idea about any underlying systemic cause we can run certain tests like estimation of full blood count, hemoglobin, C-reactive protein, erythrocyte sedimentation rate, vitamin B12 level, anti-endomysial and anti-gliadin autoantibodies.¹²

Our treatment must aim at reducing the duration and frequency of ulcers to improve the level of well being for the patient. Different patient respond differently to the various treatment regimens. Therapeutic approach may be topical or systemic as per the severity of disease. Several trials are undertaken to determine the best treatment approach for RAS. Antibiotic mouthrises are prescribed in mild initial cases. Chlorhexidine 0.2% mouth rinse or 1% gel formulation is known to reduce the duration and severity of disease.¹³ 5 ml of minocycline, 0.2% mouthrinse in aqueous solution when rinsed 6 hourly provided early relief from RAS.¹⁴

Other topical treatments include application of dexamethasone ointment (5mg) on ulcers 3 times a day post meal for 5 days accelerated healing process¹⁵. Adhesive pellicles (2mg) of amlexanox or 5% paste formulation when applied 8 hourly, reduced pain intensity and size of ulcers.^{16,17} Reduction in pain was noted from day 1 after chemical cauterization of ulcer with silver nitrate pencil (1-2%).^{18,19} We all know LASERS are paving their way as latest diagnostic and treatment modality. As far as RAS treatment is concerned Nd:YAG laser and CO2 laser treatment

presented with immediate relief.^{20,21} Topical treatment modalities mentioned above have been proved to be effective in minor form of disease. But RAS with more recurring episodes and higher severity may need systemic therapy. Vitamin B supplementation accelerates the healing process. Systemic medications includes various drug regimens. Thalidomide 100mg oral when given daily for 15 days led to complete remission of RAS.²² But it is contraindicated in pregnancy and bears numerous side effects like headache, xerostomia, constipation. Colchicine 0.5mg daily oral dose for 3 months helped in reduction in number of ulcers and intensity of associated pain.²³ 400 mg of pentoxifylline taken orally 3 times a day causes reduction in size of ulcer.²⁴ Another drug in this row is clofazimine. When it was given at a dose of 100mg orally on alternate days, increased disease free intervals.²⁵ But clofazimine has certain cutaneous side effects.²⁶

Systemic corticosteroids are well accepted treatment modalities in RAS major cases. 25mg daily administration of prednisone for 15 days followed by gradually tapered maintenance dose over next 45 days resulted in rapid healing along with decreased frequency of ulcers.²⁷ Systemic administration of corticosteroids have a series of adverse reactions on body which must be kept in concern. Montelukast 10mg/day when given for 1 month and alternate day for next 30 days resulted in resolution of ulcers.²⁷ Dapsone 100mg daily orally is also a treatment of choice.²⁸ Zinc sulfate 150 mg daily oral dose for 12 weeks reduced the number and size of ulcers without any side-effect.²⁹ Subantimicrobial dose of doxycycline (20mg) BD increased disease free periods.³⁰ Rebamipide 100 mg thrice in a day orally for 7-14 days caused reduction in number of ulcers and pain intensity.³¹ A randomized controlled trial by Volkov I et al revealed that a daily dose of vitamin B12 (1000mcg) sublingually for 6 months decreased pain intensity and number of ulcers in RAS.³² Levamisole 150mg/day oral when given on 3 consecutive days every fortnight also gave positive treatment outcomes.³³

Novel therapeutic regimens

Biologic agents are the latest trends in treatment of aphthous ulcers. They block certain immunologic or pathophysiologic pathways of disease. They have targeted approach. Either they are immunosuppressive or anti-inflammatory in action³⁴. Some names in this queue are etanercept, adalimumab, infliximab and IFN-gamma.

Structurally, etanercept is a dimeric fusion protein comprising the extracellular portion of human TNF receptor (p75) coupled to the Fc fragment of human IgG. It is a recombinant TNF soluble receptor. It competitively inhibits the binding of TNF to TNF receptors thereby preventing TNF-mediated cell responses³⁵. It is given subcutaneously, at a dose of

25mg two times a week³⁶. It can be self administered by the patient. Studies suggest significant improvement in refractory cases as well as complete remission in some.³⁵⁻³⁸

A murine monoclonal antibody named infliximab acts against TNF- α . Infliximab when administered in a dose of 3-5mg/kg intravenously every 2-6 weeks showed early healing and complete remission within 7-10 days in old RAS cases resistant to other treatment modalities.³⁹⁻⁴⁴ Adalimumab is a human monoclonal antibody. It binds to TNF- α resulting in inhibition of the activity of TNF- α . It achieves higher affinity as compared to infliximab and etanercept.⁴⁵ It has an advantage of having fewer side effects. Complete resolution or remission was found in several study cases of RAS with associated systemic disease.⁴⁵⁻⁴⁹ INF- α plays vital role in immune response. It helps in clearance of all foreign antigens and maintaining, immunological memory. Treatment with a low dose of INF- α causes de-acceleration of delayed-type hypersensitivity.⁵⁰ Topical,⁵¹ oral^{52,53} and subcutaneous^{54,56} INF- α therapy diminished oral aphthous lesions.

Conclusion

Taking a thorough patient history and performing meticulous oral examination are key to sound diagnosis and treatment planning of recurrent aphthous stomatitis. There is a strong need to rule out whether RAS is associated with any underlying systemic disease that need to be managed. Elimination of predisposing factors is mandatory for successful treatment. More studies need to be conducted to find a definite treatment protocol for RAS. There are several treatment options to which different patient responds differently. Biologic agents are recent trends that have been used to treat aphthous ulcer as well as they are a ray of hope for the old refractory cases of RAS.

References

1. Beguerie JR, Sabas M. Recurrent aphthous stomatitis: An update on etiopathogenia and treatment. *J Dermatol Nurses Assoc* 2015;7(1):8-12.
2. Vaillant L, Samimi M. Aphthous ulcers and oral ulcerations Presse Med (Paris, France: 1983). 2016;45(2):215-26.
3. Natah SS, Kontinen YT, Enattah NS, Ashammakhi N, Sharkey KA, Häyrynen-Immonen R. Recurrent aphthous ulcers today: A review of the growing knowledge. *Int J Oral Maxillofac Surg* 2004;33(3):221-34.
4. Ryu HJ, Seo MR, Choi HJ, Baek HJ. Infliximab for refractory oral ulcers. *Am J Otolaryngol* 2014;35(5):664-8.
5. Jurge S, Kuffer R, Scully C, Porter SR. Number VI recurrent aphthous stomatitis. *Oral Dis* 2006;12(1):1-21.
6. Akintoye SO, Greenberg MS. Recurrent aphthous stomatitis. *Dental Clinics North Am* 2014;58(2):281-97.

7. Preeti L, Magesh KT, Rajkumar K, Karthik R. Recurrent aphthous stomatitis. *JOMFP* 2011;15(3):252-6.
8. Iebioda Z, Szponar E, Kowalska A. Etiopathogenesis of recurrent aphthous stomatitis and the role of immunologic aspects: Literature review. *Archivum Immunologiae et al. Therapiae Experimentalis*. 2014;62(3):205-15.
9. Albanidou-Farmaki E, Markopoulos AK, Kalogerakou F, Antoniadis DZ. Detection, enumeration and characterization of T helper cells secreting type 1 and type 2 cytokines in patients with recurrent aphthous stomatitis. *Tohoku J Exp Med* 2007;212(2):101-5.
10. Taylor J, Glenny AM, Walsh T, Brocklehurst P, Riley P, Gorodkin R, et al. Interventions for the management of oral ulcers in Behçet's disease. *Cochrane Database Syst Rev* 2014;9:CD011018.
11. Ozyurt K, Çelik A, Sayarlioglu M, Colgecen E, İnci R, Karakas T, et al. Serum Th1, Th2 and Th17 cytokine profiles and alpha-enolase levels in recurrent aphthous stomatitis. *J Oral Pathol Med* 2014;43(9):691-5.
12. Tarakji B, Gazal G, Al-Maweri SA, Azzeghaiby SN, Alaizari N. Guideline for the diagnosis and treatment of recurrent aphthous stomatitis for dental practitioners. *Journal of International Oral Health: JIOH* 2015;7(5):74-80.
13. Altenburg A, Abdel-Naser MB, Seeber H, Abdallah M, Zouboulis CC. Practical aspects of management of recurrent aphthous stomatitis. *J Eur Acad Dermatol Venerol* 2007;21(8):1019-26.
14. Gorsky M, Epstein JB, Rabenstein S, Elishoov H, Yarom N. Topical minocycline and tetracycline rinses in treatment of recurrent aphthous stomatitis: a randomized cross-over study. *Dermatol Online J* 2007;13(2):1.
15. Keenan AV. Promising results for dexamethasone ointment for treatment of recurrent aphthae. *Evid Based Dent* 2012;13(3):75.
16. Meng W, Dong Y, Liu J, Wang Z, Zhong X, Chen R, et al. A clinical evaluation of amlexanox oral adhesive pellicles in the treatment of recurrent aphthous stomatitis and comparison with amlexanox oral tablets: a randomized, placebo controlled, blinded, multicenter clinical trial. *Trials*. 2009;10(1):30.
17. Fernandes R, Tuckey T, Lam P, Allidina S, Sharifi S, Nia D. The best treatment for aphthous ulcers: an evidence based study of the literature. Available at: <https://www.dentistry.utoronto.ca/system/files/aphthousulcers.pdf>. Accessed June 14, 2016.
18. Altenburg A, El-Haj N, Micheli C, Puttkammer M, Abdel-Naser MB, Zouboulis CC. The treatment of chronic recurrent oral aphthous ulcers. *Deutsches Ärzteblatt Int*. 2014;111(40):665-73. 2014;36:5.
19. Alidaee MR, Taheri A, Mansoori P, Ghodsi SZ. Silver nitrate cautery in aphthous stomatitis: a randomized controlled trial. *Br J Dermatol* 2005;153(3):521-5.
20. Tezel A, Kara C, Balkaya V, Orbak R. An evaluation of different treatments for recurrent aphthous stomatitis and patient perceptions: Nd: YAG laser versus medication. *Photomed Laser Surg* 2009;27(1):101-6.
21. Prasad S, Pai A. Assessment of immediate pain relief with laser treatment in recurrent aphthous stomatitis. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2013;116(2):189-93.
22. Mimura MA, Hirota SK, Sugaya NN, Sanches Jr JA, Migliari DA. Systemic treatment in severe cases of recurrent aphthous stomatitis: an open trial. *Clinics (Sao Paulo, Brazil)*. 2009;64(3):193-8.
23. Pakfetrat A, Mansourian A, Momen-Heravi F, Delavarian Z, Momen-Beitollahi J, Khalizadeh O et al. Comparison of colchicines versus prednisolone in recurrent aphthous stomatitis: A double blind randomized clinical trial. *Clin Invest Med* 2010;33(3):189-95.
24. Thornhill MH, Baccaglini L, Theaker E, Pemberton MN. A randomized, double blind, placebo-controlled trial of pentoxifylline for the treatment of recurrent aphthous stomatitis. *Arch Dermatol* 2007;143(4):463-70.
25. De Abreu MA, Hirata CH, Pimentel DR, Weckx LL. Treatment of recurrent aphthous stomatitis with clofazimine. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009;108(5):714-21.
26. Brocklehurst P, Tickle M, Glenny AM, Lewis MA, Pemberton MN, Taylor J, et al. Systemic interventions for recurrent aphthous stomatitis (mouth ulcers). *Cochrane Database Syst Rev* 2012;9:CD005411.
27. Femiano F, Buonaiuto C, Gombos F, Lanza A, Cirillo N. Pilot study on recurrent aphthous stomatitis (RAS): a randomized placebo-controlled trial for the comparative therapeutic effects of systemic prednisone and systemic montelukast in subjects unresponsive to topical therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010;109(3):402-7.
28. Sharquie KE, Najim RA, Abu-Raghib AR. Dapsone in Behçet's disease: a double-blind, placebo-controlled, cross-over study. *J Dermatol* 2002;29(5):267-79.
29. Sharquie KE, Najim RA, Al-Hayani RK, Al-Nuaimy AA, Maroof DM. The therapeutic and prophylactic role of oral zinc sulfate in management of recurrent aphthous stomatitis (RAS) in comparison with dapsone. *Saudi Med J* 2008;29(5):734-38.
30. Preshaw PM, Grainger P, Bradshaw MH, Mohammad AR, Powala CV, Nolan A. Subantimicrobial dose doxycycline in the treatment of recurrent oral aphthous ulceration: A pilot study. *J Oral Pathol Med* 2007;36(4):236-40.
31. Kudur MH, Hulmani M. Rebamipide: A novel agent in the treatment of recurrent aphthous ulcer and Behçet's syndrome. *Ind J Dermatol* 2013;58(5):352.
32. Volkov I, Rudoy I, Freud T, Sardal G, Naimer S, Peleg R, et al. Effectiveness of vitamin B12 in treating recurrent aphthous stomatitis: a randomized, double-blind, placebo-controlled trial. *J Am Board Fam Med* 2009;22(1):9-16.
33. Meyer JD, Degraeve M, Clarysse J, Loose FD, Peremans W. Levamisole in aphthous stomatitis: Evaluation of 3 regimens.
34. Georgakopoulou EA, Andreadis D, Arvanitidis E, Loumou P. Biologic agents and oral diseases--an update on clinical applications. *Acta Dermatovenerol Croat* 2013;21(1):24-34.
35. Robinson ND, Guitart J. Recalcitrant, recurrent aphthous stomatitis treated with etanercept. *Arch Dermatol* 2003;139:1259-62.
36. Altenburg A, Zouboulis CC. Current concepts in the treatment of recurrent aphthous stomatitis. *Skin Therapy Lett* 2008;13(7):1-4.
37. Hasan A, Patel H, Saleh H, Youngberg G, Litchfield J, Krishnaswamy G. Remission of severe aphthous stomatitis of celiac disease with etanercept. *Clin Mol Allergy* 2013;11:6.
38. Gonzalez-Lopez MA, Blanco R, Garcia-Ibarbia C, Gonzalez-Vela CM, Gonzalez-Gay MA. Etanercept-induced hypertriglyceridemia during the treatment of

- recurrent aphthous stomatitis. *Ind J Dermatol Venereol Leprol* 2013;79(3):432-33.
39. Ting PT, Koo J. Use of etanercept in human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) patients. *Int J Dermatol* 2006;45(6):689-92.
 40. Travis SP, Czajkowski M, McGovern DP, Watson RG, Bell AL. Treatment of intestinal Behçet's syndrome with chimeric tumour necrosis factor α antibody. *Gut* 2001;49(5):725-28.
 41. Almozni G, Ben-Chetrit E. Infliximab for the treatment of resistant oral ulcers in Behçet's disease: a case report and review of the literature. *Clin Exp Rheumatol* 2007;25(4 Suppl 45):S99-102.
 42. Robertson LP, Hickling P. Treatment of recalcitrant orogenital ulceration of Behçet's syndrome with infliximab. *Rheumatology (Oxford)*. 2001;40(4):473-4.
 43. Kaufman I, Caspi D, Yeshurun D, Dotan I, Yaron M, Elkayam O. The effect of infliximab on extraintestinal manifestations of Crohn's disease. *Rheumatol Int* 2005;25(6):406-10.
 44. Bañeros-Rojas P, Berrozpe-Villabona C, Peraza-Nieves JE, Díaz-Valle D. Early treatment with infliximab in bilateral occlusive vasculitis as a presenting manifestation of Behçet's disease. *Arch Soc Esp Ophthalmol* 2015;90(6):285-8.
 45. Kaji M, Kishi T, Miyamae T, Nagata S, Yamanaka H, Fujikawa S. Efficacy of adalimumab in a girl with refractory intestinal Behçet's disease. *Case Reports in Rheumatol* 2015;2015:716138.
 46. Ueda A, Takeno M, Ishigatsubo Y. Adalimumab in the management of Behçet's disease. *Therap Clin Risk Mgmt* 2015;11:611.
 47. Tanida S, Inoue N, Kobayashi K, Naganuma M, Hirai F, Iizuka B, et al. Adalimumab for the treatment of Japanese patients with intestinal Behçet's disease. *Clin Gastroenterol Hepatol*. 2015;13(5):940-8.e3.
 48. Perra D, Alba MA, Callejas JL, Mesquida M, Ríos-Fernández R, Adán A, et al. Adalimumab for the treatment of Behçet's disease: experience in 19 patients. *Rheumatology (Oxford)*. 2012;51(10):1825-31.
 49. Vujevich J, Zirwas M. Treatment of severe, recalcitrant, major aphthous stomatitis with adalimumab. *Cutis* 2005;76(2):129-32.
 50. Brassard DL, Grace MJ, Bordens RW. Interferon- α as an immunotherapeutic protein. *J Leukoc Biol* 2002;71(4):565-81.
 51. Hamuryudan V, Yurdakul S, Serdaroglu S, Tüzün Y, Rosenkaimer F, Yazici H. Topical alpha interferon in the treatment of oral ulcers in Behçet's syndrome: a preliminary report. *Clin Exp Rheumatol* 1990;8(1):51-4.
 52. Hutchinson VA, Angenend JL, Mok WL, Cummins JM, Richards AB. Chronic recurrent aphthous stomatitis: oral treatment with low-dose interferon alpha. *Mol Biother* 1990;2(3):160-4.
 53. Kılıç H, Zeytin HE, Korkmaz C, Mat C, Gül A, Coşan F, et al. Low-dose natural human interferon- α lozenges in the treatment of Behçet's syndrome. *Rheumatol (Oxford)*. 2009;48(11):1388-91.
 54. Alpsoy E, Durusoy C, Yilmaz E, Ozgurel Y, Ermis O, Yazar S, et al. Interferon alfa-2a in the treatment of Behçet disease: a randomized placebo-controlled and double-blind study. *Arch Dermatol* 2002;138(4):467-71.
 55. Karagiannidis I, Zouboulis CC. Systemic Adamantiades-Behçet's disease: adverse effects of an otherwise successful therapy with interferon- α -2a. *Dtsch Med Wochenschr*. 2015;140(2):112-3.
 56. Kötter I, Vonthein R, Zierhut M, Eckstein AK, Ness T, Günaydin I, et al. Differential efficacy of human recombinant interferon-alpha2a on ocular and extraocular manifestations of Behçet disease: results of an open 4-center trial. *Semin Arthritis Rheum* 2004;33(5):311-9.