Recurrent Aphthous Stomatitis: Towards Evidence-Based Treatment?

Challacombe, SJ; Alsahaf, S; Tappuni, A

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Stephen J Challacombe [1], Surab Alsahaf [1] and Anwar Tappuni [2]

[1] Department of Oral Medicine, King's College London Dental Institute, Guys Hospital London SE1 9RT, UK, [2] Department of Oral Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, UK

Corresponding author: stephen.challacombe@kcl.ac.uk

Abstract

Recurrent aphthous stomatitis is one of the most common oral mucosal diseases seen by dental professionals, and yet its etiology remains unclear, and its management based on less than robust evidence. The literature remains confused because of the lack of clarity in diagnosis and the lack of a standardized ulcer severity scoring system and agreed outcome measures. However, recent literature is encouraging in meeting these aims. There is agreement that RAS is a localized mucosal disease not secondary to systemic disease and therefore distinguishable from over forty other types of oral ulcers. Disease severity scores have been introduced and outcome measures have become more standardized. RAS appears to be an auto-immune disease directed at epitopes of heat shock proteins while most recent work on etiology has focused on cytokines and genetics. Pro-inflammatory cytokines including TNFa and IL-6 and IL-17 are raised in RAS and TNF inhibitors can inhibit episodes of ulceration. Many local anti-inflammatory agents will help ulcers heal, and local steroids remain the treatment of choice. Some systemic drugs have evidence based data indicating efficacy at preventing new ulcers including colchicine, prednisolone, thalidomide, pentoxyfilline and dapsone. The field would benefit from further trials combining local and systemic therapy using defined outcome measures.

Keywords : recurrent aphthous stomatitis, oral ulceration, interleukins, steroids, colchicine, levamisole, thalidomide, azathioprine, disease severity scores

Introduction

Diagnosis

The correct diagnosis of Recurrent Aphthous Stomatitis (RAS, sometimes also referred to as recurrent oral ulceration or canker sores) is central to oral medicine. There are over forty types of mouth ulcers, many related to systemic diseases, but RAS is characterized by oral ulcers, occurring singly or in crops that usually last for 7 to 21 days before healing spontaneously. These ulcers recur after a variable period, which may be a few days or several weeks. RAS can be separated clinically into three types: minor aphthous ulcers (MiAU), major aphthous ulcers (MjAU) and herpetiform ulcers (HU) (see Table I). There has been a tendency for clinicians to describe any ulcer occurring in the mouth as aphthous. However, aphthous ulcers have been carefully defined to allow differentiation from the many other types of recurrent ulcers occurring in the oral cavity and are not associated with systemic abnormalities [1].

Recurrent oral ulceration
• **Recurrent aphthous stomatitis**
Minor
Major
Herpetiform
• Recurrent aphthous ulcers with Behçet's disease
• Smoking-related aphthous ulcers
• Recurrent erythema multiforme
• Atypical recurrent oral ulceration
Persistent oral ulceration
• Secondary to hematological deficiency state/anemia
• Secondary to a gastrointestinal enteropathy
• Secondary to a dermatological condition
• Secondary to connective tissue disease

Table 1: Differential types of recurrent oral ulceration and major groups of persistent oral ulceration (modified from [1])

Prevalence of RAS

Wild overestimates of the prevalence abound, but if RAS is defined as more than two spontaneously occurring episodes per year, then an average prevalence in the population of around 10% appears reasonable. Many studies struggle with definitions and ask whether subjects ever get mouth ulcers. It is likely that such studies give a prevalence much greater than those adhering to the RAS definition.

Reported estimates vary between 1.5% and 28% in different parts of the world, suggesting that there may be genetic differences to account for these geographic variances [2-4]. The prevalence in children may be greater than adults [5, 6]

Aetiology

An impressive array of factors has been implicated in the etiology of RAS, although it is likely that many of them influence the nature of the disease rather than cause it. These include hereditary factors, hypersensitivity predisposition, socioeconomic status, psychological factors, endocrine factors, microbial agents, and chemical factors in foods. There is no evidence that food allergy is causative in RAS, although it is likely that food allergy can initiate some cases of oral ulceration which might in the unwary appear to mimic RAS. Hematological deficiencies may cause some types of oral ulceration but may also influence susceptibility to other types of ulceration. In addition, lesions clinically consistent with RAS are found in association with some systemic or multisystem illnesses such as Behçet's syndrome, clinical neutropenia, vitamin B_{12} deficiency, and celiac disease. RAS is thus best defined as being recurrent oral ulceration in the absence of known systemic factors (table 1).

Some studies have reported an association between RAS and a variety of psychological factors including anxiety, stress and depression [7-10], but salivary cortisol levels are often normal in RAS patients even during the active phase [11]. Nevertheless, the concept of initiation of RAS through expression of heat shock (stress) proteins (HSP) such as during viral illnesses and RAS reoccurrences when patients under stress with possible re-expression of HSP does relate well to the evidence of reactivity of RAS patients to epitopes of HSPs (see below).

Genetic Aspects

A family history of ulcers is found in approximately 40% of patients, and the highest incidence is found in siblings of parents both of whom have RAS. Identical twins show a 90% concordance, implicating a genetic component [12]. The prevalence of human leukocyte antigens HLA-A2 and B12 (B44 subtype) was higher in RAS patients than in controls, suggesting that major histocompatibility complex (MHC) class1 gene products may be associated [13], but it is likely that genes other than those associated with HLA may be more closely linked. Genome wide association studies (GWAS) have not yet borne fruit, possibly because of the heterogeneity of RAS and sometimes inconsistency in diagnosis.

A number of recent studies have examined polymorphisms of individual genes in factors thought to be associated with the pathogenesis of RAS. Single nucleotide polymorphisms (SNPs) of IL-10 gene (C/A-1082, C/T-819 and C/A-592) were significantly higher in RAS patients [14]. Polymorphisms of IL-1beta and TNF-alpha production were associated with an increased risk of RAS development [15]. Genotypes of IL-6 gene -572G>C and -174G>C polymorphisms were found to be significantly higher in 184 Turkish RAS subjects [16]. Matrix Metalloproteinase (MMP-9) polymorphisms have been described in RAS patients [17] and a mutation of Methylene tetrahydrofolate reductase (MTHFR) gene C677T related slightly curiously with the number of oral ulcers in RAS patients [18].

These findings taken together suggest that gene abnormalities may be associated with susceptibility to RAS and that it is likely that susceptibility is related to a number of abnormalities. The relevance of such studies would be greatly enhanced if there was further understanding of the actual mechanisms and pathways leading to RAS!.

Immunopathogenesis:

The exact pathogenesis of RAS, a common mucosal disorder is still unknown. A role for autoimmunity in RAS was first suggested in the 1960s [19]**.** Although no definitive infective microorganism has been identified, a currently accepted hypothesis is that patients are exposed to an unidentified infective or other agent, which, in susceptible patients, triggers release from normal suppression of an autoimmune response against oral mucosa. The agent is thus either in, or cross-reacts with, oral mucosa in these patients. Autoantibodies, cytotoxic lymphocytes, and circulating lymphocytes sensitized to oral mucosa have been demonstrated in RAS patients. In most RAS patients anti-epithelial antibodies, which are cytotoxic to oral epithelial cells, can be found [20].

A potential cross-reacting agent is heat shock protein (hsp). Hasan *et al.* [21] showed that T lymphocytes from patients with RAS recognized a unique peptide sequence of the mycobacterial hsp 65 antigen. Responses to a human 60-kDa hsp peptide 116-130 were also raised. This finding suggests that RAS might be initiated by the microbial hsp peptide, which stimulates the mucosal Langerhans cells to generate autoreactive T-cell clones primed to the homologous peptide. The specific peptide epitope 91-105 of the 65-kDa mycobacterial Hsp against which RAS patients react has been identified [22]. This concept that Hsp peptides contribute to RAS pathogenesis is strengthened by the demonstration that patients with Behcets syndrome react to a different peptide, and that in animal models, immunization with

this peptide leads to a form of Behcets syndrome [23] which can be blocked by inducing oral tolerance in models or in patients with Behcets [23].

Others have suggested that TLR2 (Toll-like receptor) stimulating peripheral blood mononuclear cells could be involved in the pathogenesis of RAS [24]. TLRs are a group of membrane receptors which can recognise molecules derived from bacteria, viruses and fungi that are involved in both immune regulation and control of epithelial barrier integrity. The hypothesis suggests that RAS occurs due to an imbalance of Th1/Th2 immune response as well as epithelial barrier dysfunction of the oral mucosa caused by impairment of TLR2 pathways, which permitted the contact of immune competent cells from the lamina propria with oral antigens that are rich in Th1 cytokines and that will influence the onset of RAS [24, 25]

RAS is characterised histopathologically by a marked inflammatory infiltrate that initially consists predominantly of lymphocytes which then becomes mixed with neutrophils as the lesion develops [26] and adjacent keratinocytes become HLA-DR (an MHC class II cell surface receptor) and ICAM-1 (Intercellular Adhesion Molecule-1) positive [27,28]. Activated endothelial cells expressing adhesion molecules including intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1) and E-selectin could become the target for the cytotoxic damage. The early expression of ICAM-1 by keratinocytes could be important in the early recruitment of lymphocytes. This interaction between keratinocytes and CD8+ cytotoxic T cells binding with ICAM-1 of keratinocytes could be responsible for the epithelium destruction and ulcer formation at the site [28]. The predominance of CD8+ cytotoxic T cells in the ulcerative stage has been demonstrated [27, 28].

The role of Oral Flora

These theories of pathogenesis suggest that the oral flora and the host-pathogen interface are important components in the aetiology of RAS and have stimulated new study of both. Early studies had suggested that L-forms of bacteria (those without a cell wall), mycoplasma, lactobacilli or species of streptococci might be carrying the offending cross reacting antigen.
Using DNA analysis, the microbiota of the non-inflamed buccal mucosa in RAS appears to differ between patients and controls, especially if lesions were present. This suggested that a

disturbance in the normal buccal microbiota triggers the presence of lesions or that presence of lesions alters the microbiota [29, 30]. Using high-throughput 16S rRNA gene sequencing, mucosal microbiome changes in mucosae of patients with RAS were demonstrated, including increased Bacteroidales species [31]. Several studies have suggested the possible involvement of *Helicobacter pylori* infection in individuals with RAS, but the relationship remains controversial. A recent meta-analysis by Li et al [32] supports the weak association between RAS and *H. pylori* infection (30% in RAS versus 20% in controls) and suggests that in a minority of patients *H pylori* eradication might be of clinical benefit.

Analysing current oral flora in patients who have a history of RAS seems unlikely to determine a triggering role of a specific microbial species, but may shed light on perturbations associated with RAS.

Role of cytokines in RAS

Cytokines are crucial mediators of immune reactivity and have been a major focus in the immunopathogenesis of RAS. Current evidence suggests that RAS may result from an abnormal cytokine cascade in the oral mucosa that leads to a cell-mediated immune response directed towards focal area of the oral mucosa [33]. There are two types of cytokines: Pro-inflammatory cytokines that induces cell-mediated immunity and produced by Th1 (IL-2, IL-12, IFN-g and TNF-a) and anti-inflammatory cytokines (IL-4, IL-5, IL-10 and IL-13) produced by Th2 and promote humoral immunity and suppression of cell-mediated immunity. The imbalance of Th1/Th2 immune response is strongly influenced by their cytokine environment [33,34]. The predominance of pro-inflammatory cytokines (IL-2, IL-12 TNF-a, and IFN-g) in lesional biopsies of RAS patients were demonstrated in several studies [35, 33]. Type 1 pro-inflammatory cytokines like interleukin-2 (IL-2), interleukin-12 (IL-12), interferon-gamma (IFN-g) and tumour necrosis factor-alpha (TNF-a) have been suggested to be implicated in the aetiopathogenesis of RAS [34]

Tumour necrosis factor-alpha (TNF-a) is an important inflammatory mediator and critical cytokine for adequate host defences and because it can have direct toxic effects on epithelial cells is a clear candidate for damage in RAS as well as protection in general. TNF-a is thought to play a major role in the activation of the inflammatory process in RAS by its effect on endothelial cells adhesion molecules and its chemotactic effect on neutrophils [36]. A direct role for TNFa in RAS is suggested by the efficacy of medications which inhibit TNF

including thalidomide and pentoxifylline [37, 38] and infliximab [39]. Serum TNF, presumably reflecting local production, has been reported as raised in a third of patients with RAS, and related both to disease severity and stage of RAS [40] but findings were not confirmed in all studies [37]. However, salivary TNF-a levels were reported as raised in both ulcerative and remission stages of RAS [41], and in the ulcer phase [42].

IL-6 is a multifunctional pro-inflammatory cytokine produced by macrophages, lymphocytes, keratinocytes, fibroblasts and endothelial cells in response to a variety of external stimuli. Raised serum concentrations of IL-6 and IL-8 were found in 25% and 60% of RAS respectively and in both major and minor types [43, 44, 45] suggesting that serum IL-8 may be a more sensitive marker than IL-6 in monitoring disease activity of RAS. Other studies have not found significant differences in levels of IL-6 in serum [46] or in saliva [41].

IL-8 is a chemokine produced by keratinocytes, macrophages, mast cells and endothelial cells. It is known as neutrophil chemotactic factor. Keratinocytes in the pre-ulcerative stage of RAS may produce a significant level of IL-8 which in turn activate neutrophils and attract cytotoxic T cells. Sun et al [44] found that serum concentrations of IL-8 were raised in RAS patients and significantly increased levels of serum IL-8 are found in Behcet's disease patients associated with recurrent oral ulcers [46, 47].

Recently a newer subset of Th17 lymphocytes producing IL-17 were described in relation to mucosal diseases. The main function of Th17 cells is thought to be their ability to recruit neutrophils and increase the production of cytokines and chemokines by epithelial cells. Serum levels of IFN-g and IL-17 were significantly increased in RAS patients [48]. Human oral keratinocytes can produce IL-17 and stimulate the production of IL-8 and TNF-a in RAS patients compared with healthy controls [49].
Overall, there seems to be sufficient evidence to suggest that pro-inflammatory cytokines may be associated with RAS activity.

Assessing Ulcer Severity

The need for a standardised method for assessing ulcer severity and its use in determining treatment responses has long been recognised. However, authors have used such a variety of outcome measures that a Cochrane review of RAS treatment was not possible [50]. However,

recently Tappuni et al [51] have reported an ulcer severity scoring system which converts RAS characteristics of number of ulcers, size, duration, length of ulcer free period, site affected and pain score into numerical values out of 10 and combined to give a total out of 60. Its use has been demonstrated in a study on the efficacy of betnesol mouthwashes and systemic colchicine in RAS treatment [51]. This Ulcer Severity Score (USS) scoring system aided in monitoring the progress of the condition, helped in assessing the efficacy of any treatment and in the management of the ulcers as well as being easy to use. An example of sequential scores in major RAS patients using Colchicine is shown (see figure)

Studies measuring the effect of RAS on quality of life have been reported [52]. The Oral Health Related Quality of Life (OHR-QoL) score of RAS patients provided an additional dimension which may help to improve the impact of RAS on an individual's life. Oral Health Impact Profile (OHIP-14) measured the degree of RAS impact on functional limitation, pain, psychological discomfort, physical disability, psychological disability, social disability and handicap. Improvement after treatment with colchicine was found and thus provides a patient based assessment of the effectiveness of treatment [52].

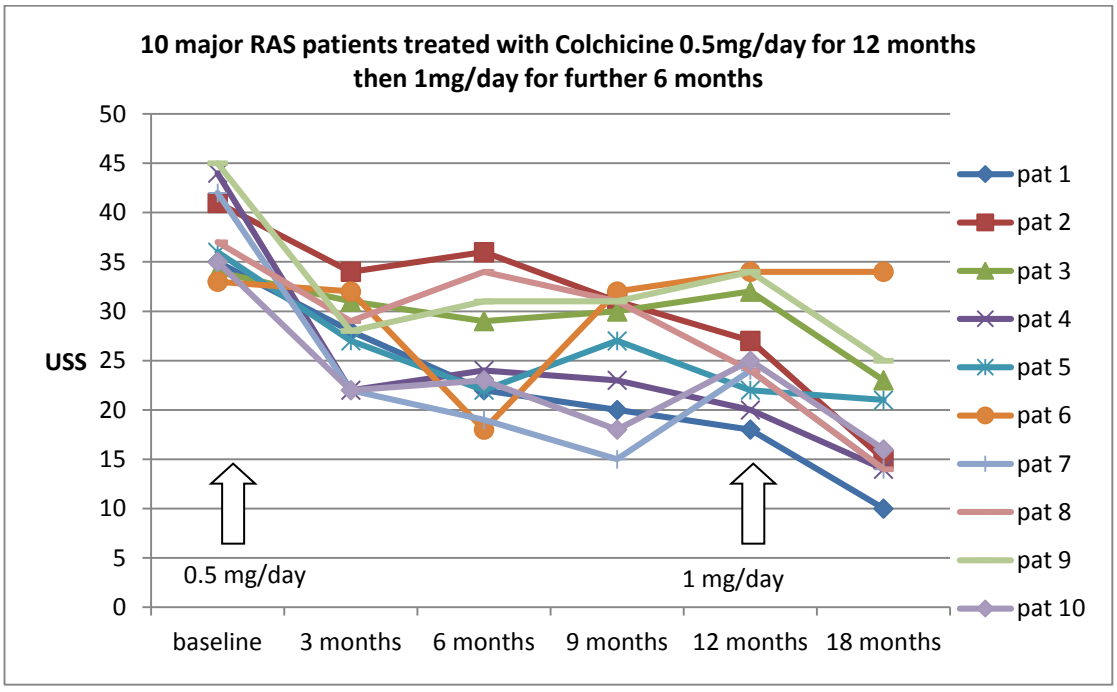

Figure. Ulcer severity scores of individual Major RAS patients (n=10) who were treated with colchicine 0.5mg/day for 12 months and then 1mg/day for 6 months. USS = Ulcer severity score [51]. Arrows indicate times of drug administration. (modified from Alsahaf S [92])

Management of RAS

There are no internationally accepted guidelines for RAS treatment despite RAS being one of the most common oral disorders. Apart from the relief of pain, there are two main therapeutic approaches a) to help heal current ulcers and b) to prevent new episodes of ulceration. Many topical preparations attempt to help the healing process and many have claimed efficacy, whilst prevention of new occurrences usually requires systemic medications.

Topical therapies

Steroid tablets used as a mouthwash are one of the most common treatments used in specialised clinics. It is a recognised therapy for RAS and generally accepted as effective in controlling this common oral condition [53], despite the limited clinical evidence to support its efficacy.

Betnesol mouthwash is a Betamethasone sodium phosphate tablet 500mcg dissolved in 10 ml of water and used as a mouthwash for 3 minutes then discarded. It is administered four times a day (QID) in the presence of ulcers and twice a day (BID) in between ulcer attacks [1] A three-month study by Tappuni et al [51] compared Betnesol mouthwash (four times a day) with Betnesol mouthwash and Colchicine tablets 0.5mg a day. Using an ulcer severity scoring (USS) system, the authors showed significant improvement in USS of most patients in the Betnesol group, as well as in the combined treatment of Colchicine plus Betnesol.

A wide range of topical therapies have been used in the treatment of RAS but there are very few published randomised clinical trials to support their efficacy. Not all are available worldwide. **Dexamethasone ointment** applied 3 times a day for 5 days can reduce ulcer size and pain alongside an improvement in healing time [54]. **Dexamucobase** was at least as effective as **triamcinolone acetonide in Orabase** in improving healing time [55]. **Amlexonax** is an anti-inflammatory, anti-allergic and immunomodulatory (not currently available in the USA). Two reasonably sized double blind trials (100-200 RAS patients) showed that Amlexonax oral adhesive tablets applied 4 times a day for 5 days were effective at promoting healing and reducing pain [56, 57]

Topical Tetracycline mouthwash has been used alone or in combination with liquid anti-fungals or topical steroids, especially in the treatment of Herpetiform RAS and remains the treatment of choice in this type of RAS which appears largely resistant to steroids [58]. In major and minor RAS, topical Tetracycline or Minocycline mouthwashes as a local anti-bacterial can be expected to reduce the severity of the ulcerations and pain but not prevent

recurrences [59, 60]. Similar effectiveness in promoting healing and reducing pain has been reported with **Penicillin G mouthwashes** [61].

Several **topical herbal treatments** have shown efficacy as alternative therapies including Aloe Vera gel [62], Berberine gelatine [63]. Yunnan baiyao [64], Myrtus communis [65] and Citrus oil with magnesium salts [66]. All of these topical herbal therapies have been used for the treatment of Minor RAS only. Lalla et al [67] demonstrated in a randomised, placebo-controlled, double-masked, parallel-arm, clinical trial that **daily multivitamin supplements** did not improve the number or duration of RAS episodes in 160 subjects.

Systemic Therapies:

The main goals of systemic therapies are to reduce the frequency of recurrences and to minimise the duration of ulcers. Systemic immunomodulatory medications have therefore been tried for the treatment and management of severe and constantly recurring RAS, including systemic **Prednisolone** [68], **Dapsone** [69], **Levamisole** [70], **Azathioprine** [71], **Pentoxifylline** [37], **Colchicine** [73, 51] and **Thalidomide** [38] (see table 2). These may produce remission or reduction in symptoms but all have side effects. Therefore the treatment choices should be guided by the balance between the severity of the RAS and the potential adverse effect of medications.

Table 2: Examples of Systemic treatment of RAS

TREATMENT	RESULTS	COMMENTS	AUTHORS
Levamisole 50mg/tds	Reduction in ulcers in up to 66%	Levamisole alone effective mode of therapy	40,47, 70, 71,86, 89 90
Infliximab Adalimumab Golimumab	Complete remission In up to 89%	Long term expensive 25% side effects	88,
Dapsone 50-125mg	Improvement in 60%	Gastric side effects in 25%	69, 78
Colchicine 500ugm/day	Effective in over 70%	Gastric side effects at higher doses	72, 78, 79, 80, 81, 82
Prednisolone 25mg/day	Pain, Ulcer number and duration reduced	2 months Not for long term	68, 71, 87
Azathioprine 25mg/day	Reduction of RAS in Behcets (see table 1)	Effective in Behcets. Perform TPMT assay	73, 74
Thalidomide 50mg/day	Complete remission in 85%. Beware side effects of neuropathy	3 months minimum	38, 76, 77
Tetracycline Mouthwash four times daily	Remission in majority but not all	Herpetiform RAS	58, 59, 60

Pentoxifylline 400mg/tds	Ulcer pain, size, number reduced. ulcer free period increased	2 months minimum	37,

TPMT= Thiopurine methyltransferase

Azathioprine is an immunosuppressive drug which belongs to the chemical class of purine analogues and is used in treatment of autoimmune diseases. 1 in 500 patients have a genetic deficiency of the enzyme Thiopurine Methyltransferase (TPMT) which metabolises azathioprine so assay is mandatory. There are very few published studies using Azathioprine for the management of RAS; it has been used more in the treatment of Behcet's disease. Azathioprine 25mg/day was found to be an effective therapy in the management of oral and genital ulcerations, uveitis and arthritis in 73 patients with BD [73] and at 2.5mg/kg very effective in controlling uveitis [74]

Thalidomide is an anti-TNF-a therapy which was first marketed as a sedative medication in 1957. Afterwards, Thalidomide was used for the treatment of nausea and morning sickness in pregnant women but soon became infamous for its teratogenicity. This led to the establishment of more structured regulations and control over drug uses, particularly in females. It is recommended that use of Thalidomide should be accompanied by Nerve Conduction Studies (NCS) and Electromyography (EMG) every 6 months to rule out peripheral neuropathy.

Nevertheless, thalidomide is considered to be an effective therapy for the managements of major RAS, and can be considered when other treatments have failed. Complete remission in 85% -90% of patients with severe RAS has been reported using thalidomide 100mg a day for a range of periods from 3-6 months. [38,75]. Two open trials in patients with complex aphthosis (ie oral and genital ulceration not fulfilling the criteria for Behcets syndrome) showed that thalidomide could be very effective at doses from 50 to 150mg a day over 4 years. Peripheral neuropathy was detected in some patients [76]. Remission in complex aphthosis without adverse events with low dose thalidomide (25mg/day) has also been reported [77]

Levamisole. Used at a dose of 50mg daily has been shown to be effective in reducing ulcer duration, number and frequency of recurrences [90]. Some variation in studies and not all have found uniformly positive results. Most trials are short term and longer terms are needed [70, 71, 86, 90]. Some RAS actually get worse but few side effects have been reported [91].

Dapsone has been reported to reduce ulcer recurrences in Complex aphthosis with a daily dose of 50 -125 mg [75, 76, 78]. The exact mechanism is thought to be due to its anti-neutrophilic action. However, Dapsone should not be administered to patients with a glucose-6-phosphate dehydrogenase (G6PD) deficiency and regular monitoring for haemolytic anaemia or methemaglobinaemias is essential

Colchicine is an anti-inflammatory agent that limits leukocyte activity by binding to Beta-Tubulin, a cellular microtubular protein, and therefore inhibiting protein polymerization [79]. Although Colchicine is generally well tolerated, the most frequent gastrointestinal adverse events include nausea, diarrhoea, vomiting, and abdominal pain. Colchicine at 1.5mg/day over 3 months showed a significant improvement of ulcers in over two thirds of patients,[72, 80, 81], but over 25% of patients reported side effects, mainly abdominal pain [80]. Similar results have been reported in other trials with 1.8mg/day showing effectiveness in complex aphthosis but a high rate of side effects [78]. Colchicine has been shown to be safe with a low dose of 0.5-1mg a day in children aged 3.5-11 years old with Periodic fever, Aphthous stomatitis, Pharyngitis and Adenitis disease (**PFAPA)** [82].

Lower doses (500ugm/day) appear effective when combined with topical steroids for 3 months [51]. These findings suggested that in the short-term topical steroids improved ulcer symptoms, while Colchicine seemed to prevent recurrences. This study used an Ulcer Severity Score (USS) (see above). A comparison of Prednisolone 5mg/day or Colchicine 0.5mg/day for 3 months in a double-blind clinical trial of RAS showed effectiveness of both modalities of treatments. Adverse events were reported in Colchicine group (52.9%) compared to 11.8% in the Prednisolone group [68].

Other treatments of RAS

The use of **intra-lesional injections of steroids** in severe cases of RAS with large single ulcers affecting quality of life such as eating, talking and swallowing, can be considered. Immediate relief of pain and a significant improvement in healing time with a single session of **Carbon dioxide (CO2)** laser treatment in patients with minor RAS has been reported in randomised controlled trials [83,84] More recently injection of **Botulinum toxin** has been reported as effective in relieving pain [85]. However, they are directed at healing current ulcers, and concurrent systemic treatment is usually needed for prevention of new ulcers

Table 3. Recommended treatments in three different types of RAS Effectiveness of treatment to be monitored in every patient by use of Ulcer Severity Score [51] and OHIP quality of life score [52]. There is not as yet an evidence based consensus for protocols.

	First line treatment	2nd line treatment	maintenance treatment
Minor RAS	For three months Local steroid mouthwash four times a day when ulcers present, twice daily when not.	Colchicine 500-1000 ugm/day for three to six months	Local steroid mouthwash four times a day when ulcers present,
Major RAS	Colchicine 500-1000 ugm/day for 6 months. Short course of systemic steroids may precede	Azathioprine 50-100 mg/day	Local steroid mouthwash four times a day when ulcers present
Herpetiform RAS	Tetracycline mouthwashes four times a day when ulcers	Colchicine 500-1000 ugm/day for 3-6 months	Tetracycline mouthwashes four times a day in prodrome
RAS in children	Hydrocortisone hemisuccinate pellets 2.5mg four times daily	Local steroid mouthwash four times a day when ulcers present,	Continue for 3 months, twice daily if no ulcers

Conclusions

A variety of treatments for RAS abound in Oral Medicine, but even with what have become standard therapies such as local steroids, there are few clinical trials. The failure to standardize clinical diagnoses, and the failure to have robust clinical severity scores for RAS has lead to reporting a variety of clinical outcomes. The use of an ulcer severity score should allow both the severity of the entry of patients with RAS to be compared, but also the effectiveness of treatments to be followed on a routine basis. The recent report that an evidence based review of treatments was not possible because of the variety of outcomes used, emphasises the need for agreed outcome measures.

A second issue in the literature is the failure to clearly distinguish between treatments designed to heal current ulcers and the much more difficult challenge of preventing new ulcer episodes. Almost any anti-bacterial agent, or anti-inflammatory agent can be expected to aid healing and pain, but few would be expected to prevent new ulcers episodes. Local steroid mouthwashes appear to be efficacious and the topical therapy of first choice, and there is evidence that local steroid mouthwashes can reduce the ulcer frequency as well as aid healing of current ulcers.

Prevention of new ulcers normally requires systemic therapy. There was strong evidence in the majority of the studies that supported the efficacy and safety of Colchicine in the management of RAS in spite of a high proportion of gastric upsets at the doses used. However, the majority of the studies were for a short period (3-6 months) and there was a lack of a randomised clinical trial with a good sample size. Thalidomide demonstrated conclusive benefits with a dose of 50-150mg/day in the managements of Major RAS, but should not be a treatment of first choice. Azathioprine is relatively untried in Major RAS and would not seem to be the agent of first choice in minor RAS. Pentoxifylline and dapsone appear worthy of further trials for efficacy. A suggested protocol is seen in table 3.

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