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Dent Clin N Am 49 (2005) 31–47

THE DENTAL
CLINICS
OF NORTH AMERICA

Recurrent aphthous stomatitis

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Recurrent aphthous stomatitis (RAS) is the most common ulcerative disease of the oral mucosa making the diagnosis and management of these recurring oral lesions common problems in general and specialty dental practice. RAS is an ulcerative disease that most often occurs in otherwise healthy individuals and presents as a painful lesion of the buccal and labial mucosa and tongue. Involvement of the heavily keratinized mucosa of the palate and gingiva is much less common. Lesions that clinically resemble RAS can result from a number of diseases such as Behçet's disease, neutropenia, anemia, or immune deficiency or gastrointestinal diseases such as Crohn's disease and ulcerative colitis. One responsibility of a clinician managing oral disease is to distinguish systemic disease from localized RAS.

Several factors have been proposed as possible causative agents of RAS. These proposed causes include local factors, such as trauma in individuals who are genetically susceptible to RAS, microbial factors, nutritional factors, such as deficiency of folate and B-complex vitamins, immunologic factors, psychosocial stress, and allergy to dietary constituents. Extensive research has focused predominantly on immunologic factors, but a definitive etiology of RAS has not been conclusively established.

RAS is classified into minor, major, and herpetiform ulcers. More than 85% of RAS presents as minor ulcers that are less than 1 cm in diameter and heal without scars (Fig. 1). Ulcers in major RAS, also known as Sutton's disease or periadenitis mucosa necrotica recurrens, are larger than 1 cm in diameter, persist for weeks to months, and heal with scars (Fig. 2). Herpetiform ulcers are clinically distinct because they appear as clusters of multiple ulcers scattered throughout the oral mucosa; despite the name,

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doi:10.1016/j.cden.2004.08.001 dental.theclinics.com

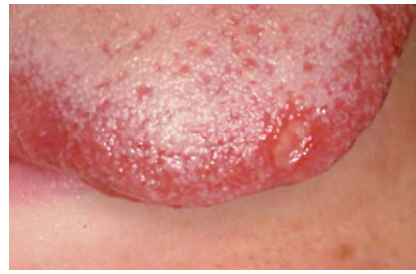

Fig. 1. A 21-year-old women with a 3-day-old lesion of minor RAS of the tongue. Note the symmetrical nature of the lesion and the inflammatory halo.

these lesions have no association with herpes simplex virus. General characteristics of the three types of RAS are summarized in Table 1.

Management of RAS depends upon the frequency and severity of the lesions. Most cases can be adequately managed with topical therapy, but systemic therapy is available for patients with major RAS or those who experience large numbers of minor lesions.

Epidemiology

Approximately 20% of the general population is affected by RAS, but incidence varies from 5% to 50% depending on the ethnic and socioeconomic groups studied [1]. Epidemiologic studies have shown that the prevalence of RAS is influenced by the population studied, diagnostic criteria, and environmental factors [2,3]. In children, prevalence of RAS may be as high as 39% and is influenced by the presence of RAS in one or both parents [3]. Children with RAS-positive parents have a 90% chance of developing RAS compared with 20% in those with RAS-negative parents [4]. In children of high socioeconomic status, RAS is five times more

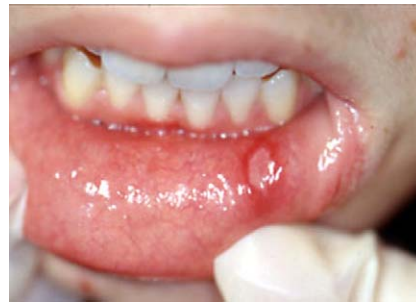

Fig. 2. A 17-year-old patient with an aphthous ulcer of the labial mucosa. This patient did well with topical fluocinonide gel therapy.

Table 1
Characteristics of the three types of recurrent aphthous stomatitis

Characteristic	Minor	Major	Herpetiform
Gender predilection	M = F	M = F	F > M (usually)
Age of onset (years)	5–19	10–19	20–29
Number of ulcers	1–5	1–10	10–100
Size of ulcers (mm)	<10	>10	1–2 (larger if coalesced)
Duration (days)	4–14	>30	<30
Recurrence rate (months)	1–4	<1	<1
Site predilection	Lips, cheeks, tongue, floor of mouth	Lips, cheeks, tongue, palate, pharynx	Lips, cheeks, tongue, pharynx, palate, gingiva, floor of mouth
Permanent scarring	Unusual	Common	Unusual

Data from Porter SR, Scully C, Pedersen A. Recurrent aphthous stomatitis. Crit Rev Oral Biol Med 1998;9(3):306–21.

prevalent and represents 50% of oral mucosal lesions in this cohort [5]. Activities of daily living affect the prevalence of RAS. RAS prevalence was higher (male, 48.3%; female, 57.2%) among professional-school students than in the same subjects 12 years later when they had become practicing professionals. This finding led some investigators to theorize that stress during student life is a major factor in RAS, although the difference in age groups should also be considered (Fig. 3).

The onset of RAS seems to peak between the ages of 10 and 19 years before becoming less frequent with advancing age and does not seem to depend on geographic influences, age, gender, or race [6]. RAS beginning or worsening well into adult life should increase suspicion that the oral ulcers are being caused by an underlying medical disorder such as hematologic, immunologic, or connective tissue disease or Behçet's syndrome.

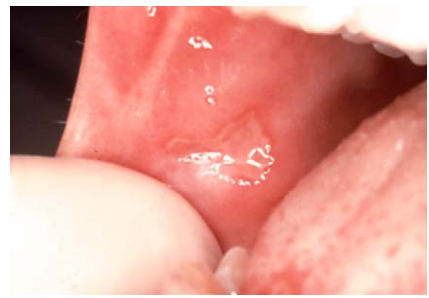

Fig. 3. A major aphthous ulcer of the buccal mucosa. Extensive laboratory testing demonstrated no evidence of an underlying medical disease.

Predisposing etiologic factors

The etiology of RAS lesions is unknown, but several local, systemic, immunologic, genetic, allergic, nutritional, and microbial factors have been proposed as causative agents (Table 2).

Local factors

Local trauma is regarded as a causative agent for RAS in susceptible individuals [7]. Trauma predisposes to RAS by inducing edema, early cellular inflammation associated with an increased viscosity of the oral submucosal extracellular matrix [8]. Not all oral trauma lead to RAS, because denture wearers are usually three times more susceptible to oral mucosal ulceration, but RAS is not the most prevalent ulceration in this cohort [9]. In addition, habitual smokers who constantly expose their oral mucosa to nicotine have demonstrated a negative association between smoking and RAS [10–13];

Table 2
Etiologic factors associated with recurrent aphthous stomatitis

Local	Trauma
	Smoking
	Dysregulated saliva composition
Microbial	Bacterial: streptococci
	Viral: varicella zoster, cytomegalovirus
Systemic	Behçet's disease
	Mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome
	Crohn's disease
	Ulcerative colitis
	HIV infection
	Periodic fever, aphthosis, pharyngitis, and adenitis (PFAPA) or Marshall's syndrome
	Cyclic neutropenia
	Stress, psychologic imbalance, menstrual cycle
Nutritional	Gluten-sensitive enteropathy
	Iron, folic acid, zinc deficiencies
	Vitamin B_1, B_2, B_6, and B_{12} deficiencies
Genetic	Ethnicity
	HLA haplotypes
Allergic/immunologic	Local T-lymphocyte cytotoxicity
	Abnormal CD4:CD8 ratio
	Dysregulated cytokine levels
	Microbe-induced hypersensitivity
	Sodium lauryl sulfate sensitivity
	Food sensitivity
Other	Antioxidants
	Nonsteroidal anti-inflammatory drugs
	Beta blockers

Data from Ship JA. Recurrent aphthous stomatitis. An update. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996;81(2):141–7.

thus local trauma predispose to RAS only those individuals who have a hereditary predilection to the disease.

Some changes in salivary composition, such as pH, that affect the local properties of saliva and a stress-induced rise in salivary cortisol have been correlated with RAS [14]. Although direct association of salivary gland dysfunction with RAS has not been demonstrated [15], patients with a combination of RAS and xerostomia may experience increased symptoms.

Microbial factors

Several well-designed studies have demonstrated that RAS is not caused by herpes simplex virus although both laymen and some clinicians confuse RAS with herpes simplex virus infection [16]. Herpes simplex virus virons and antigens have neither been identified in aphthous lesions [17] nor successfully isolated in RAS biopsy tissues [18]. Although it has been suggested that reactivation of varicella zoster virus or human cytomegalovirus is associated with frequent recurrence of aphthous ulcers [19], evaluation of biopsy tissue of RAS with polymerase chain reaction (PCR) for possible involvement of human herpes virus 6, cytomegalovirus, and varicella zoster virus as causative factors did not find evidence to support the role of these viruses in the pathogenesis of RAS [20]. Thus, it is the clinician's responsibility to distinguish RAS from recurrent herpes infections and to reassure RAS patients that they do not have an infectious disease and that antiviral therapy is not necessary or effective [16,17].

It has been proposed that *Helicobacter pylori* may have a causative role in RAS because it is a common risk factor for gastric and duodenal ulcers. Studies using molecular techniques have demonstrated *H pylori* in both affected and nonaffected mucosa of RAS patients and found no association with RAS [21,22]; thus patients with stomach ulcer may not be unusually susceptible to RAS even though both diseases have been linked to dysregulated immune functions.

There have been considerable speculations regarding the possible involvement of Streptococci species in the etiology of RAS especially *S sanguis* 2A [23]. The hypothesis proposed is that oral streptococci act as antigenic stimulants that cross-react with mitochondrial heat shock proteins of oral keratinocytes; this reaction induces a T-cell–mediated immune response that causes oral mucosal damage [24]. This theory is still unproven. Epstein-Barr virus (EBV) and lactobacillus are other organisms that have been studied in RAS patients. A study of the possible role of lactobacillus in RAS has yielded no significant finding [25], but in a small study EBV was associated with epithelial cells of preulcerative RAS [26]. Using PCR techniques, 39% of preulcerative RAS lesions were positive for EB-DNA. Their peripheral blood lymphocytes and serum were also positive for EB-DNA. The report suggested that lymphocytes may serve as reservoir for latent

EBV infection and viral shedding into the plasma. A causal relationship between EB viral load and RAS was not evaluated.

Underlying medical disease

Several medical disorders are associated with oral ulcerations that resemble RAS (see Table 2). Most prominent is Behçet's syndrome, characterized by recurring oral ulcers, recurring genital ulcers, and eye lesions. Behçet's syndrome is a multisystem disorder [27] resulting from vasculitis of small and medium-sized vessels and inflammation of epithelium. The abnormal inflammatory response in Behçet's syndrome is caused by immune complexes induced by T lymphocytes and plasma cells [28]. Behçet's syndrome usually affects adults, but a number of cases have been reported in children [29].

Clinicians have long been interested in how to distinguish between RAS and Behçet's disease. Recently, a high titer of anti-*Saccharomyces cerevisiae* antibodies (ASCA) has been detected in Behçet's patients compared with RAS patients and apparently healthy individuals [30]. The report suggested that ASCA test might be a method to distinguish between these two patient populations. This distinction may not be as simple as reported, because up to 70% of patients with Crohn's disease and 15% of patients with ulcerative colitis are ASCA positive. Both diseases are associated with RAS.

Another variant of Behçet's syndrome that includes relapsing polychondritis, a disorder characterized by mouth and genital ulcers with inflamed cartilage, has been labeled MAGIC syndrome [31,32].

Inflammatory bowel diseases such as Crohn's disease and ulcerative colitis have been associated with oral ulcers that may resemble RAS, but Crohn's lesions often have indurated borders and are histologically different because of the granulomatous nature of the lesion [33]. Approximately 10% of patients with Crohn's disease have oral mucosal ulcers, and the oral manifestations occasionally precede intestinal symptoms [34,35]. Some researchers believe inflammation of minor salivary glands to be the cause of the oral ulcers (Fig. 4) [36].

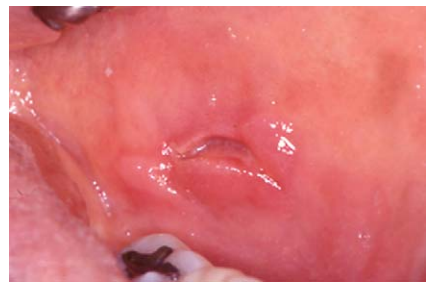

Fig. 4. Lesion of the buccal mucosa in a patient with Crohn's disease.

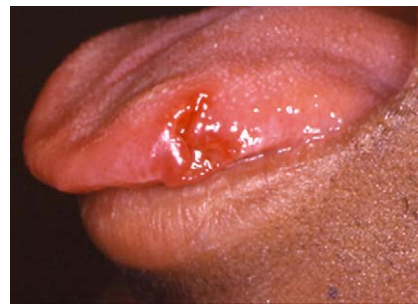

Fig. 5. An aphthouslike ulcer of the tongue in a patient with advanced HIV disease.

In HIV-positive individuals, RAS occurs more frequently, lasts longer, and causes more painful symptoms than in healthy individuals and is a common finding in HIV-positive children (Fig. 5) [37,38]. RAS is usually a late finding in AIDS patients with CD4+ lymphocyte counts below 100 cells/mm^3, but it may occasionally be a presenting sign of HIV infection.

Cyclic neutropenia, a rare disorder that presents at childhood, is also associated with recurring oral ulcers during periods when the neutrophil count is severely depressed [39]. Another condition described as periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) or Marshall's syndrome has a presentation similar to that of cyclic neutropenia and is commonly associated with oral ulcers that cannot be distinguished from RAS [40,41].

Hereditary and genetic factors

The role of heredity is the best-defined underlying cause of RAS.

Susceptibility to RAS is significantly increased by its presence in one or both parents [3]. Studies of identical twins also have demonstrated the hereditary nature of this disorder [42]. When patients have a positive family history of RAS, they tend to develop RAS at an early age. Specifically, children with RAS-positive parents have a 90% chance of developing RAS [4]. Their RAS lesions appear more frequently and demonstrate more severe symptoms. Certain genetically specific HLAs have been identified in RAS patients: HLA-A2, HLA-B5, HLA-B12, HLA-B44, HLA-B51, HLA-B52, HLA-DR2, HLA-DR7, and HLA-DQ series. A confounding finding is that certain ethnic groups have been associated with different HLA alleles or haplotypes [43–46], with no HLA consistently associated with RAS. More studies are still needed to clarify the variability of RAS in host susceptibility.

Allergic factors

Allergy has been suspected as a cause of RAS, and hypersensitivity to certain food substances [47], oral microbes such as *Streptococcus sanguis* [23], and microbial heat shock protein [48] have been suggested as possible

causative factors, although there remains no strong evidence that allergy is a major cause of this disorder. Although some studies have reported that RAS patients tend to have a higher hypersensitivity to environmental allergens, other reports did not find significant correlation between hypersensitivity and RAS. In one report, patients wearing nickel-based orthodontic appliances developed RAS that coincided with fitting of the appliance; the mucosal lesion regressed when the appliance was replaced with a nickel-free type. RAS in this population was attributed to the systemic effect of ingested nickel rather than direct contact, because a patch test to nickel sulfate did not reactivate the mucosal ulceration [49]. In patients presenting with refractory cases of RAS and known allergy to food items such as milk, cheese, and wheat, sequential elimination of these dietary items has been found beneficial in a small subset of RAS patients, thereby suggesting a possible link between food allergy and some cases of RAS [50].

The denaturing effect of sodium lauryl sulfate (SLS) commonly found in toothpastes has also been discussed as a cause of RAS. It was proposed that SLS may erode the oral mucin layer, exposing the underlying epithelium, and thereby making the individual more susceptible to RAS [51,52]. This theory is questionable, because a more recent study demonstrated that use of SLS-free toothpastes did not affect development of new lesions in RAS patients [53].

Immunologic factors

For the past 30 years, much of the research on the cause of RAS focused on detecting an abnormality in the immunologic response. Early work suggested a relationship between several immune-mediated reactions and development of RAS. These reactions include cytotoxicity of T lymphocytes to oral epithelium, antibody-dependent cell-mediated cytotoxicity, and defects in lymphocyte subpopulations [54–57]. One theory is that multiple immune reactions cause damage induced by deposition of immune complexes within the oral epithelium. More recent studies have shown an association between RAS severity and abnormal proportions of CD4+ and CD8+ cells [58], alteration of the CD4+:CD8+ ratio [59], and elevated levels of interleukin 2, interferon gamma, and tumor necrosing factor–α (TNFα) mRNA in RAS lesions [60]. Immunohistochemical studies of RAS biopsy tissues have demonstrated numerous inflammatory cells with variable ratios of CD4+:CD8+ T lymphocytes depending on the ulcer duration. CD4+ cells were more numerous during the preulcerative and healing stages, whereas CD8+ cells tended to be more numerous during the ulcerative state of the ulcer [61]. Similar studies on nonaffected sites were negative, making researchers focus more on the theory that RAS may be caused by an antigen-triggering effect. Because levels of serum immunoglobulins and natural killer cells are essentially within normal limits in RAS patients, the focus is still on a dysregulated, local, cell-mediated immune response conducive to

accumulation of subsets of T cells, mostly CD8+ cells. The local immune response causes eventual tissue breakdown that manifests as RAS.

Nutritional factors

The role of nutritional deficiency as a cause of RAS has been highlighted by the association of a small subset of 5% to 10% of RAS patients with low serum levels of iron, folate, zinc, or vitamins B_1, B_2, B_6, and B_{12} [62–64]. Some of these nutritional deficiencies may be secondary to other diseases such as malabsorption syndrome [65] or gluten sensitivity associated with or without enteropathy [66–68]. Hematologic screening of RAS patients for anemia or deficiency of iron, foliate, and B vitamins is appropriate for patients with major RAS or cases of minor RAS that worsen during adult life [69,70]. A deficiency of calcium and vitamin C has also been recently proposed in patients with RAS, but these findings were in association with vitamin B_1 deficiency, supporting the idea of combined nutritional deficiency in RAS patients [70]. The recovery of some RAS patients after treatment of the nutritional deficiency has further corroborated the causative role of nutritional deficiency in a subset of RAS patients [71].

Psychologic stress

Stress and psychologic imbalance have been associated with RAS [14,72]. In women, appearance of RAS may coincide with menses [73]. Stress of student life may be the precipitating factor for the higher prevalence of RAS in a cohort of professional students [74]. A clinician should consider questioning patients with worsening episodes of RAS regarding psychosocial or environmental stress.

Other factors

The role of antioxidants in RAS is currently attracting attention because blood levels of antioxidants such as erythrocyte superoxide dismutase and catalase seem to be higher in patients with RAS and Behçet's syndrome than in normal controls [75], but their causative roles in RAS are yet to be clearly defined.

There also have been several reported cases of drug-induced RAS. A recent case-control study associated a higher risk of RAS with drug exposure and found significant association with nonsteroidal anti-inflammatory drugs and β-blockers [76]. The medication history and current medications of RAS patients should be closely scrutinized to identify any pattern associated with the frequency and duration of RAS lesions.

Clinical manifestation and pathogenesis

RAS patients usually experience prodromal burning sensations that last from 2 to 48 hours before an ulcer appears. Ulcers are round with

well-defined erythematous margins and a shallow ulcerated center covered with yellowish-gray fibrinous pseudomembrane. Like viral ulcers, RAS ulcers are symmetric but do not have tissue tags as seen in irregular ulcers such as erythema multiforme, pemphigus, and pemphigoid. Although multiple ulcers may be present, the number, size, and frequency vary. RAS ulcers usually develop on nonkeratinized oral mucosa, the buccal and labial mucosa being the most common sites. They last approximately 10 to 14 days without scar formation (see Table 1). Microscopic characteristics of RAS are nonspecific. The preulcerative lesion demonstrates subepithelial inflammatory mononuclear cells with abundant mast cells [77], connective tissue edema, and lining of the margins with neutrophils. Damage to the epithelium usually begins in the basal layer and progresses through the superficial layers, leading eventually to ulceration and surface exudate. The presence of extravasated erythrocytes around the ulcer margin, subepithelial extravascular neutrophils, numerous macrophages loaded with phagolysosomes, and the nonspecific binding of stratum spinosum cells to immunoglobulins and complements may be a result of vascular leakage and passive diffusion of serum proteins. These findings suggest that pathogenesis of RAS may be mediated by immune complex vasculitis [78,79].

Management

The proper treatment of RAS depends on the frequency, size, and number of the ulcers. Patients who experience occasional episodes of minor aphthous ulcers experience significant relief with appropriate topical therapy. Symptoms resulting from occasional small lesions are often adequately controlled with use of a protective emollient such as Zilactin (Zila Pharmaceuticals, Phoenix, Arizona) or Orabase (Bristol Myers Squib, Princeton, New Jersey), used either alone or mixed with a topical anesthetic such as benzocaine. Other topical agents that can minimize patient discomfort include diclofenac, a nonsteroidal anti-inflammatory drug, or amlexanox paste, which has been also been shown to decrease the healing time of minor aphthae [80].

In patients with more frequent or more severe disease, use of a topical glucocorticoid is an effective therapy to decrease both the size and healing time of the ulcers, especially when the medication is used early in the developing stage of the lesion. Patients should be counseled regarding the proper use of high-potency topical steroids and be instructed to place only small amounts of the medication on the areas of involved mucosa; this precaution will significantly decrease the chance for side effects such as candidiasis. Some clinicians advocate mixing high-potency steroids with an adhesive such as Orabase. When patients have large, slowly healing lesions of major RAS, topical steroids may not be effective, and use of intralesional steroids is helpful in decreasing the healing time.

Topical antibiotics have been advocated as therapy for RAS for more than 40 years [81,82]. Tetracycline mouth rinses have been reported to decrease both the healing time and the pain of the lesions in several trials, but the association of these rinses with oral candidiasis and reports of allergic reactions have limited the use of this form of therapy. The effectiveness of topical tetracycline may result from a combination of the antibacterial and the anti-inflammatory effects of this group of antibiotics. More recently, a placebo-controlled study of the topical use of penicillin G troches to treat minor RAS showed efficacy in reducing both pain and the healing time RAS [83]. The risk of allergic reactions from this potentially useful form of therapy has not been determined in studies involving large numbers of RAS patients.

Although topical therapy is sufficient treatment for most RAS patients, topical therapy alone does not decrease the formation of new lesions and may not be sufficient treatment for patients with major RAS or patients who experience frequent episodes of multiple minor RAS. Systemic therapy should be considered for this relatively small group of patients, but the potential benefit of the drug should always be carefully weighed against potential side effects, and systemic therapies should be used by clinicians trained in their use.

A short course of systemic corticosteroids such as prednisone may occasionally be used to treat a particularly severe episode of major RAS, but long-term use of systemic steroids is rarely, if ever, indicated because the serious side effects of long-term steroid therapy outweigh the benefits for RAS patients [84]. Because systemic steroids are indicated only occasionally, clinicians who treat patients with major RAS have been searching for a substitute that will prevent formation of new RAS as well as reduce or eliminate any serious side effects. Medications that have demonstrated potential effectiveness in reducing the formation of new lesions include pentoxifylline (PTX), colchicine, and thalidomide.

PTX, a methylxanthine related to caffeine, has been used for many years to treat intermittent leg cramps in patients with peripheral vascular disease. PTX improves the circulation of blood to the extremities by increasing the flexibility of red blood cells, making it easier for them to squeeze through atherosclerotic vessels. PTX has also been shown to decrease inflammation by its effect on white blood cell function and inflammatory cytokines, making it a useful therapy for inflammatory diseases such as rheumatoid arthritis, vasculitis, and diabetic leg ulcers. There have been several reports of the successful use of PTX, 400 mg three times/day, in the management of RAS. More than 60% of patients in one open clinical trial showed significant improvement and no major side effects while receiving PTX therapy [85,86].

Another drug that has been advocated for management of major RAS is colchicine, which has been used for decades to manage gouty arthritis. Because colchicine has anti-inflammatory activity and inhibits cell-mediated response, it has proven useful in the management of a number of dermatologic

diseases including psoriasis, Behçet's syndrome, dermatitis herpetiformis, and leukocytoclastic vasculitis. Although there have not been controlled clinical trials, open trials have shown encouraging results [87–89].

The medication that has been most carefully studied for the management of major RAS is thalidomide, a drug with a long history of major side effects including severe life-threatening and crippling birth defects. Thalidomide was originally marketed in Europe in the 1950s as a nonaddicting sedative but was withdrawn from the market when the risk of major teratogenic defects including phocomelia and neural tube abnormalities were discovered. Later, investigators discovered its potent anti-inflammatory and immunomodulating properties, so limited use of the drug was permitted for patients with recalcitrant diseases such as erythema nodosum leprosum and Behçet's syndrome.

Controlled clinical trials have demonstrated the effectiveness of thalidomide in treating major RAS in HIV-infected patients and in otherwise normal individuals. Thalidomide therapy results in either complete remission or substantial improvement in a majority of major RAS patients [90–92]. To minimize the risk of birth defects resulting from thalidomide therapy, clinicians prescribing the drug must register in the System for Thalidomide Education and Prescribing Safety (STEPS) program. This program educates physicians and dentists on the proper use of the drug, provides counseling for patients, and closely monitors thalidomide use. For example, the program mandates that women in childbearing years must use two forms of birth control and have a monthly pregnancy test. In addition to birth defects thalidomide also may cause peripheral neuropathy, neutropenia, and drowsiness.

Other drugs that have been advocated for the management of major RAS not responding adequately to topical therapy include dapsone, a sulfone derivative which is used to manage a number of mucocutaneous disorders; azathioprine, an immunosuppressive drug; and etanercept, a recombinant TNF-soluble receptor that has been shown to be effective in managing rheumatoid arthritis and psoriasis [92–94]. With several basic science and clinical researchers focusing on RAS, it is anticipated that more effective medications will become available to treat RAS in the near future.

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