

Una mirada al tratamiento actual de la estomatitis aftosa recurrente: Revisión de la literatura

A look at the current management of recurrent aphthous stomatitis. Literature review

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Abstract

Recurrent aphthous stomatitis (RAS) is a chronic idiopathic ulcerative pathology, which, although it does not compromise the life of patients, it can impair their quality of life. It has a high incidence in the population with a high percentage of recurrence. In view of its importance, the aim of this review is to provide an update on pharmacological and laser therapies for the management of recurrent aphthous stomatitis. A literature search was performed in PubMed, Science Direct, EBSCO HOST and LILACS databases from January 2010 to October 2020, identifying publications in English and Spanish.

The articles that were included had to be related to aphthous stomatitis and its treatment, focusing on pharmacological or laser management. The search strategy yielded 4536 bibliographic citations, of which 19 were included in this review. Most of the studies were randomized clinical trials where the target population was adults that demonstrated the use of anti-inflammatory drugs, immunomodulators, monoclonal antibodies, antiseptics, anesthetics, among others, for the management of recurrent aphthous stomatitis. From the articles analyzed, it was possible to conclude

that pharmacological therapy should be established in a particular way, according to the clinical and patient history.

The first-choice drugs are of topical use, reserving those of systemic use for moderate or severe cases and for patients with refractory treatment. Likewise, adjuvant recommendations such as nutrition and hygiene can help in the resolution of the disease. Laser therapy emerges as an alternative treatment with low risk and positive results for recurrent aphthous stomatitis.

Keywords: Stomatitis, Aphthous; Oral Ulcers; Anti-Inflammatory Agents; Anesthetics; Laser Therapy (MeSH).

Resumen

La estomatitis aftosa recurrente (EAR) es una patología ulcerativa crónica idiopática, que, aunque no llega a comprometer la vida de los pacientes, si puede desmejorar su calidad de vida. Presenta una alta incidencia en la población con un alto porcentaje de recurrencia. Atendiendo a su importancia, el objetivo de esta revisión es brindar una actualización respecto a las terapias farmacológicas y con láser para el manejo de la estomatitis aftosa recurrente. Se realizó una búsqueda bibliográfica en las bases de datos PubMed, Science Direct, EBSCO HOST y LILACS desde enero de 2010 a octubre de 2020, identificando publicaciones en inglés y español. Los artículos que fueron incluidos debían estar relacionadas con la estomatitis aftosa y su tratamiento, enfocándose en el manejo farmacológico o con láser. La estrategia de búsqueda arrojó 4536 citas bibliográficas, de las cuales fueron incluidas 19 en esta presente revisión. La mayoría de los estudios fueron ensayos clínicos aleatorizados donde la población objeto fueron adultos que demostraron el uso de antiinflamatorios, inmunomoduladores, anticuerpos monoclonales, antisépticos, anestésicos, entre otros, para el manejo de la estomatitis aftosa recurrente. De los artículos analizados se pudo concluir que la terapia farmacológica debe ser instaurada de manera particular, de acuerdo a la clínica y antecedentes del paciente. Los fármacos de primera elección son de uso tópico, reservando los de uso sistémico para casos moderados o severos y para pacientes con tratamiento refractarios, asimismo, las recomendaciones coadyuvantes como alimentación e higiene pueden ayudar a la resolución de la enfermedad. La terapia láser surge como alternativa de tratamiento con bajo riesgo y buenos resultados para la EAR.

Palabras claves: Estomatitis aftosa, úlceras bucales, antiinflamatorios, anestésicos, terapia por láser (DeCS).

Introduction

Recurrent Aphthous Stomatitis (RAS) is a chronic inflammatory disease of multifactorial origin, characterized by the repetitive appearance of ulcers in the oral mucosa. Its incidence in the world population ranges from 6 to 66% (1) according to sociodemographic data, which is why it is considered the most prevalent ulcerative pathology (2,3).

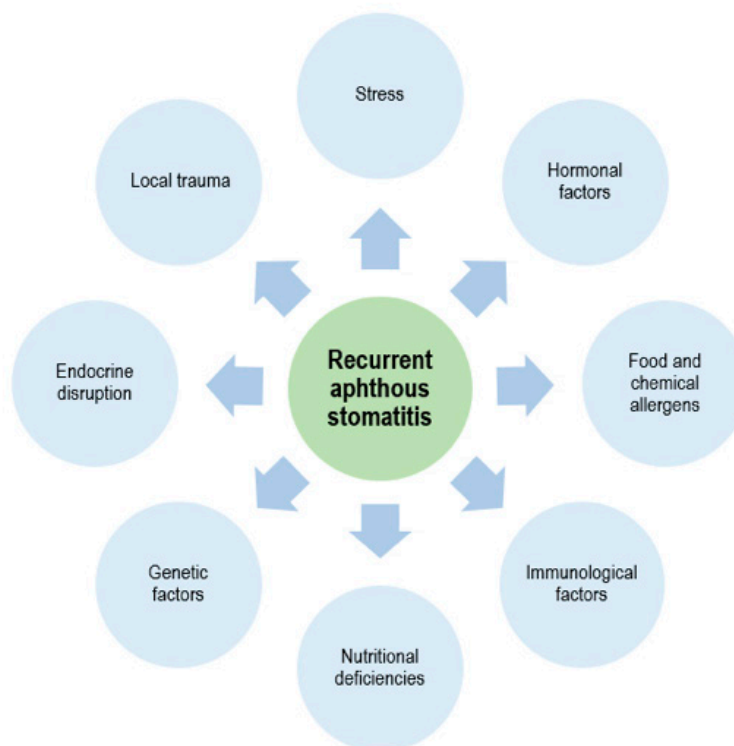
The term "aphthous ulcer" derives from the Greek "aphtha" which means ulcer of the oral mucosa (2), it can also be called "recurrent oral ulcers" or "recurrent oral aphthosis" (2), regularly, it has its peak incidence between 10 to 19 years of age, however, in adulthood it continues to occur and persists throughout life (2,4,5).

The pathogenesis of RAS is not entirely clear, different factors at the local and systemic level have been proposed that may influence the onset of the disease and the triggers vary from one individual to another. One of the hypotheses proposed is an immune response mediated by autoantibodies against the oral mucosal membrane, therefore, it is considered as a pathology with some degree of autoimmunity (5,6). In the same sense, the production of proinflammatory cytokine cascades triggered by some factor has also been studied, which initially provokes the activation of T lymphocytes and neutrophil chemotaxis (7). Tumor necrosis factor is also relevant in this process since it has been associated with the pathogenesis of this disease (8,9). In general, some etiological factors described are trauma, endocrine alterations and menstrual cycle, genetic predisposition, food allergens, chemical and microbial, among others (Figure 1) (3,10–12).

«The pathogenesis of RAS is not entirely clear, different factors at the local and systemic level have been proposed that may influence the onset of the disease and the triggers vary from one individual to another.»



Figure 1. Etiology of recurrent aphthous stomatitis.



The diagnosis is mainly based on the clinical manifestations of the disease; however, it is important to investigate if there is an association with underlying systemic pathologies, especially if it is of first appearance in adults (16). Paraclinical tests can be useful as complementary studies, therefore, the indication of a complete blood count is of great help, likewise, the indication of other tests for the measurement of levels of iron, ferritin, folic acid, zinc, magnesium, vitamins B1, B2, B6 and B12 can be useful, due to the association of their deficiencies with RAS (4,19,20).

The indication of biopsies is usually not necessary because the clinical manifestation of the disease is characteristic (21), however, in cases where ulcers have not resolved after 2 weeks of appearance, an incisional biopsy is considered to discard other pathologies (21), even when the histopathological study is not characteristic, it can help to discard other pathologies such as cancer and pemphigus (22). In initial stages it will reflect an inflammatory infiltrate with T lymphocytes and monocytes, while for more advanced stages the particularity will be to find nuclear polymorphous leukocytes in the center of the lesion (4,5).

Regarding the treatment of RAS, different studies have been carried out with a wide range of therapeutics; however, due to the fact that its etio-

pathogenesis is not well defined and to the large number of associated triggering factors, there is no single management with high effectiveness. In addition, its high incidence in the population and the recurrent periods of the pathology make it an object of interest. The aim of this work is to review the literature of the last 7 years regarding the pharmacological and laser treatment alternatives that have been published for RAS.

Materials and methods

A literature search was conducted in PubMed, Science Direct, EBSCO HOST and LILACS databases.

Eligibility Criteria

- Descriptive and analytical articles, clinical trials, and case reports on the use of pharmacological and laser therapy for the management of RAS.
- Articles published between January 2013 and October 2020
- Articles in English or Spanish

Other types of studies such as systematic reviews were excluded.

Search strategy

The search for articles was performed with 12 different combinations of keywords, all validated in health sciences descriptors (MeSH and DeCS). The keyword combinations were the following: "Stomatitis, Aphthous AND Laser Therapy"; "Stomatitis, Aphthous AND Analgesics"; "Stomatitis, Aphthous AND Stomatitis, Aphthous/physiology", "Stomatitis, Aphthous AND Therapeutics"; "Stomatitis, Aphthous AND Stomatitis, Aphthous/drug therapy"; "Stomatitis, Aphthous AND Adrenal Cortex Hormones"; "Stomatitis, Aphthous AND Antibodies, Monoclonal", "Stomatitis, Aphthous AND Histamine Antagonists"; "Stomatitis aphthous AND anaesthetics"; "Stomatitis, Aphthous AND Anti-Inflammatory Agents"; "Stomatitis aphthous AND Glucocorticoid".

Phase 1: articles were searched with the key words in the different databases, the titles were verified, and only those articles that contained the name of the pathology "recurrent aphthous stomatitis" were included, in this phase a total of 4536 articles were searched, but only 226 that met the inclusion criteria of the title were selected. The full texts were obtained. A total of 122 duplicate articles were eliminated, so only 104 articles were selected.

Phase 2: the abstract of each publication was evaluated; 43 articles were selected that contained information on the treatment of recurrent aphthous

stomatitis with drugs or laser in their abstract.

Phase 3: a review of the complete content of the 43 articles was carried out and 19 publications were finally selected, corresponding to original articles and clinical cases whose objective was to communicate the effect of drugs or lasers for the treatment of RAS.

Results

Through the search strategy, a total of 4536 articles were traced, of which 19 were selected for the review, most of the studies were randomized controlled clinical trials and the most frequent population to intervene were adults. Some case reports were selected due to the relevance of the treatment.

A number of studies were conducted in America such as the United States and Brazil (21), some Asian countries such as Iran and India and others in Europe such as Turkey (22). The individuals participating in the interventions were from urban areas and controlled in hospitals or universities. The patients selected in the investigations did not usually present any association with other pathologies (see Table 1 and 2)).

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Table 1. Characteristics of selected items.

Author	Type of study	Treatment	Population	Effect
Gasparini J y cols. (2018)	Randomized clinical trial.	Topical Ropivacaine alone and combined with other substances	80 patients Over 18 years of age Healthy	Reducción de síntomas y cicatrización más rápida
Yarom N y cols. (2017)	Randomized, double blind, clinical trial	Minocycline in oral rinse (0,5%), (0,2%)	14 patients Over 18 years of age Healthy	Pain reduction
Ofluoglu y cols. (2017)	Randomized, double-blind, controlled clinical trial	Glycerol triester oxide gel and triamcinolone acetonide cream	180 patients Over 18 years of age Healthy	Glycerol triester gel reduces pain and improves healing
Ozler y cols. (2014)	Randomized controlled clinical trial	Chlorhexidine rinse and sucralfate suspension	70 patients Over 20 years old Healthy	Sucralfate suspension reduces pain and improves wound healing
Qingxiang y cols. (2019)	Randomized controlled clinical trial	Thalidomide (100 mg/day) progressive tapering Prednisone 0, mg/kg/day	60 patients Over 18 years of age Healthy	Thalidomide improves the time to recurrence of RAS
Bardellini y cols. (2020)	Randomized controlled clinical trial	Diode laser (wavelength 645 nm, power 100 mW, spot size 1 cm ² , 30s per cm ² , energy density 10 J / cm ² , continuous mode	60 patients 5- 12 years old	Reduction of pain and lesion size
Guney y cols. (2017)	Randomized clinical trial	Erbium laser (600 µm diameter, 6 mm length, non-contact mode).	40 patients Over 18 years old	Reduced pain and improved healing
Mekkadath (2016)	Randomized clinical trial	Amlexanox 5% cream Diode Laser (810 nm, 6 J/cm ² , 0.1 w, for 30 sec in non-contact mode	50 patients 15 - 55 years old	Reduction of lesion size
Akbari y cols. (2020)	Randomized clinical trial	Diphenhydramine and licorice solution	70 patients 18-60 years old	Pain reduction Reduction of healing time
Nosratzahi y cols. (2020)	Randomized clinical trial	Omega 3 1000 mg	50 patients Over 13 years old	Frequency and pain reduction
Martins y cols. (2017)	Double-blind experimental design	Probiotics	90 patients Between 18-60 years old	Pain reduction
Zeng Yang y cols (2020)	Retrospective observational study	Topical application of hyaluronic acid gel 0.2% twice daily. Topical dexamethasone three times a day (after food) per 5 days	104 patients Under 18 years of age	Reduction of pain and size of lesions
Liu y cols (2015)	Randomized clinical trial	Vitamin B12 Cream 500 mg, Triamcinolone 0.1%	42 patients Over 18 years of age Healthy	Pain reduction with Vitamin B12
Ghorbani y cols. (2020)	Randomized clinical trial	Zinc sulfate mucoadhesive tablet	42 patients 16-45 years old Healthy	Reducción del dolor y tamaño de las lesiones Reduction of pain and size of lesions
Mustafa y cols. (2018)	Pilot study	Er, Cr Laser: YSGG 0.5 W - 30 Hz, 30sec/lesion Triamcinolone acetonide 0.1% Cream 2 times/day/7 days	30 patients 18-27 years old Healthy	Pain reduction More effective laser

Source: Own elaboration

Table 2. Characteristics of selected case reports

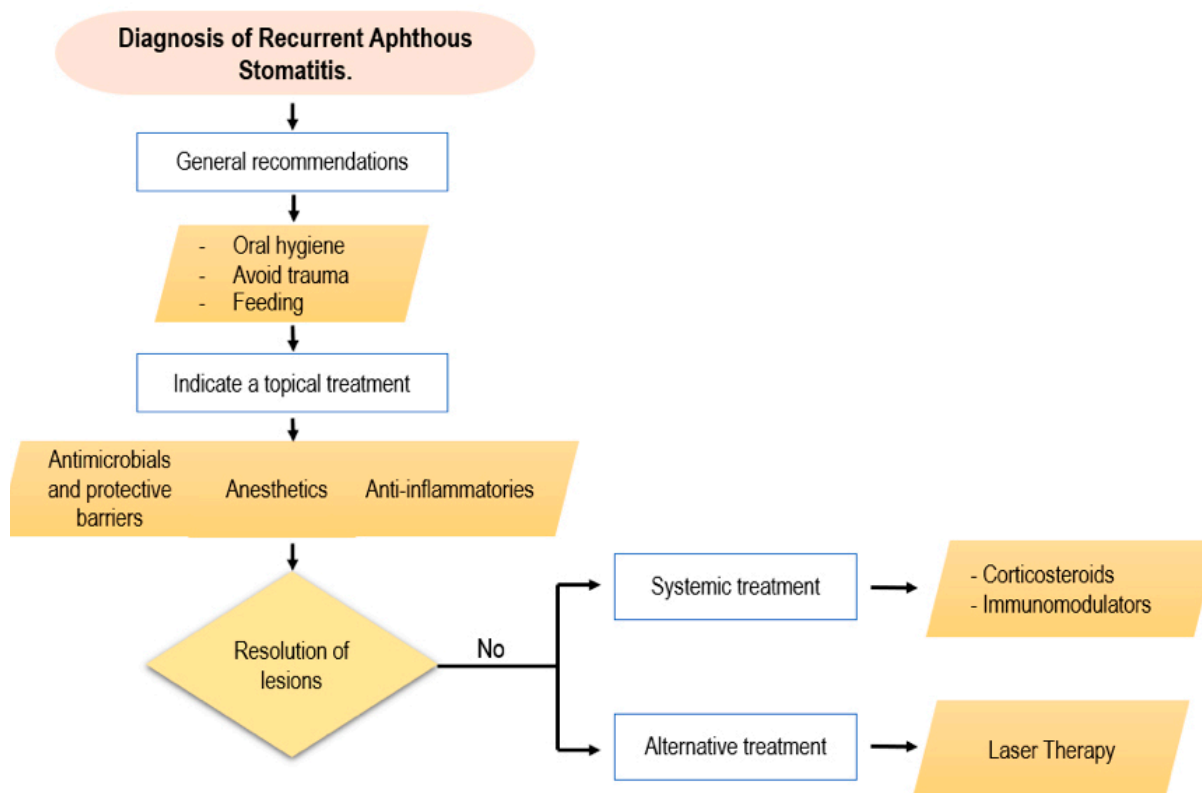
Author	Type of study	Medication	Population	Effect
De Perozans y cols. (2019)	Case Report	Adalimumab 80 mg subcutaneous	Male patient 17 years old Refractory Healthy	Frequency reduction. Injury resolution in severe cases
Schibler y cols (2017)	Reporte de caso	Apremilast 30 mg/12h/day	Male patient 60 years old Refractory Healthy	Frequency reduction. Injury resolution in severe cases
Rzepecki y cols (2019)	Case Report	Etanercept	Male patient 38 years old HIV + Refractory	Injury resolution. Prolongation of injury-free period
Sand y cols (2013)	Case Report	Adalimumab 40 mg two/month 8 patients etanercept 50 mg one/week. 9 patients (50%) were treated with a different TNF- α inhibitor (infliximab or golimumab) before finally obtaining a sustained reduction in disease activity.	18 patients Severe, refractory RAS	Resolution of lesions, prolongation of recurrence period. Side effects: headache, rash, anaphylaxis, infection, fatigue.

Source: Own elaboration

Treatments reported against recurrent aphthous stomatitis

According to the review carried out, it was observed that the objectives of the treatment of recurrent aphthous stomatitis (RAS) will be focused on reducing the duration of the lesion, frequency, severity and increasing the periods free of disease appearance (3). Each patient will be managed in a particular way due to the multiple related etiopathogenic factors (23). Therefore, it is not possible to establish the same therapeutic pattern for all individuals suffering from the disease and the treatment will be in accordance with the clinical characteristics and medical history of each patient (23,24). The therapeutic measures studied in this review are summarized in Figure 2.

Figure 2. Dental Management Protocol reported in the literature for recurrent aphthous stomatitis.



1. General measures

a. Oral hygiene

It is recommended to maintain a good oral hygiene, this avoids superinfections and allows an increase in the healing speed of the lesions (25), in addition, given that trauma is one of the etiological factors associated, the use of soft bristle toothbrushes is suggested, as well as a non-aggressive brushing technique (4). Although there is mention of the components of toothpastes and RAS, Kaya-Ozden et al (26) in 2020 found no association between these components and RAS.

b. Feeding

Some studies report the appearance of RAS with low levels of iron, vitamin B12, vitamin D, zinc, among others (27). Öztekin et al. found low serum levels of vitamin D in patients with oral aphthosis (28), while Volkov et al. (29) administered vitamin B12 in patients with severe RAS, obtaining reduction of pain, resolution of lesions in weeks and recurrence-free periods for up to 6 months. These antecedents suggest the effectiveness of indicating a balanced diet rich in these elements even when the patient's deficiency

has not been typified. On the other hand, it is important to highlight the identification of foods that may trigger episodes of this disease such as very hot and cold foods or added additives and preservatives (16,30).

2. Pharmacological management

The therapeutic regimen can be topical or systemic, the use of one or the other will be conditioned by the clinical condition of the patient. Topical treatment will be used for less complex cases, for example, patients with sporadic episodes of minor ulcerations where general recommendations and the localized use of some drugs can resolve the lesions. While systemic treatment will be used for individuals with severe events of major ulcers that limit feeding, recurrent periods of disease onset and those where topical drugs did not have a significant efficacy (3,23).

a. Topical Pharmacological Treatment

i. Anesthetics

Anesthetics have been one of the most widely used elements for pain management in patients with RAS. They are usually used in combination with other agents that act as a protective barrier for the tissues. Gasparini et al (31) in 2018, used Ropivacaine in patients with RAS obtaining immediate decrease in pain in those where it was applied, making it more manageable.

The most commonly used anesthetic is Lidocaine (1% or 2%) which can be used in spray or gel, however, to obtain greater control and better distribution in the desired area at the time of application, it is recommended to use the gel presentation. Benzocaine 20% as well as Ropivacaine, are other anesthetics that can be used for pain management, these can be combined with other substances that promote healing and avoid superinfection (31).

Among these other substances with which they can be combined we find Sucralfate, a complex of sucrose-aluminum hydroxide and sulfate, which acts as a protective barrier. Soylu-Özler et al (25) describe that Sucralfate favors healing and reduces pain in aphthous ulcers. Its use is recommended in the form of oral rinses 4 times a day for 1-2 minutes, it can also be mixed with aluminum hydroxide and even topical application of this compound on the lesion exclusively is recommended. It has a buffering effect that will prevent over-infection of the lesions (25).

ii. Topical anti-inflammatories

It has been suggested that corticosteroids can reduce the formation of autoantibodies and lysosomal activity, in addition, they have other actions such as reduction of leukocyte activity, hydrolytic enzymes, phagocytosis,

suppression of T cells, among others, hence their efficacy in the treatment of RAS (32). In general, they have good results in reducing the duration and severity of the lesions, but not so much in the recurrence of RAS.

Kuswah et al (33), in 2019, obtained a reduction in size, pain and erythema with topical application of 0.1% triamcinolone acetonide in patients with aphthous ulcers. In their results, a significant reduction of both pain and lesion size was evidenced between the 4th-7th day after application. Their results were compared with amlexanox 5%, used topically, both drugs were effective in the management of RAS (33). Abbasi et al. also compared both drugs for the management of aphthous ulcers, finding effectiveness of the drugs in reducing lesion size and pain intensity in the first 7 days (34).

Regarding the therapeutic protocol, the use of amlexanox in ointment form is recommended at a concentration of 5%, applied 2 to 4 times a day, while triamcinolone acetonide in Orabase at 0.1%, applied 3 to 4 times on the lesion, indicated especially on small and mild lesions (33,34).

Other corticosteroids used are fluocinolone acetonide and clobetasol propionate, both of which are more potent than triamcinolone. Both drugs can be used in cream form or in Orabase for localized lesions or in oral rinses when ulcers are multiple (19). The recommended use of fluocinolone is at a concentration of 0.025-0.05%, used 5 to 10 times a day. While clobetasol 0.025% should be used as a last option for the most severe or moderate cases (19).

Diphenhydramine is an H1 receptor antagonist that in combination with other agents can achieve pain reduction. Akbari et al. applied diphenhydramine in combination with licorice, which has anti-inflammatory and antimicrobial effects, achieving a reduction in pain levels and a reduction in the healing time of the lesions (35).

iii. Protective barriers and antiseptics

They have the function of adhering to the mucosa, reducing pain and maintaining tissue moisturization, it is suggested that they be used before each meal and before going to sleep. They can be combined with other substances such as corticoids, antihistamines, anesthetics, vitamins, and so on. (4).

Glycerol Triester Oxide has been used as a moisturizing and protective agent due to its ability to adhere to tissues through the formation of a lipid film (36), this layer allows the protection of tissues from mechanical trauma and, due to its anti-inflammatory properties it reduces pain. Ofluoglu et al.

in 2017, found a reduction in pain and size of ulcerative lesions in patients with RAS (24), also, when compared with the results of triamcinolone acetonide, a better score was obtained in the visual analog scale of patients after its application; the advantage over corticosteroids is that it does not have the side effects that the later ones have (24).

Hyaluronic acid (HA) is another substance used in RAS, it presents properties that favor cell migration and proliferation, as well as angiogenesis, favoring healing. Yang et al in 2020, concluded that HA reduces pain intensity as well as lesion size, however, there was no statistical difference with the results of dexamethasone. They emphasize that a greater number of studies should be carried out to confirm its efficacy (37).

As for antiseptics, they are adjuvants, they avoid the occurrence of superinfections on the lesions (25). The most popular is chlorhexidine, given its low cost and efficacy, it presents among its characteristics, the adhesion to salivary proteins that allow its gradual release for up to 24 hours after its absorption. It is anti-inflammatory due to its detergent and antioxidant properties (25).

Antibiotics such as penicillins or tetracyclines have also been used topically, especially in the form of mouthwashes. Minocycline has a regulatory effect on tumor necrosis factor α , which has already been described as a cytokine that may be related to RAS (38). Yarom et al. describe in their results a reduction of pain and improvement of healing after the application of minocycline 0.5% in rinses in aphthous ulcers (39).

The following is a list of topical drugs reported in the literature (see Table 3).

Table 3. Topical treatment drugs for Recurrent Aphthous Stomatitis Aftosa.

TOPICAL TREATMENT			
Drug	Dose	Benefit	Presentation
Anti-inflammatory agents			
Triamcinolone acetonide	0,1-0,5% 3 to 4 times applied	Reduction of swelling and pain	Cream
Fluocinolone acetonide	0,025 % 5 to 10 times a day	Reduction of swelling and pain	Cream
Clobetasol propionate	0.025% 3 to 4 times a day	Reduction of swelling and pain	Cream
Amlexanox	5% applied 3 to 4 times a day	Reduction of ulcer pain and size	Cream
Diphenhydramine	3 to 4 times a day	Reduced pain and improved healing speed	Rinses
Protective barriers and antiseptics or antimicrobial agents			
Chlorhexidine	0,2%	Pain reduction. Faster healing	Rinse or gel
Glycerol Triester	5%	Protective, pain reducing and moisturizing	Orabase
Hyaluronic acid	4 times a day	Reduces pain and improves healing speed	Orabase
Minocycline	0,2 – 0, 5%	Reduction of pain and lesion size	Rinse
Anesthetics			
Lidocaine	1 or 2% before each meal	Pain reduction	Spray or gel
Benzocaine	20% application before each meal	Pain reduction	Spray or gel
Ropivacaine	5% application before each meal	Pain reduction	Spray or gel

Source: own elaboration.

b. Systemic pharmacological treatment

Those patients who are refractory to treatment with severe or frequent episodes of RAS are candidates for systemic pharmacologic management; it can be combined with the use of topical medication to obtain better results. First-line medications will be corticosteroids, followed by immunomodulators as a second choice. In case of not obtaining a good efficacy, there are alternative treatments such as laser, homeopathy, traditional medicine, and

acupuncture, among others.

i. Anti-inflammatories and immunomodulators

To initiate systemic treatment, the following should be evaluated: clinical condition and degree of tolerance of the patient, highlighting the presence or absence of comorbidities and severity of episodes, history of refractory treatments, patient preferences and interdisciplinary management (3). Table 4 below shows the anti-inflammatory drugs most frequently used for the treatment of aphthous ulcers.

Table 4. Systemic treatment drugs for recurrent aphthous stomatitis.

SYSTEMIC TREATMENT			
Drug	Dose	Benefit	Presentation
Anti-inflammatory and immunomodulatory agents			
Prednisone	Initial dose 1.0 mg/kg	Pain reduction and remission	Compressed
Thalidomide	100 mg daily for 15 days	Complete remission	Compressed
Apremilast	30 mg every 12 hours	Pain reduction and recurrence	Compressed
Infliximab	3-5 mg daily	Severity reduction	Ampoule
Adalimumab	80 mg initial dose 40 mg dose for 2-6 weeks	Severity reduction	Ampoule

Source: own elaboration.

Among the anti-inflammatory agents we find Prednisone, this drug is also an immunosuppressant, associated with multiple side effects such as hyperglycemia, polyphagia, insomnia, arthralgia, gastrointestinal problems, among others, however, its results in the management of RAS are remarkable. Systemic treatment with Prednisone is a single starting dose of 1.0 mg/kg per day and then reduced within the following 7 to 14 days, considering taking a single dose per day or every other day (2).

Thalidomide and its analogues have been used as second-line drugs for the management of RAS. They possess immunosuppressive activity, regulating the activity of T lymphocytes, natural killer cell and inhibition of cytokines, in particular tumor necrosis factor. It has been described that they can reduce the number of lesions and pain (8).

Qingxiang et al (8) in 2019, demonstrated that Thalidomide prolongs the recurrence interval of RAS, as well as a reduction of pain and number of lesions. Their results were compared with Prednisone, for both cases, a good

response of patients to the drug was obtained, however, for Thalidomide a better disease recurrence period was obtained. The authors suggest the use of Thalidomide at an initial dose of 75 to 100 mg/d with a gradual reduction to avoid the side effects of this drug (8).

Apremilast is also used as an alternative drug in RAS. Schibler et al (40), reported a case managed with Apremilast in an individual with treatment-resistant RAS, after 12 months and having maintained a dose of 30 mg every 12 hours/day, the patient had no relapses (40). Kolios et al (41) in 2019, reported a reduction of disease activity in a series of retrospective refractory cases, however, they indicated gastrointestinal side effects, as well as headache and weight loss, which led to discontinuation of treatment in some individuals. In general, they recommend a dose of 30 mg every 12 hours daily with a gradual onset to start treatment (41).

ii. Monoclonal antibodies

They are glycoproteins produced by B cells that exert their activity in different ways, they can affect growth factor receptors and inhibit cell proliferation and apoptosis. They have also been described to generate antitumor activity through immunological mechanisms and to be transport vehicles for other drugs (3).

Infliximab is a murine monoclonal antibody that acts against TNF- α . Infliximab is administered at a dose of 3-5 mg/kg by IV every 2-6 weeks (3). Adverse effects observed with Infliximab include hypersensitivity infections, perfusion reaction, nausea, vomiting, dizziness, among others.

Another monoclonal antibody used is Adalimumab, which produces TNF- α inhibition and has greater affinity for it than Infliximab. It can be applied in the form of a subcutaneous ampoule with a half-life of up to 2 weeks. Perozans-Lobo et al (42), treated patients with severe refractory RAS with Adalimumab, after 6 weeks the active lesions had been resolved without recurrence at 12 months, however, the side effects of monoclonal antibodies are many, therefore their administration must be rigorous (43), in the case presented by Perozans-Lobo they did not describe side effects.

On the other hand, there is the use of drugs such as Etanercept, which acts on tumor necrosis factor and is used in rheumatic diseases (44). Rzepecki et al. in 2019 (44), administered Etanercept in patients with HIV and persistent RAS, obtaining good results after administration and complete resolution of ulcerations after 6 months.

3. Laser treatment

It is reported in the literature that the laser promotes healing (45), however, it is not entirely clear the mechanisms by which it works, it is believed that it has activity on the mitochondrial cytochrome and that when stimulated it generates ATP, used by the cell for its different activities (46,47), however, and despite its possible benefits, Hawkins et al. in 2008, report that the laser can generate damage on tissues, specifically on cellular DNA, so its use should be rigorous (48). Even when this risk exists, its use could be of greater benefit, among those described by Han et al. as: collagen production, vasculogenesis, cell growth and differentiation, among others (49).

Bardellini et al (47), using diode laser for RAS (wavelength 645 nm, power 100 mW, spot size 1 cm², 30s per cm²) (see table 1), reported a significant statistical difference in the reduction of pain and lesion size between the group managed with laser and placebo; they describe at 4 days a reduction of pain in favor of the laser group, as well as a smaller lesion size for this group in comparison with the placebo group (47). Mekkadath et al, (46) also obtained efficacy in the reduction of pain and improvement in healing with the implementation of diode laser (810 nm, 6 J/cm², 0.1 w, for 30 sec) in RAS (see table 1), although the latter author did not find a difference in results with Amlexanox.

4. Other treatments

Use of Omega 3 and probiotics

Another alternative treatment is the use of omega 3, Nosratzahi et al (50) in 2016, carried out the administration of omega 3 (1000 mg daily) in patients with RAS (see table 1), they affirm that there was a reduction of the associated symptomatology and changes in the frequency of the appearance of the disease from the 5th and 6th month of the beginning of the treatment. Khouli et al. also reported a decrease in the number of lesions, average level of pain and healing time, even with the results obtained, they recommend carrying out a greater number of studies to corroborate the efficacy of the treatment (51). It is believed that the mechanism of action of omega 3 is related to the capacity to inhibit the inflammatory process, through the regulation of leukocyte chemotaxis, production of proinflammatory cytokines, prostaglandins and endothelial junctions (50,51).

Martins et al. found a reduction in the average pain in patients who were administered probiotics for the management of RAS, establishing that their effect may be related to the modulation in the activity of nociception genes

such as cannabinoid receptors and also their intervention with the production of cytokines. As adverse effects of its use, they report gastrointestinal problems in patients (52). Trinchieri et al (53), when administering probiotics, found a reduction of pain in cases, without describing side effects.

Conclusions

The treatment for RAS should be individually developed according to the clinical characteristics and medical history of the patients. There is no defined and effective treatment for RAS. Topical drugs are the first choice for its management, while systemic drugs should be reserved for moderate or severe cases and patients with refractory treatments.

The use of topical corticosteroids shows good effectiveness in the management of associated symptomatology and improvement in healing time; however, it shows no effect on disease-free time.

Immunomodulators and monoclonal antibodies demonstrate efficacy in TNF control, thus, they demonstrate resolution of lesions in severe cases and prolong time to recurrence. Further studies should be carried out.

The laser improves the healing period; however, its mechanism of action and its effects should be further explored.

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The authors declare that there are no conflicts of interest.

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«The use of topical corticosteroids shows good effectiveness in the management of associated symptomatology and improvement in healing time; however, it shows no effect on disease-free time.»



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