BRITISH JOURNAL OF HOSPITAL MEDICINE

REVIEW

Management of orofacial granulomatosis

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Abstract

Orofacial granulomatosis is a chronic relapsing-remitting inflammatory condition that shares a similar phenotypic presentation to some other granulomatous diseases, particularly Crohn's disease. However, subtle clinical and pathological differences justify it as a separate disease entity. Previous studies have assessed the effectiveness of interventions used in the management of orofacial granulomatosis. This article reviews the management options available.

A literature search was conducted to identify studies, in English, which assessed the effect of non-pharmacological and pharmacological interventions in the treatment of orofacial granulomatosis. The interventions were categorised into dietary modification, pharmacological (topical, intralesional and systemic therapy), surgery and psychological. A combination of interventions is often required to effectively manage each patient. There is convincing evidence that diet plays a role in disease severity. In patients where dietary manipulation alone is unsuccessful, topical, intralesional and/or systemic treatment may be considered to manage the condition.

Key words: Crohn's disease; Dietary manipulation; Inflammatory bowel disease; Management challenges; Oral medicine; Orofacial granulomatosis

Submitted: 17 September 2022; accepted following double-blind peer review: 4 November 2022

Introduction

Orofacial granulomatosis is a rare chronic inflammatory condition of unknown aetiology primarily presenting with swelling, predominantly of the lips, but also involving the buccal mucosa, gingivae and floor of mouth (Wiesenfeld et al, 1985). Crohn's disease is also a chronic inflammatory condition, affecting any part of the gastrointestinal tract, including the oral cavity and perioral tissues. It is unclear whether orofacial granulomatosis is a separate disease or part of a spectrum with other granulomatous conditions. Orofacial granulomatosis may occur with concomitant symptoms of Crohn's disease of the gut. Patients with oral Crohn's disease, with or without gut involvement, often present with lip swelling and intraorally with sulcal ulceration, scarring and aphthous ulceration, and may have oral signs in isolation without gut involvement or may have a background of known Crohn's disease.

Gastroenterologists should be familiar with orofacial granulomatosis and the oral manifestations of Crohn's disease, as patients may first present to a gastroenterology clinic. These complex cases often require multidisciplinary input from oral medicine clinicians, gastroenterologists, dietetics, psychology and oral and maxillofacial surgery, so are often managed in specialist centres.

Aetiology

Orofacial granulomatosis presents in both children and adults with a median age of 23 years, with men and women being equally affected (Campbell et al, 2011a; Alawi, 2013). The aetiology remains uncertain with contributing factors including infection, hypersensitivity to various food preservatives and dental materials (Wray, 2000; Apaydin et al, 2004; White et al, 2006). Possible associations with *Mycobacterium tuberculosis*, *M. paratuberculosis* and *Borrelia burgdorferi* have been proposed (Apaydin et al, 2004). Patients with Crohn's disease have a relatively stable oral microbiome compared to the gut microbiome. Relative levels of *Streptococcus salivarius* in the oral microbiome were raised in both patients with orofacial granulomatosis and Crohn's disease compared to healthy controls (Goel et al, 2019).

How to cite this article:
Joshi S, Mawdsley J, Hullah E, Ormond M, Carey B. Management of orofacial granulomatosis. Br J Hosp Med. 2023. https://doi.org/10.12968/hmed.2022.0416

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There is mounting evidence to support an association between allergens such as benzoic acid and cinnamaldehyde in patients with orofacial granulomatosis (Wray, 2000; Sanderson et al, 2005; Al-Hamad et al, 2015). In a study of 264 patients, Wray (2000) demonstrated hypersensitivities to preservatives including benzoic acid, food additives, flavourings and perfume, proven by skin patch testing. Up to 82% of patients with isolated orofacial granulomatosis are atopic, in contrast to 15% of the general population, and may concomitantly have asthma, eczema, hay fever or oral allergy syndrome (Sanderson et al, 2005; Al-Hamad et al, 2015). The prevalence of atopy in patients with Crohn's disease was reported as 39%, which is significantly lower than in those with concomitant orofacial granulomatosis and Crohn's disease at 87% (Patel et al, 2013).

Presentation

Extraintestinal involvement is relatively common in Crohn's disease, with about 10% of patients having oral involvement (Vavricka et al, 2011). Orofacial granulomatosis most commonly presents with swelling of one or both lips, with a slight predilection for the lower lip (Campbell et al, 2011a). The swelling can persist for weeks to months, and may involve the submental, submandibular, buccal and zygomatic regions. There may be erythema of the overlying skin and cervical lymphadenopathy can occur in up to 20.4% (10/49) (Al Johani et al, 2010). The gingiva may be hypertrophied. The floor of the mouth can show hypertrophic changes, so-called 'staghorning' (Porter et al, 2017).

Both oral Crohn's disease and orofacial granulomatosis may present with ulceration and cobblestoning of the buccal mucosa (Figures 1 and 2) (Sanderson et al, 2005; Zbar et al, 2012). A propensity of 'posterior pattern' of disease involving the buccal and labial vestibules with sulcal ulceration and scarring at the back of the mouth has been described in those with Crohn's disease and an 'anterior pattern' with predominantly lip swelling and buccal involvement in those with orofacial granulomatosis (Campbell et al, 2011a).

Orofacial granulomatosis and inflammatory bowel disease

Ileocolonoscopy of 35 patients with orofacial granulomatosis revealed evidence of gut mucosal abnormalities in 54% (19/35), and 49% (17/35) had macroscopic evidence of either scattered aphthoid-type ulceration, erythema only or pleomorphic ulceration, most frequently affecting both the colon and ileum (Sanderson et al, 2005). Upper gastrointestinal endoscopy in six patients found aphthous duodenitis in one case and erythematous gastritis in three

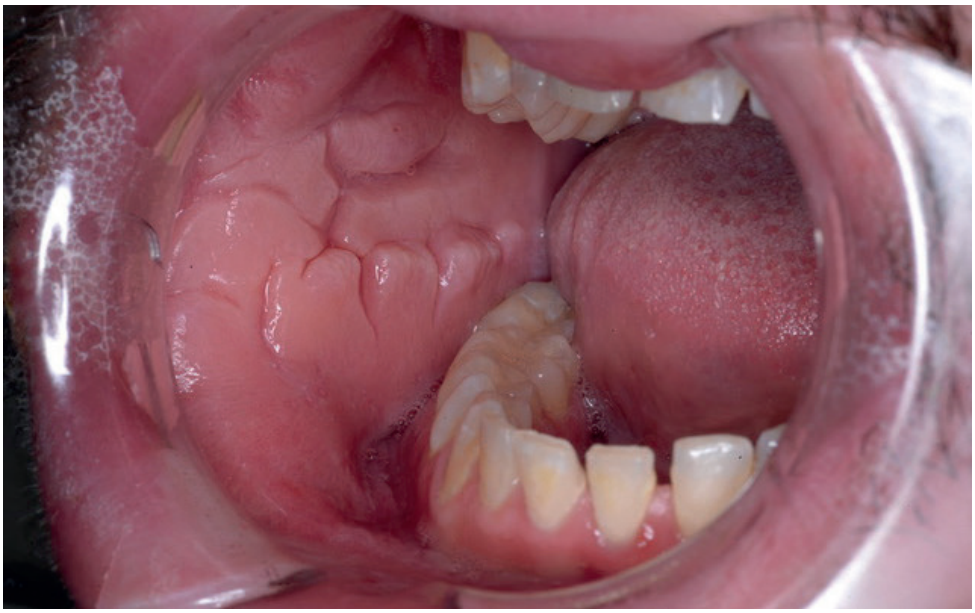

Figure 1. Cobblestoning of the right buccal mucosa.

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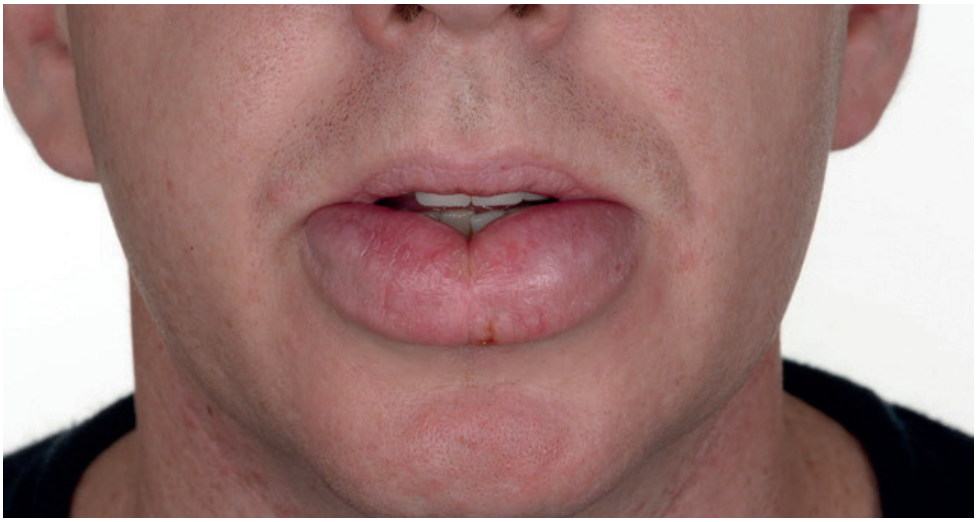

Figure 2. Pronounced enlargement of the lower lip.

cases. Histology of intestinal biopsies of the 19 patients with gut mucosal abnormalities on ileocolonoscopy showed evidence of neutrophilic infiltration in 79% (15/19) and granulomas in 68% (13/19) (Sanderson et al, 2005). Patients with orofacial granulomatosis without any gastrointestinal symptoms were more likely to develop intestinal involvement if onset of orofacial granulomatosis was <30 years of age (Sanderson et al, 2005). There was an estimated 24% probability of developing Crohn's disease in those presenting with orofacial granulomatosis before the age of 16 years, compared with ~10% in adulthood over a 10-year period (Campbell et al, 2011a).

Perianal involvement in Crohn's disease is common and a known predictor of severe disease but its relevance as a feature in patients with orofacial granulomatosis is not as well understood. In one retrospective study of 263 patients with orofacial granulomatosis, 55 patients had concomitant orofacial granulomatosis and Crohn's disease, of which 38 had perianal disease (Goel et al, 2015). All patients with orofacial granulomatosis and perianal disease had evidence of intestinal Crohn's disease.

Investigations

Haematological investigations (full blood count, ferritin, folate, vitamin B_{12}, iron studies, C-reactive protein, erythrocyte sedimentation rate, serum angiotensin converting enzyme) are useful and in patients with orofacial granulomatosis with no intestinal symptoms, these results are typically normal (Sanderson et al, 2005). In contrast, patients with Crohn's disease often have evidence of anaemia, leucocytosis and thrombocytosis in active inflammation and possible deficiencies secondary to malabsorption.

Table 1 outlines the differential diagnosis of granulomatous conditions that may mimic orofacial granulomatosis.

In patients with orofacial granulomatosis, histological examination reveals deep-seated non-caseating granulomas with perivascular, lymphohistiocytic inflammatory infiltrate with prominent plasma cells in up to 73% (16/22) of biopsies (Marcoval and Penín, 2016). Obstruction and dilatation of lymphatic vessels, resulting in lymphostasis, manifests as oedema seen clinically. Histologically, differentiating oral Crohn's disease and orofacial granulomatosis can be challenging but Th1 CD4 lymphocytes are typically seen in oral Crohn's disease, while Th2 lymphocytes are seen in orofacial granulomatosis (Zbar et al, 2012).

Management

Orofacial granulomatosis is a challenge for both the patient and the clinician. A single treatment may not be sufficient, and patient education is crucial. Effective management requires a combination of dietary modification, pharmacological therapy and surgical approaches. The algorithm in Figure 3 is used in the authors' institution.

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Table 1. Differential diagnoses and investigations to consider when evaluating a patient with suspected orofacial granulomatosis

Diagnosis	Investigations
Sarcoidosis	Full blood count, renal profile, liver profile, calcium level, serum angiotensin-converting enzyme level, chest X-ray
Crohn's disease	Full blood count, liver profile, renal profile, haematinics, iron studies, C-reactive protein, erythrocyte sedimentation rate, faecal calprotectin
Angioedema	Full blood count, C4, C1 esterase inhibitor levels and function, C1q levels
Tuberculosis	Full blood count, interferon gamma release assay, chest X-ray, sputum acid-fast bacillus culture, nucleic acid amplification test
Cheilitis glandularis	Labial gland biopsy
Foreign body reaction	Labial gland biopsy

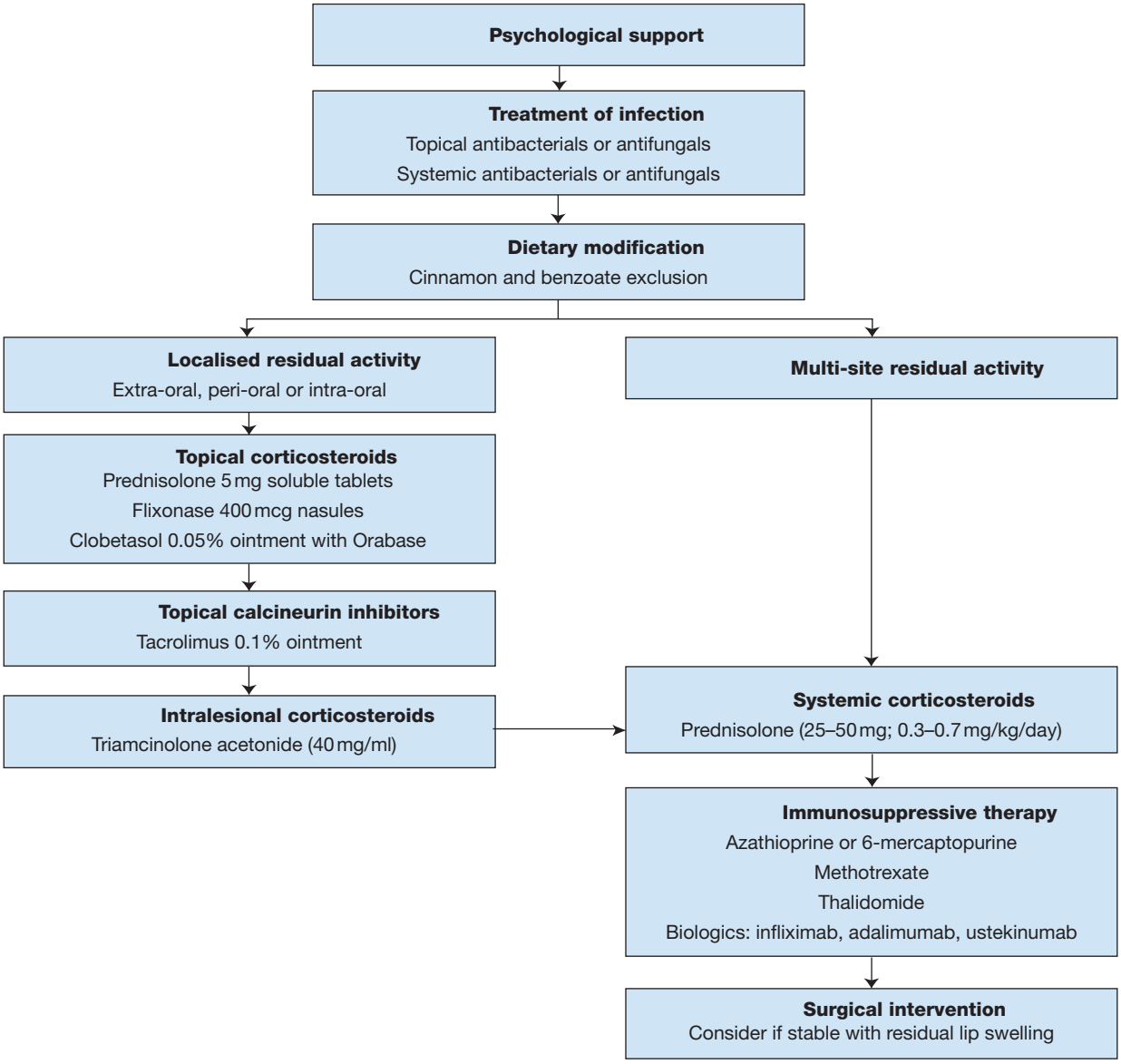

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Figure 3. Treatment algorithm for patients with orofacial granulomatosis.

Dietary modification

A number of studies have explored the role of dietary allergens and exclusion diets (Wray, 2000). There is a significant link between orofacial granulomatosis and food additives, benzoic acid, cinnamaldehyde and cosmetic products, such as perfumes (Wray, 2000). Cinnamaldehyde is often used as a flavouring additive, and its inclusion in toothpaste, dental hygiene products, chewing gum, curry and soft drinks has been associated with orofacial granulomatosis. Monosodium glutamate (E621), a food additive, has also been reported to be an aggravating factor. A retrospective study of 80 patients revealed 18% (14/80) to be clinically atopic with patch testing of this subgroup revealing positive responses in 93% (13/14) to cinnamaldehyde, carvone, aspartate, cocoa or piperitone. Sun yellow dye, carmoisine and tartrazine have also been implicated.

Chocolate has been reported as a dietary trigger of orofacial granulomatosis and an exclusion diet achieved a subjective and objective improvement in 70% (7/10) (Armstrong et al, 1997). Exclusion of cinnamon and benzoates (E210-E219) in 25 patients with orofacial granulomatosis over 8 weeks resulted in an overall improvement in 72% (White et al, 2006). There was no difference in treatment response between patients with biopsy-proven intestinal involvement and those without intestinal involvement. Fibrotic changes associated with chronic disease were less likely to respond to an exclusion diet (White et al, 2006).

A cinnamon- and benzoate-free diet should be initiated with the support of a dietician, taking into account any individual dietary intolerances (Campbell et al, 2011b). Education regarding food labelling, school meals and dining out ensure better adherence. Dietary exclusion of cinnamon and benzoate should be strictly followed for 12 weeks, followed by gradual introduction to identify specific triggers to be avoided longer term (Campbell et al, 2011b). Mobile applications (eg Foodmaestro app) can be used to support patients.

Pharmacological

Topical

Several topical medications have been used alone or in combination with systemic medications in the management of orofacial granulomatosis, although evidence on their effectiveness is limited. The mainstay of topical therapy includes corticosteroids, antimicrobials, antifungals or immunosuppressants (Table 2). Topical tacrolimus has been evaluated in atopic dermatitis, with ointments at 0.03% and 0.1% concentration minimally absorbed systemically (Undre et al, 2009).

No studies have been conducted for the following treatments, although they are occasionally prescribed to treat superimposed infection: hydrocortisone sodium succinate 2.5 mg pellets, benzydamine hydrochloride 0.15% mouthwash, triamcinolone acetonide in 0.1% carmellose paste, fluticasone propionate 0.05% cream, fluticasone propionate 50 mcg/dose inhaler, fluticasone propionate 400 mcg dissolved in 10 ml water and used as a mouthwash, sodium fusidate 20 mg/g ointment (Fuscidin) 2%, miconazole oromucosal gel 20 mg/g, hydrocortisone 10 mg/g and miconazole nitrate 20 mg/g (Daktarin ointment), prednisolone 5 mg soluble tablet dissolved in 10 ml water and used as a mouthwash.

Intralesional

Use of intralesional triamcinolone acetonide for the management of orofacial granulomatosis was first described by Eisenbud et al (1971) in a 25-year-old man with progressive upper lip swelling. A total of 20 doses of triamcinolone acetonide 10 mg/ml were given, at intervals of 2–4 weeks, over a 1-year period, with no relapse at 9 months follow-up after this period. A case series of five patients reported complete resolution in three and partial resolution in two (Allen et al, 1990).

Triamcinolone has been used successfully at concentrations ranging between 25 mg/ml (Mignogna et al, 2013) and 40 mg/ml (Sakuntabhai et al, 1993). Triamcinolone acetonide (40 mg/ml) given on three occasions, 1 week apart, in 22 patients with orofacial granulomatosis (Fedele et al, 2014) showed improvement in all patients, with 64% (14/22) achieving complete remission at 1 week, 91% (20/22) at 2 weeks and 100% (22/22) at 4 weeks, with a recurrence rate of 36% (8/22) at 6 months. Associated unwanted effects include hypo- or hyper-pigmentation, swelling, headache and atrophy. These studies are summarised in Appendix 1.

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Table 2. Topical agents used in management of orofacial granulomatosis

Reference	Drug used	Adjunctive systemic therapy	Duration	Response	Number of participants	Comment
Hegarty et al (2003)	Betamethasone sodium phosphate 500 mcg dissolved in 10 ml water and used as a mouthwash	Deflazacort 24 mg once daily	4 weeks	No	1	
	Fluticasone propionate aqueous spray 50 mcg (two sprays, three times daily	Deflazacort 12 mg once daily	10 days	Yes		Transient improvement in oral ulcers but no improvement in lip swelling
	Tacrolimus ointment 0.1%, twice daily	n/a	4 weeks	Yes	1	Slight improvement to oral ulcers and slight reduction in lip swelling
Mignogna et al (2013)	Pimecrolimus 1% cream	Triamcinolone acetonide 25 mg/ml	1 year	Yes	8	Thin layer applied to lips. Unclear if it alone was result of improvement in all patients

Longstanding fibrotic changes are less likely to respond to intralesional injections. Fedele et al (2014) reported 64% (14/22) required only one while 9% (2/22) required three courses of therapy.

Systemic

Systemic agents are reserved for patients with recalcitrant disease. The evidence for their use is primarily case reports and small case series (**Appendix 1**). Clinical response with systemic agents in patients with orofacial granulomatosis only is less effective than in patients with oral Crohn's or orofacial granulomatosis with concomitant intestinal involvement.

Antimicrobials

There is limited evidence that antimicrobials are effective in patients with orofacial granulomatosis.

Azithromycin: In a case series of five patients with orofacial granulomatosis, azithromycin 500 mg weekly pulsed therapy (three consecutive days every week) resulted in a clinical improvement within 1 month, 80–90% improvement at 3 months and complete resolution by 5 months (Yadav et al, 2015). Another case series using the same regimen reported minimal improvement in two cases and no improvement in three (Atkin and Simms, 2018).

Metronidazole: Metronidazole (1000 mg daily for 3 months) was reported as achieving progressive improvement in a 30-year-old patient with recurring lip swelling (Miralles et al, 1995), and two further studies reported limited improvement (Wiesenfeld et al, 1985; Kano et al, 1993).

A further case report of a 3-year-old boy with biopsy-confirmed orofacial granulomatosis treated with metronidazole 250 mg daily, alongside methylprednisolone 8 mg, reported complete resolution of lip swelling and sustained remission at 18 months (Dummer et al, 1999). Metronidazole has been used in conjunction with intralesional corticosteroid injections (Coskun et al, 2004).

Tetracyclines: Six patients with biopsy-confirmed orofacial granulomatosis were prescribed minocycline 100 mg for 4–6 months with an 80% initial improvement in one patient, and no improvement in five (Veller Fornasa et al, 1992). Two children with orofacial granulomatosis received systemic corticosteroids, in combination with minocycline 100 mg twice daily for 5–9 months (Stein and Mancini, 1999), with significant improvement noted at 5 months in one case and 9 months in the other. There is one report of successful treatment of orofacial granulomatosis with lymecycline (Pigozzi et al, 2004), and two

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cases of orofacial granulomatosis treated with doxycycline reported no improvement (Tonkovic-Capin et al, 2006; Antonyan et al, 2014).

Clofazimine: Clofazimine 100 mg four times weekly for 3–11 months given to ten patients with biopsy-confirmed orofacial granulomatosis achieved complete resolution in 50% (5/10) and clinical improvement in 30% (3/10) (Sussman et al, 1992). Clofazimine 50 mg once daily, combined with intralesional corticosteroid injections, demonstrated improvement in two patients (Sciubba and Said-Al-Naief, 2003). Its use in four patients over 4 months resulted in complete resolution in 50% (2/4) with histological examination showing complete clearance of granulomas (Podmore and Burrows, 1986). Clofazimine improved symptoms in two further studies (Cusano et al, 1993; Fdez-Freire et al, 2005), although the latter case series observed hyperpigmentation and elevation in levels of liver enzymes.

In contrast, a case series of six patients reported no improvement with clofazimine (Veller Fornasa et al, 1992). A retrospective study of 13 patients, of which four were prescribed clofazimine, described 'moderate' improvement in one and no response in three (Van der Waal et al, 2002).

Corticosteroids

Systemic corticosteroids achieve rapid disease control when there is severe disease or worsening symptoms (Hegarty et al, 2003; Kauzman et al, 2006). They are only suitable for short-term use because of their side-effect profile, typically a short course at 0.3–0.7 mg/kg/day to rapidly reduce orofacial swelling (Van der Waal et al, 2002).

Two patients with orofacial granulomatosis saw a reduction in lip swelling and intraoral oedema following a course of corticosteroids 50 mg for 10 days (Kauzman et al, 2006). Short-term improvement was seen in four patients on a tapering dose of corticosteroids (Sciubba and Said-Al-Naief, 2003) and a short course of corticosteroids achieved a good response in another group of four patients (Van der Waal et al, 2002).

Deflazacort: One case found no improvement with deflazacort 24 mg daily for 4 weeks and deflazacort 12 mg daily combined with fluticasone propionate spray showed no changes in lip swelling (Hegarty et al, 2003).

Thiopurines

Azathioprine and its active metabolites, 6-mercaptopurine and thioguanine, are immunomodulatory drugs frequently used in the management of inflammatory bowel disease. The dosing of azathioprine is influenced by thiopurine methyltransferase levels. Thioguanine nucleotide levels >230 pmol/8x10^8 red blood cells resulted in 65% remission rate in inflammatory bowel disease (Dubinsky et al, 2000). Leukopoenia is associated with thioguanine nucleotide levels >450 pmol/8x10^8 red blood cells (Dubinsky et al, 2000).

Azathioprine is typically used as a steroid-sparing agent because of experience in its use in the treatment of Crohn's disease (Dubinsky et al, 2000; Chande et al, 2016). It is effective in the management of patients with concomitant orofacial granulomatosis and Crohn's disease, with 54.5% (12/22) showing a statistically significant improvement (Mentzer et al, 2016). In contrast, only 21.1% (10/38) of patients with orofacial granulomatosis alone showed a response at 4 months (Mentzer et al, 2016). Azathioprine should be reserved for patients with evidence of concomitant orofacial granulomatosis and Crohn's disease. Its dosing is typically 2 mg/kg/day for patients with normal thiopurine methyltransferase.

Methotrexate

Oral methotrexate 5 mg weekly for 2 months in a 36-year-old patient with orofacial granulomatosis and Crohn's disease, unresponsive to azathioprine, dapsone and doxycycline, achieved a partial response with efficacy decreasing over 2–3 years (Tonkovic-Capin et al, 2006). Methotrexate 5 mg weekly resulted in a marked reduction in facial swelling with 10 mg weekly yielding complete resolution. Methotrexate may be considered in patients with orofacial granulomatosis and concomitant Crohn's disease.

Thalidomide

Thalidomide's primary effects are thought to be mediated by its inhibition of the production of interleukin 6 (IL-6) and selective inhibition of tumour necrosis factor alpha.

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Thalidomide was used in five patients with orofacial granulomatosis recalcitrant to topical and systemic therapy (Hegarty et al, 2003), all of whom showed a short-term improvement in lip swelling and oral ulceration. Its successful use has been documented in other studies (Odeka and Miller, 1997; Weinstein et al, 1999), with doses typically between 50 mg and 100 mg daily.

In light of its teratogenic potential, women of childbearing potential should have a pregnancy test on the day of or within 3 days of starting treatment and every 4 weeks thereafter, and effective contraception should be used. A risk assessment for thromboembolism should be undertaken, as well as nerve conduction studies to exclude pre-existing peripheral neuropathy and repeated if symptomatic and at annual intervals. Leukopenia and thrombocytopenia may occur.

Dapsone

There are two case reports of dapsone for the treatment of orofacial granulomatosis (Al Johani et al, 2010; Kemmler et al, 2012). A 14-year-old was treated with dapsone 50 mg daily, alongside infliximab, with complete resolution at 13 weeks and no relapse at 32 months (Kemmler et al, 2012). The concurrent use of infliximab and dapsone makes it difficult to determine the precise role of either.

Hydroxychloroquine

In one study of 13 patients, three had no improvement in lip swelling (Van der Waal, 2002). There were limited data on the dosing or outcome of two patients in a study of 42 patients with orofacial granulomatosis (Zimmer et al, 1992). A 36-year-old male reported improved orofacial granulomatosis-related lip swelling with hydroxychloroquine (Allen et al, 1990) alongside corticosteroids and intralesional triamcinolone acetonide.

Mycophenolate mofetil

Mycophenolate mofetil 500 mg twice daily achieved complete resolution of lip swelling at 6 months, with no relapse at 1 year in one case report (Antonyan et al, 2014). However, commonly reported gastrointestinal side effects limit its use.

Pentoxifylline

There is limited literature available in the use of pentoxifylline in the treatment of orofacial granulomatosis. Al Johani et al (2010) used pentoxifylline in 6% (3/49) but did not report outcome. The lack of available data does not support its use in orofacial granulomatosis.

Sulfasalazine/5-aminosalicylate

Sulfasalazine exerts its pharmacological effects through its metabolites, sulfapyridine and mesalazine. Sulfasalazine 500 mg daily in two children with orofacial granulomatosis was effective in reducing intra-oral signs but they relapsed at 2.5 years on cessation of treatment (Clayden et al, 1997). There are a limited number of case reports using 5-aminosalicylic acid in the management of orofacial granulomatosis. Two cases describe its use (1 g three times daily) in combination with a tapering course of systemic corticosteroids (Girlich et al, 2002), with complete resolution of clinical features reported at 4 weeks in one case.

Biologic therapy

Biologic agents have been trialled in patients with orofacial granulomatosis, including a case series of 14 patients with orofacial granulomatosis unresponsive to dietary manipulation, and topical and systemic therapy. All patients commenced infliximab 5 mg/kg at 0, 2 and 6 weeks, followed by monthly maintenance infusions (Elliott et al, 2011). Concomitantly, 64.3% (9/14) patients were receiving 6-mercaptopurine 75 mg daily, thioguanine 20 mg daily, azathioprine 150 mg daily or methotrexate 15 mg weekly. There was a short-term response in 71% (10/14), with 57% (8/14) remaining responsive at 1 year and 33% (4/12) at 2 years. Patients with oral sulcal involvement were more likely to be responsive to biologic therapy. Success with tumour necrosis factor-alpha inhibitors has also been demonstrated (O'Neill and Scully, 2012; Badshah et al, 2017).

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Ustekinumab was used in a 70-year-old male with orofacial granulomatosis (Taxonera et al, 2020), with complete resolution of lip swelling at 24 months. A significant reduction in lip swelling, with Crohn's disease remission at 26 months, was reported with ustekinumab in a case of biopsy-proven orofacial granulomatosis and Crohn's disease (Gilmore et al, 2020).

Psychological support

Chronic oral diseases significantly impact on quality of life. The unpredictable nature of orofacial granulomatosis can make living with the condition distressing. The role of psychological support for patients and parents of affected children requires further research (Hegarty et al, 2003).

Surgery

In patients where non-surgical therapy has provided a suboptimal outcome, surgical intervention may be appropriate. This should be reserved for severely disfiguring cheilitis and only when the condition is quiescent.

Techniques include facial liposuction, Z-plasty, commissuroplasty and tangential muscle resection. A combination of surgical techniques was used in four patients with orofacial granulomatosis and achieved a good aesthetic and function outcome, with no relapse reported at 6–26 months (Tan et al, 2006). Recurrence (between 1 month and 12 years) was reported in a study of 13 patients who underwent reduction cheiloplasty (Ellitsgaard et al, 1993). Some have advocated the adjuvant use of intralesional corticosteroids to minimise this risk.

Low-level laser therapy has been used and complete resolution at 4 weeks was reported in a 51-year-old with orofacial granulomatosis (Merigo et al, 2012), with no relapse at 2 years. Low-level laser therapy is thought to promote tissue healing and reduce inflammation.

Conclusions

The evidence available in the management of orofacial granulomatosis is weak and conflicting. A single treatment modality is often ineffective. This review highlights the need for high-quality research to validate and explore existing therapies. The lack of standardised outcome measures limits transparency and reduces the ability to compare findings across studies. A validated disease severity score system is needed to enable reliable comparison of management approaches.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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Key points

- Orofacial granulomatosis is a relapsing-remitting inflammatory condition that shares features with other granulomatous conditions including Crohn's disease.
- Patients with orofacial granulomatosis present to both medical and dental care professionals with significant physical and mental morbidity and therefore knowledge of its typical presentation is invaluable.
- Investigation includes common haematological tests for granulomatous investigation and effective management strategies start with dietary manipulation.
- Management of orofacial granulomatosis requires a multidisciplinary approach, including a combination of topical, intralesional and/or systemic treatments.

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Appendix 1. Studies of the management of orofacial granulomatosis

Reference	Drug used	Adjunctive systemic therapy	Duration	Response	No of participants	Comment
Eisenbud et al (1971)	Triamcinolone acetonide 10 mg/ml	n/a	1 year	Yes	1	Total of 20 doses, each 1.5–2 ml, with 2–4 weeks between each dose. No relapse at 9 months
Allen et al (1990)	Triamcinolone acetonide 10 mg/ml	Hydroxy-chloroquine and oral prednisolone in one patient	3–15 months	Yes	5	Complete resolution 3/5 (60%), partial resolution 2/5 (40%)
Mignogna et al (2004)	Triamcinolone acetonide 40 mg/ml	n/a	2–14 days	Yes	7	Complete resolution or cosmetically acceptable improvement achieved in all patients. Unclear how this was determined
Mignogna et al (2013)	Triamcinolone acetonide 25 mg/ml	Pimecrolimus 1% topical cream in 8 out of 19 patients	12 weeks	No	19	Complete resolution 11/19 (57.9%) at 12 weeks; adjunctive topical therapy required in 8/19 (42.1%)
Sakuntabhai et al (1993)	Triamcinolone acetonide 10 mg/ml	n/a	2 weeks	Yes	5	Performed under mental and infraorbital nerve block. Noticeable improvement at 2 weeks. Continued improvement at 6 weeks
Fedele et al (2014)	Triamcinolone acetonide 40 mg/ml	n/a	5–9 weeks	Yes	22	One course treatment consisted of injections on three occasions 1 week apart. 14/22 (64%) patients noticed improvement after one course. Complete remission in all by 4 weeks
Yadav et al (2015)	Azithromycin 500 mg pulsed therapy (3 consecutive days every week)	n/a	5 months	Yes	5	80–90% improvement at 3 months and complete resolution at 5 months
Atkin and Simms (2018)	Azithromycin 500 mg pulsed therapy (3 consecutive days every week)	n/a	5 weeks–9 months	No	5	
Miralles et al (1995)	Metronidazole 1000 mg	n/a	3 months	Yes	1	Progressive improvement
Wiesenfeld et al (1985)	Metronidazole	n/a	Unknown	Yes	2	Limited improvement

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Appendix 1. Studies of the management of orofacial granulomatosis (continued)

Reference	Drug used	Adjunctive systemic therapy	Duration	Response	No of participants	Comment
Kano et al (1993)	Metronidazole	Unknown	Unknown	Unknown	1	
Dummer et al (1999)	Metronidazole 250 mg daily	8 mg methylprednisolone every other day	18 months	Yes	1	Complete resolution
Veller Fornasa et al (1992)	Minocycline 100 mg/day	n/a	4–6 months	Yes	6	80% improvement in one patient
Stein and Mancini (1999)	Minocycline 100 mg/ twice daily	Corticosteroid	18 months	Yes	2	
Pigozzi et al (2004)	Lymecycline	n/a	Unknown	Yes	1	
Tonkovic-Capin et al (2006)	Doxycycline	Triamcinolone acetonide injection	Unknown	No	1	Partial response
Antonyan et al (2014)	Doxycycline	Unknown	Unknown	No	1	
Mentzer et al (2016)	Azathioprine	n/a	1–96 months	Yes	60	Concomitant orofacial granulomatosis and Crohn's disease responded with statistical significance in contrast to orofacial granulomatosis alone. Orofacial granulomatosis alone 10/38 (26.3%) showed a response at 4 months
Sussman et al (1992)	Clofazimine 100 mg four times weekly	n/a	3–11 months	Yes	10	Complete resolution in 50%
Sciubba and Said-Al-Naief (2003)	Clofazimine 50 mg/day	Triamcinolone acetonide intralesional injection	Unknown	Yes	2	Improvement in symptoms
Podmore and Burrows (1986)	Clofazimine 100 mg twice daily then 100 mg twice weekly	n/a	6 months	Yes	4	Complete resolution in 2/4. One patient saw a reversible reddish brown cutaneous discolouration
Fdez-Freire et al (2005)	Clofazimine 100–200 mg/ daily	n/a	3–6 months	Yes	3	Improvement in symptoms. Hyperpigmentation and raised levels of liver enzymes noted
Cusano et al (1993)	Clofazimine 100 mg, daily for 10 days, then twice weekly for 16 weeks	n/a	4 months	Yes	4	Complete resolution in 3/4 patients (75%), in remission at 2 years

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Appendix 1. Studies of the management of orofacial granulomatosis (continued)

Reference	Drug used	Adjunctive systemic therapy	Duration	Response	No of participants	Comment
Veller Fornasa et al (1992)	Clofazimine	n/a	5–7 months	No	6	No improvement seen
Van der Waal et al (2002)	Clofazimine	n/a	n/a	Yes	4	Moderate improvement in one patient
Kauzman et al (2006)	Corticosteroid 50 mg	n/a	10 days	Yes	2	Relapse in 2 months in one patient
Sciubba and Said-Al-Naief (2003)	Corticosteroid	n/a	Short period	Yes	4	
Van der Waal et al (2002)	Corticosteroid	n/a	Unknown	Yes	4	Moderate–good response
Al Johani et al (2010)	Dapsone	Unknown	Unknown	Unknown	1	
Kemmler et al (2012)	Dapsone 50 mg/day	Infliximab	32 months	Yes	1	Complete resolution at 13 weeks. No relapse at 32 months
Hegarty et al (2003)	Deflazacort 12–24 mg	Betamethasone sodium phosphate 500 micrograms mouthwash Fluticasone propionate spray	4 weeks	Yes	2	No improvement in one patient. Transient improvement to oral ulcers in second patient
Al Johani et al (2010)	Deflazacort	Unknown	Unknown	Unknown	8	
Van der Waal et al (2002)	Hydroxy-chloroquine	Unknown	Unknown	No	3	
Allen et al (1990)	Hydroxy-chloroquine Triamcinolone acetonide 10 mg/ml	Triamcinolone acetonide 10 mg/ml and oral prednisolone in one patient	6 months	Yes	1	Partial resolution
Tonkovic-Capin et al (2006)	Methotrexate 5 mg/weekly, maintenance dose: 10 mg	n/a	16 months	Yes	1	Marked reduction in facial swelling
Antonyan et al (2014)	Mycophenolate mofetil 500 mg twice daily	n/a	6 months	Yes	1	Significant improvement by 1 months and complete resolution by 6 months
Al Johani et al (2010)	Mycophenolate mofetil	Unknown	Unknown	Unknown	2	
Al Johani et al (2010)	Pentoxifylline	Unknown	Unknown	Unknown	3	
Clayden et al (1997)	Sulfasalazine 500 mg/daily	n/a	2.5 years	Yes	2	Improvement maintained only while on treatment

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Appendix 1. Studies of the management of orofacial granulomatosis (continued)

Reference	Drug used	Adjunctive systemic therapy	Duration	Response	No of partici-pants	Comment
Girlich et al (2002)	5-amino-salicylate 1 g three times daily	Corticosteroid 60 mg/day tapering by 10 mg weekly	4 weeks	Yes	2	Complete resolution of lip swelling in one patient at 4 weeks. One patient lost to follow up
Hegarty et al (2003)	Thalidomide 50 mg	n/a	4 weeks	Yes	5	Oral ulcerations improvement in 2 weeks. Lip swelling improved in 4 weeks
Odeka and Miller (1997)	Thalidomide 50 mg daily	n/a	2 weeks	Yes	1	Complete resolution. Relapses controlled with thalidomide 50 mg for short periods
Weinstein et al (1999)	Thalidomide 25 mg daily	n/a	1 year	Yes	1	Complete resolution
Elliott et al (2011)	Infliximab or adalimumab	6-mercaptopurine or 6-thioguanine or azathioprine or methotrexate	2 years	Yes	14	
Taxonera et al (2020)	Ustekinumab 90 mg 12-weekly	n/a	24 months	Yes	1	Complete resolution
Gilmore et al (2020)	Ustekinumab 90 mg	n/a	26 months	Yes	1	Significant reduction in lip swelling at 12 weeks and sustained till review at 26 months

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