A comprehensive review of current treatments for granulomatous cheilitis
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Summary
Granulomatous cheilitis (GC) is a poorly understood disease process belonging to the larger group of orofacial granulomatosis. The treatment of GC has proven exceedingly difficult. While various treatments have been applied to GC, there has been no uniform or predictably successful model demonstrated in the literature. Poor understanding of the aetiological mechanisms underpinning GC has significantly hampered the development of an effective approach to treatment. Those therapies that have shown promise principally consist of agents with anti-inflammatory activity such as corticosteroids and immunomodulatory medications. On a careful review of the literature, we have found no systematic review and assessment of current treatments. We seek to address this absence in the available literature by providing a consolidated overview of current treatment for GC.

Corticosteroids
Used both in the form of local injection and systemically, corticosteroids have remained a consistent mainstay of many GC treatment regimens. Whether as sole treatment or as an adjunct to other medical or surgical options, corticosteroids have been employed as a potent agent in decreasing the inflammation evident on histological examination of patients with GC.10,11 While oral prednisone has been used as systemic treatment, intralesional use of triamcinolone has been the predominant form of corticosteroid treatment in more recent case reports.10–12 Although oral doses are not well established, intralesional triamcinolone dosing varies from 10 to 20 mg doses with intervals from weeks to months between injections.13,14 Although success has been noted with such use, it is often temporary and no large studies exist examining the long-term efficacy of corticosteroids in GC.

Clofazimine
Clofazimine is a medication derived from phenazine dye, which has also been used in the treatment of lepromyelone, pyoderma gangrenosum and discoid lupus erythematosus.15 First used in a case series by Podmore and Burrows15 in 1986, this...
Medication has been reported to be an effective treatment for GC. It has been used in doses ranging from 100 to 300 mg per dose in both daily and every other day dosing regimens. Through its antibacterial, anti-inflammatory and immunomodulatory effects, clofazimine’s broad spectrum of action speaks to the equally nebulous character of GC’s underlying aetiology. The principle side-effect is a dose-related, red-brown pigmentation of the skin, with gastrointestinal upset and rarely hepatotoxicity also reported.

**Antibiotics**

As noted previously, several antibiotics including sulfa drugs, tetracycline and isoniazid have been used unsuccessfully in the past; however, recent reports indicate a continued use for antibiotic agents. No infectious agent has been clearly linked with GC and it is probably the associated anti-inflammatory activity and modulation of the ongoing immune reaction that is responsible for the effect of these drugs. Among the antibiotics that have gained more recent prominence are minocycline (100 mg daily) and roxithromycin (150–300 mg daily), which belong to the tetracycline and macrolide classes, respectively. Further attention has been garnered by metronidazole, particularly given the association of GC with Crohn disease noted in much of the literature. Mixed but promising results have been obtained in the treatment of GC with metronidazole using doses of 750–1000 mg daily.

**Other immunomodulators**

A few case reports document successful use of a variety of other immunomodulatory agents. Infliximab, a chimeric monoclonal antibody that targets tumour necrosis factor (TNF-α) and has been effective in the treatment of Crohn disease, has also been touted as a promising agent for use in GC in infusion doses ranging from 3 to 5 mg/kg. Similarly, in a case report by Thomas et al., thalidomide was successfully used in a patient with GC in doses of 100 mg daily which were decreased to every other day. Thalidomide also demonstrates TNF-α inhibitory action, which may explain its effectiveness. Although these agents and the targeting of TNF-α represent a promising avenue for future treatment, their long-term safety and efficacy remains to be seen in addressing GC.

A few studies have examined the use of disease-modifying agents known to reduce the proliferation of immune cell lines. Among these studies are several case reports on the use of methotrexate. The doses for such treatments range from 5 to 10 mg of oral methotrexate administered weekly. Interestingly, a case report by Tonkovic-Capin et al. addresses the use of methotrexate in a patient with Crohn disease and GC, leading the authors to comment on the potential utility of periodically searching for underlying Crohn disease in patients with GC. Another form of treatment offering antiproliferative effects on immune cells are the fumaric acid esters such as Fumaderm (Biogen Idec, Weston, MA, U.S.A.).

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<thead>
<tr>
<th>Medication</th>
<th>Case report or study</th>
<th>Dose</th>
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<tbody>
<tr>
<td>Triamcinolone</td>
<td>Coskun et al. 19</td>
<td>10–20 mg per dose (intraleisonal) with weeks to months between doses</td>
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<td></td>
<td>Eisenbud et al. 11</td>
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<td></td>
<td>Perez-Calderon et al. 12</td>
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<tr>
<td>Clofazimine</td>
<td>Podmore and Burrows 13</td>
<td>100–300 mg daily or every other day</td>
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<td></td>
<td>Fernandez Freire et al. 16</td>
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<tr>
<td>Minocycline</td>
<td>Veller Fornasa et al. 19</td>
<td>100 mg daily</td>
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<td></td>
<td>Ishiguro et al. 18</td>
<td>150–300 mg daily</td>
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<td></td>
<td>Inui et al. 19</td>
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<tr>
<td>Roxithromycin</td>
<td>Miralles et al. 11</td>
<td>750–1000 mg daily</td>
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<td></td>
<td>Kano et al. 11</td>
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<tr>
<td>Metronidazole</td>
<td>Coskun et al. 19</td>
<td>750–1000 mg daily</td>
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<td>Miralles et al. 11</td>
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<td></td>
<td>Kano et al. 11</td>
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<tr>
<td>Infliximab</td>
<td>Ratzinger et al. 22</td>
<td>3–5 mg/kg per infusion</td>
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<td></td>
<td>Barry et al. 24</td>
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<tr>
<td>Thalidomide</td>
<td>Thomas et al. 25</td>
<td>100 mg daily to every other day</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Tonkovic-Capin et al. 26</td>
<td>5–10 mg administered orally on a weekly basis</td>
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<td></td>
<td>Leicht et al. 22</td>
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<tr>
<td>Fumaric acid esters</td>
<td>Kleine et al. 28</td>
<td>120–720 mg daily</td>
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<tr>
<td>(Fumaderm)</td>
<td>Breuer et al. 29</td>
<td></td>
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<tr>
<td>Tranilast</td>
<td>Chiba et al. 31</td>
<td>200–400 mg daily</td>
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cations have found use in the treatment of psoriasis and two case reports indicate possible benefit in the treatment of GC using doses of 120–720 mg daily.28,29

Finally, tranilast, a medication used in the treatment of sarcoidosis and also in allergy-driven disease processes due to its inhibition of chemical mediator release from mast cells, has been used in the management of GC.30 Chiba et al.31 presented two cases in which the medications tranilast and ketotifen were used in prolonged courses in doses of 200–400 mg daily and 2 mg daily, respectively.

**Surgical management**

Surgical management through cheiloplasty is frequently discussed in the literature as an option reserved for severe or deforming GC.32,33 The removal of tissue from the affected lip(s) can be effective in restoring function and cosmetic appearance, providing an added benefit in addressing the social impairment felt by many patients with GC.32 Another reported procedure, while not surgical, is the use of helium-neon laser radiation treatment. Bugay and Lialina published the results of 83 patients who underwent this treatment, which was reported to provide significant benefit particularly to those with disease duration of less than 4 years.34 The benefits of surgery and other procedural options must be weighed against side-effects such as loss of normal sensation in the affected lip(s) and of recurrence despite surgery. In effect, surgery should remain as an option only for those patients who are severely affected or who have impairment of function due to GC.14

**Conclusion**

GC is a chronic and potentially disfiguring disease process whose unknown origin has hindered the development of effective treatment regimens. Affording some promise, the association between GC and Crohn disease has been noted widely in the available literature, as has a shared effectiveness for some of the treatment modalities used to treat Crohn disease. While agents that address the inflammatory response have been demonstrated to provide benefit to patients, evidence in the literature remains restricted to case reports with no larger studies available. Although surgical management remains an option for those severely affected patients, it does not represent a definitive cure and continued investigation of medical options should be pursued.

**What does this study add?**

- Our paper uniquely provides a concise but extensive overview of the various treatment regimens used in the hope of guiding future research and treatment for this rare and poorly understood disease process.

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**References**

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