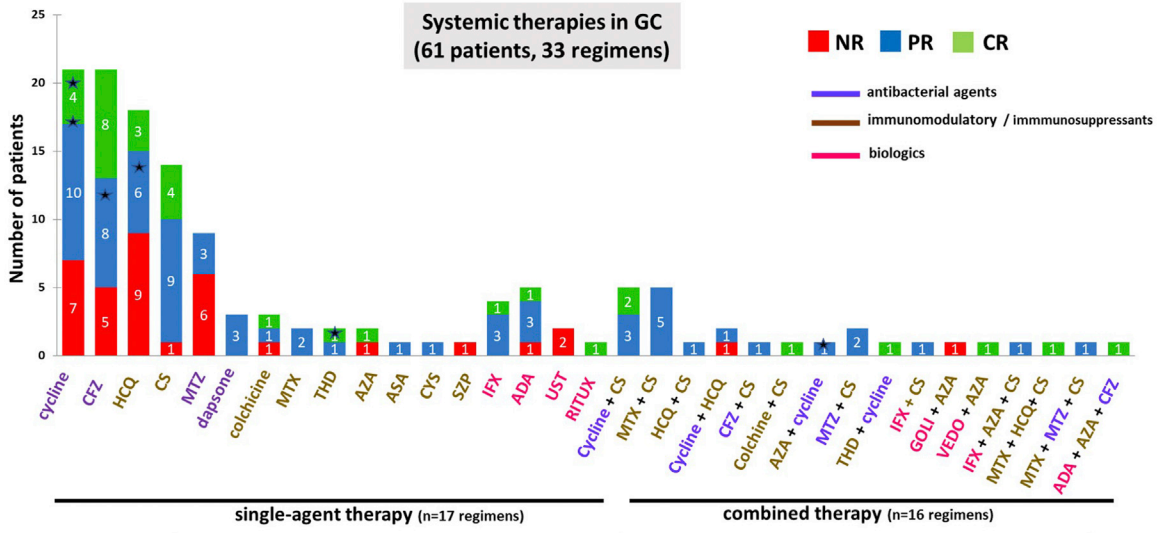
Letter

Research letter

Response to systemic therapies in granulomatous cheilitis: Retrospective multicenter series of 61 patients

To the Editor: Granulomatous cheilitis (GC) is a rare condition and can be primary (Miescher's macrocheilitis, Melkersson-Rosenthal syndrome) or associated with systemic granulomatosis.[1,2] Because intralesional or systemic corticosteroids are hardly manageable in the long term, various systemic therapies have been suggested for GC[1,3] (Supplemental Table I; available via Mendeley at https://doi.org/10.17632/543528fvbd.1). This retrospective study, conducted among the *Groupe d'Etude de la Muqueuse Buccale* network,[4] included 61 patients (median age, 45.0 years; quartiles [Q1-Q3] 26.0-59.0; 41 females) with primary GC (38 patients with Miescher's GC and 9 with Melkersson-Rosenthal syndrome) or secondary GC (10 patients with Crohn's disease and 4 with sarcoidosis) treated with a systemic drug between 1995 and 2019. The patients had received 1 (n = 23; 67.6%), 2 (n = 19; 31.2 %), or 3 or more (n = 19; 31.2%) distinct lines of systemic therapies (median duration 6.0 months; Q1-Q3 3.0-9.2), resulting in 136 distinct cycles of treatment (Fig 1).

Response to treatment was assessed retrospectively according to the Physician Global Assessment[5] as follows: complete response (CR), partial response (PR), or no response. With the 136 cycles of treatment, 100 cases showed either a PR or CR (73.5%, 95% CI, 66.1-80.9), including CR in 35 cases (23.5%, 95% CI, 16.4-30.6). The median duration of response was 7 months (Q1-Q3, 4.75-14.25). The proportion of response (PR or CR) was higher with combined versus single-agent therapies, but the proportion of CR or relapse rates did not differ between groups (Fig 1). Response rates and CR rates did not differ among antibacterial agents (66.7%, 95% CI, 45.1-79.2 and 22.2%, 95% CI, 11.1-33.3), immunomodulatory and/or immunosuppressive drugs (71.4, 95% CI, 57.8-85.1 and 23.8, 95% CI,



Proportion of responses (CR+PR) (%, 95%CI)	**69.0** (60.4-77.7)	**92.3** (82.1-100.0)	P=0.008
Proportion of CR (%, 95%CI)	**22.7** (14.9-30.6)	**26.9** (9.9-43.9)	NS
Relapse rates (%, 95%CI)	**37.5** (18.1-56.9)	**34.2** (23.5-44.9)	NS

Fig 1. Responses to systemic therapies in the whole study population of granulomatous cheilitis in 61 patients. Best response is indicated: nonresponse (NR), complete response (CR), or partial response (PR). Proportional analysis was assessed by the 2-tailed Fisher exact test. *ADA*, adalimumab; *ASA*, 5-aminosalicylic acid; *AZA*, azathioprine; *CFZ*, clofazimine; *CS*, corticosteroids; *CYS*, cyclosporine; *GOLI*, golimumab; *HCQ*, hydroxychloroquine; *IFX*, infliximab; *MTX*, methotrexate; *MTZ*, metronidazole; *RITUX*, rituximab; *SZP*, salazopyrine; *THD*, thalidomide; *UST*, ustekinumab; *VEDO*, vedolizumab.

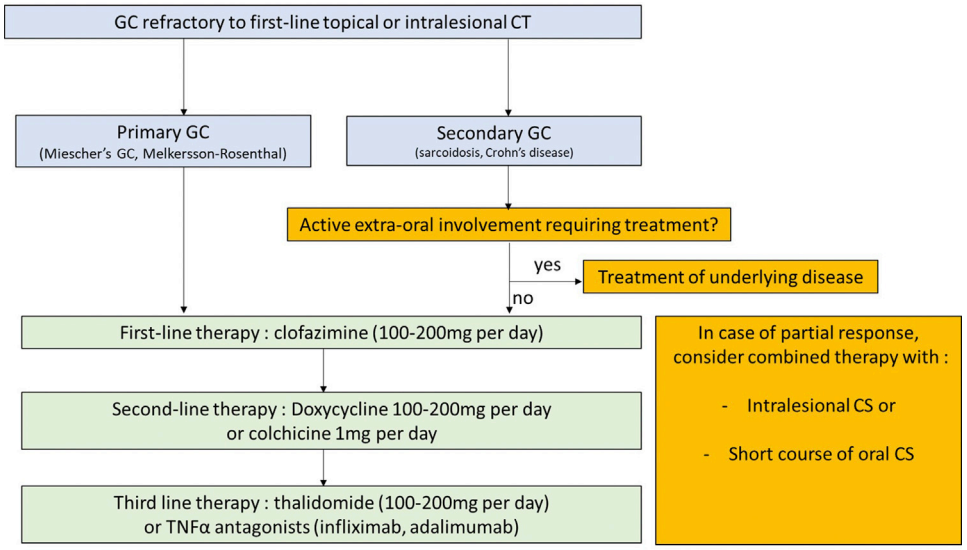


Fig 2. Therapeutic algorithm for granulomatous cheilitis refractory to first-line topical or intralesional therapy. *CS,* Corticosteroids; *GC,* granulomatous cheilitis.

10.9-36.7), or biologics (75.0%, 95% CI, 50.5-99.5 and 25.0%, 95% CI, 0.5-49.5%).

Among treatments assessed in at least 3 patients, clofazimine produced higher CR rates (38.1%, 95% CI, 17.3-58.9; Supplemental Table II; available via Mendeley at https://doi.org/10.17632/543528fvbd.1). Assessment of responses according to underlying disease (Supplemental Figs 1 and 2; available via Mendeley at https://doi.org/10.17632/543528fvbd.1; Supplemental Table II) showed that the proportion of responses (77.5% [95% CI, 69.3-85.8] vs 63.2% [95% CI, 47.8-78.5]) and CR (24.5% [95% CI, 16.0-33.0] vs 21.0% [95% CI, 8.1-34.0]) did not differ between primary and secondary GC. During follow-up, CR increased over time (Supplemental Fig 3; available via Mendeley at https://doi.org/10.17632/543528fvbd.1), showing a CR at 1 year (25.7%, 95% CI, 11.2-40.2) and at 5 years (41.2%, 95% CI, 17.8-64.5) corroborating the previously described remitting behavior of GC.[5]

Most systemic therapies were at least partially successful in GC, but CR was achieved in only 20% of cases, with a short duration of response. Clofazimine provided the highest CR in our series, whereas the benefit/risk ratio of immunosuppressive drugs was questionable because they were associated with only partial and transient responses. Thalidomide seemed more successful than immunosuppressants, whereas TNF-α antagonists produced a response in nearly all of our cases with a long-term duration of response (Supplemental Table II). Despite the limitations of small sample size, nonstandardized regimens, no severity or quality of life scores, and progressive remitting profile due to the natural history of the disease, we suggest a therapeutical algorithm considering response rates, benefit/risk ratio, and long-term duration of response for each drug (Fig 2).

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Conflicts of interest

Dr Girard declares conflicts of interest with AbbVie, Janssen, Lilly, Novartis, Amgen, and UCB. Dr Misery declares conflicts of interest with AbbVie (lecture, clinical trial, advisory board), Amgen (lecture, clinical trial), Celgene (grant, consultant), Janssen (lecture, clinical trial, advisory board), Pfizer (clinical trial, advisory board), and Sanofi (clinical trial, advisory board). Stephane Nahon declares lectures or advisory board fees from AbbVie, MSD, Vifor Pharma, Pfizer, Janssen, and Ferring. Dr Sibaud declares fees and honoraries from Novartis, Bristol Myers Squibb, Bayer, Incyte, Pierre Fabre, Sanofi, and Bayer. Dr Samimi has received fees from Bristol Myers Squibb for speaking at an educational meeting for residents and has received reimbursement for travel and accommodation expenses from Bristol Myers Squibb, Janssen, AbbVie, and MSD. Authors Frédéric Jaouen and Fricain and Drs Tessier, Vaillant, Azib-Meftah, Bénéton, Delaporte, Kaddour, Ingen-Housz-Oro, Masson-Regnault, and Bessis have no conflicts of interest to declare.

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