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Frédéric JAOUEN

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

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Macrochéilites granulomateuses : efficacité des traitements systémiques dans une série rétrospective multicentrique de 61 patients

Introduction. La macrochéilite granulomateuse est une entité inflammatoire rare, qui peut être isolée, associée au syndrome de Melkersson-Rosenthal ou à des maladies systémiques (maladie de Crohn, sarcoïdose). L'évolution est souvent chronique, entrecoupée de poussées inflammatoires. Bien que la corticothérapie, intra-lésionnelle ou systémique, soit efficace à court terme, son utilisation au long cours ne peut être préconisée. Il existe très peu de données sur l'efficacité des traitements systémiques dans la macrochéilite granulomateuse. Notre objectif était d'évaluer l'efficacité des traitements systémiques dans une série rétrospective de macrochéilites granulomateuses, en fonction de l'étiologie sous-jacente.

Matériel et méthodes. Il s'agissait d'une étude rétrospective des cas de macrochéilites granulomateuses, toutes étiologies confondues, traitées par au moins une ligne de traitement systémique entre 1995 et 2019 par les praticiens du réseau GEMUB (Groupe d'Etudes de la Muqueuse Buccale). L'efficacité était évaluée rétrospectivement et classée en « réponse complète », « réponse partielle » et « absence de réponse » ; le délai et la durée de réponses étaient également collectées.

Résultats. Parmi les 61 patients inclus, la macrochéilite correspondait à une forme idiopathique de Miescher (n=38, 62.3%), à un syndrome de Melkersson-Rosenthal (n=9, 14.7%), à une maladie de Crohn (n=10, 16.5%) ou une sarcoïdose (n=4, 6.5%). Le délai median entre le diagnostic et l'introduction d'un traitement systémique était de 10 mois (Q1-Q3 4.0-15.0). Les patients avaient été traités par une ligne (n=23, 37.7%), deux lignes (n=19, 31.2%), trois lignes (n=10, 16.4%), ou quatre lignes et plus (n=9, 14.7%) de traitements systémiques, correspondant à 136 séquences thérapeutiques évaluables (durée médiane de traitement 6.0 mois, Q1-Q3 3.0-9.2), réparties en 33 modalités de traitements (monothérapies, n=17 ; traitements combinés, n=16). La durée médiane de réponse était de 7 mois (Q1-Q3, 4.75-14.25). Toutes étiologies confondues, les monothérapies par doxycycline, clofazimine, hydroxychloroquine, corticoïdes, dapsone, colchicine, infliximab, adalimumab permettaient des réponses (partielles ou complètes) dans plus de 50% des cas, tandis la clofazimine, la colchicine et les corticoïdes oraux permettaient des réponses complètes dans plus de 30% des cas. En cas de macrochéilite de Miescher, seule la clofazimine, l'infliximab et la doxycycline permettaient des réponses complètes dans plus de 30% des cas. L'effectif des patients traités pour les autres étiologies étaient faibles, mais les traitements par doxycycline, clofazimine, corticostéroïdes et adalimumab étaient les plus fréquemment efficaces.

Discussion. Nous décrivons la série de plus large effectif sur l'efficacité des traitements systémiques dans cette pathologie rare. Bien que de nombreuses molécules ait permis une réponse partielle ou complète, celle-ci était en général de courte durée, motivant plusieurs lignes thérapeutiques successives. La clofazimine, la colchicine, la doxycycline et les biologiques anti-TNF alpha étaient les traitements les plus efficaces.

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Introduction générale :

Les macrochéilites granulomateuses (MG) sont caractérisées par une augmentation en taille, d'une ou des deux lèvres, en lien avec un infiltrat inflammatoire granulomateux. Cette pathologie inflammatoire, décrite pour la première fois par Miescher en 1945 [1], est classifiée depuis 1985 au sein des « granulomatoses oro-faciales » par Wiesenfeld [2]. Il s'agit d'une pathologie rare, dont l'incidence est estimée à 0,08% dans la population générale [3,4].

Le diagnostic des MG est avant tout suspecté sur l'aspect clinique (aspect de tuméfaction(s) labiale(s), localisée(s) ou diffuse(s), évoluant initialement de manière intermittente puis permanente) [5]. Dans les formes débutantes d'évolution intermittente, le diagnostic différentiel est celui d'un angioedème muqueux ; toutefois, dans la majorité des cas, le caractère permanent ou quasi-permanent de l'œdème permet d'éliminer ce diagnostic. Devant cet aspect de macrochéilite chronique, une biopsie muqueuse est réalisée et met en évidence une histologie évocatrice (présence de granulomes épithéloides giganto-cellulaires sans nécrose caséeuse associé à infiltrat inflammatoire non spécifique à prédominance lymphocytaire). Toutefois, dans les publications de séries de cas ainsi que dans l'expérience des praticiens, les granulomes de localisation profonde au contact des fibres musculaires, peuvent être absents de cette biopsie (jusqu'à 50% des séries de cas) [6–8].

Les MG peuvent être distinguées selon leur étiologie, primitive ou secondaire. Les formes idiopathiques regroupent l'atteinte isolée des lèvres ou macrochéilite de Miescher et une forme syndromique, le syndrome de Melkersson-Rosenthal (associant classiquement la triade MG, langue fissuraire et paralysie faciale périphérique, bien que des formes incomplètes soient décrites). Il existe en réalité un « spectre clinique » des granulomatoses oro-faciales avec atteinte labiale, orofaciale, et/ou atteinte neurologique, dont l'étiopathogénie est inconnue [9–12]. Les formes secondaires sont liées à des granulomatoses systémiques avec atteinte muqueuse ; il s'agit de la maladie de Crohn et de la sarcoïdose. En revanche, les infiltrats granulomateux d'origine infectieuse (tuberculose, mycobactéries atypiques, syphilis tertiaire, leishmaniose) sont inclus dans les diagnostics différentiels.

L'exhaustivité du bilan étiologique devant une MG est variable selon les équipes. Il est habituel de réaliser un bilan sanguin standard (NFS, CRP), un dosage de l'enzyme de

conversion de l'angiotensine et une radiographie pulmonaire, et d'orienter les autres examens en fonction du tableau clinique (imagerie thoraco-abdominale, endoscopie digestive avec biopsies). Actuellement, le dosage de la calprotectine fécale est un outil sensible et non invasif de dépistage des maladies inflammatoires digestives, qui peut être facilement réalisé au bilan initial.

L'évolution de la MG est chronique, caractérisée par un œdème labial semi-permanent ou permanent comportant des épisodes inflammatoires aigus. Le traitement des MG est mal codifié ; il n'existe aucune recommandation en raison de l'absence d'essai clinique prospectif randomisé. Selon l'intensité des symptômes et la qualité de vie du patient (en lien avec une gêne fonctionnelle ou esthétique) [13], le traitement de première intention comporte des corticoïdes locaux de très forte activité voire des injections intralésionnelles de corticoïdes retard, à répéter environ chaque mois [14]. En l'absence de gêne, une abstention thérapeutique est possible. En cas d'atteinte sévère ou après échec des traitements locaux, l'arsenal thérapeutique comporte de multiples traitements systémiques immunomodulateurs ou immunosuppresseurs, une prise en charge chirurgicale (uniquement en dehors des poussées inflammatoires) [15,16] ou par lasers ablatifs [17].

En ce qui concerne les traitements systémiques, nous avons réalisé au préalable une revue bibliographique via Pubmed, et n'avons retrouvé que des publications de cas cliniques isolés ou de petites séries de cas, comportant très rarement des effectifs importants (seulement quatre séries de cas rapportent plus de 10 patients, dont une seule plus de 20 patients) [18–21]. Cette synthèse bibliographique est rapportée dans le ***Tableau 3*** de l'article scientifique. Seule une revue de la littérature, publiée en 2011 dans le British Journal of Dermatology, synthétise les données sur les traitements systémiques, mais ne repose là encore que sur des séries de cas comportant très peu de patients [22]. En résumé, la corticothérapie systémique est le traitement le plus souvent utilisé (souvent en combinaison) mais il existe une rechute lors de la décroissance, et ce traitement ne peut être proposé au long cours. Un large éventail de traitements systémiques a été proposé (***Tableau 3***) : antibiotiques à visée anti-inflammatoire (métronidazole, clofazimine, dapsone, cyclines, macrolides), agents immuno-modulateurs (salazopyrine, mesalazine, hydroxychloroquine, colchicine, azathioprine, mathotrexate, thalidomide, mycophénolate mofetil), dtraitements biologiques (infliximab, adalimumab, certolizumab, ustekinumab, omalizumab). Le choix du traitement dépend de plusieurs critères : formes primaire ou secondaire de MG, effets secondaires des traitements associés aux comorbidités et antécédents du patient, voie d'administration, habitudes locales du praticien.

L'objectif principal de notre étude était de recueillir rétrospectivement l'efficacité de traitements systémiques chez des patients atteints de MG, primaire ou secondaire, en recrutant les cas au sein du GEMUB (Groupe d'Etudes de la Muqueuse Buccale), réseau pluridisciplinaire francophone regroupant des dermatologues, chirurgiens oraux, chirurgiens maxillofaciaux, dentistes, avec une expertise dans la prise en charge des pathologies orales. Le GEMUB est une association loi 1901, qui a été créée en 2017 et regroupe une cinquantaine de praticiens en France et dans les pays francophones (Belgique, Suisse, pays du Maghreb) [23]. Nous avons envoyé entre septembre 2019 et février 2020, un appel un cas (suivi de deux relances) via le mail de diffusion du groupe (gemub@medicalistes.org) avec un questionnaire standardisé et anonymisé (**Annexe 1**).

Douze centres hospitalo-universitaires du GEMUB ont collecté leurs cas entre 1995 et 2019 et complété les questionnaires (CHU de Tours, Bordeaux, Toulouse, Nantes, Lille, Montpellier, Marseille, Alger, Brest, Poitiers, Le Mans, Créteil-Henri Mondor), nous permettant d'analyser rétrospectivement l'efficacité des traitements systémiques parmi 61 patients ayant une MG. Parmi les 61 patients inclus, la macrochéilite correspondait à une forme idiopathique de Miescher (n=38, 62.3%), à un syndrome de Melkersson-Rosenthal (n=9, 14.7%), à une maladie de Crohn (n=10, 16.5%) ou une sarcoïdose (n=4, 6.5%). Toutes étiologies confondues, il n'existait pas de différence statistiquement d'efficacité entre les différentes classes médicamenteuses (antibiotiques, immunomodulateurs/immunosuppresseurs, traitements biologiques). Les monothérapies par doxycycline, clofazimine, hydroxychloroquine, corticoïdes, dapsone, colchicine, infliximab, adalimumab permettaient des réponses (partielles ou complètes) dans plus de 50% des cas, tandis la clofazimine, la colchicine et les corticoïdes oraux permettaient des réponses complètes dans plus de 30% des cas. En cas de macrochéilite de Miescher, seule la clofazimine, l'infliximab et la doxycycline permettaient des réponses complètes dans plus de 30% des cas. L'effectif des patients traités pour les autres étiologies étaient faibles, mais les traitements par clofazimine, corticostéroïdes et anti-TNFalpha étaient les plus fréquemment efficaces. En conclusion, il s'agit de la série de plus large effectif sur l'efficacité des traitements systémiques dans cette pathologie rare. Bien que de nombreuses molécules ait permis une réponse partielle ou complète, celle-ci était en général de courte durée, motivant plusieurs lignes thérapeutiques successives.

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Granulomatous cheilitis: effectiveness of systemic therapies in a retrospective multicenter series of 61 patients

Authors: Frédéric Jaouen (1,2), Marie-Hélène Tessier, MD (3), Loic Vaillant, MD PhD (1,2), Selma Azib-Meftah, MD (4), Laurent Misery, MD PhD (5), Nathalie Beneton, MD (6), Emmanuel Delaporte, MD PhD (7), Amina Kaddour, MD (8), Saskia Oro, MD (9), Marie Masson-Regnault, MD (10), Vincent Sibaud, MD (11), Jean-Christophe Fricain, (12), Celine Girard, MD (13), Mahtab Samimi, MD PhD (1,2)

(1) Université François Rabelais, Tours, France, 37044 Tours Cedex, France

(2) CHU Tours, Dermatology Department, avenue de la République 37170 Tours Cedex, France

(3) CHU Nantes, Dermatology Department, 5 allée de l'île Gloriette 44093 Nantes Cedex, France

(4) CHU Lilles, Dermatology Department, rue Michel Polonowski 59037 Lille Cedex, France

(5) CHU Brest, Dermatology Department, boulevard Tanguy Prigent 29200 Brest Cedex, France

(6) CHR Le Mans, Dermatology Department, 194 avenue Rubillard 72037 Le Mans Cedex, France

(7) Hôpitaux de Marseille, Dermatology Department, 80 rue Brochier 13354 Marseille Cedex, France

(8) CHU Alger, Dermatology Department, 1945 place du 1er Mai 16000 Sidi M'Hamed Cedex, Algérie

(9) AP-HP Henri Mondor, Dermatology Department, 51 avenue du Maréchal de Lattre de Tassigny 94010 Créteil Cedex, France

(10) CHU Poitiers, Dermatology Department, 2 rue de la Milétrie, 86021 Poitiers Cedex, France

(11) CHU Toulouse, Dermatology Department, 9 place Lange 31300 Toulouse Cedex, France

(12) CHU Bordeaux, Oral Surgery Dermatology Department, Place Amélie Raba Léon 33000 Bordeaux Cedex, France

(13) CHU Montpellier, Dermatology Department, 191 avenue du Doyen Gaston Giraud 34295 Montpellier Cedex, France

Corresponding author: Mahtab Samimi, Université François Rabelais, Tours, France ; INRA, UMR 1282, Tours, France ; Department of Dermatology, CHU Tours, Avenue de la République, 37170 Tours, France ; Phone: +332 47 47 46 25 Fax: +332 34 38 95 15 E-mail: mahtab.samimi@univ-tours.fr

Introduction.

Granulomatous cheilitis (GC) is a rare condition characterized by a chronic granulomatous inflammatory disorder affecting one or both lips, which results to their recurrent or permanent swelling. GC first described by Miescher[1] then classified among the spectrum of orofacial granulomatosis (OFG), which ranges from localized granulomatous cheilitis (Miescher's macrocheilitis) to more complex syndromes with neurological involvement, the most characteristic being the Melkersson-Rosenthal syndrome which includes OFG, facial nerve palsy and lingual fissuring [2]. GC can also be a mucosal manifestation of systemic conditions such as Crohn's disease or sarcoidosis. GC usually displays a chronic course punctuated with intermittent flares, resulting in functional or esthetic discomfort impairing patients' quality of life[13]. Treatment of GC is challenging, without any therapy which has been demonstrated to be effective in reducing permanently the labial enlargement. Although intralesional corticosteroids, with different administration schedules and drug concentration, are currently used as first-line therapies[14], such procedures may be painful, with transient efficacy, and their repeated course mat carry the risk of mucosal atrophy. Systemic corticosteroids often achieve a rapid decrease of the labial swelling in the acute setting, but cannot be used in the long term. By analogy with other chronic inflammatory conditions, immunomodulatory drugs have therefore been suggested as alternative therapies or as corticosteroid-sparing agents for treating GC, in either single case reports or small case series. As such, a comprehensive literature review in 2011 had reported that, beyond corticosteroids, the most promising systemic therapies of CG were antibiotics, clofazimine, methotrexate and biologics, although this was only supported by a few case reports [22]. Therefore, the aim of our study was to assess retrospectively the efficacy of systemic therapies among CG cases recruited within a multidisciplinary french-speaking Oral Mucosa Study Group.

Methods.

Study design, location and settings.

This study was conducted between September 2019 and Februrary 2020 among the GEMUB group, a multidisciplinary french-speaking network involving dermatologists, oral surgeons, maxillo-facial surgeons and odontologists with expertise in managing oral diseases [23]. Cases were collected retrospectively by 12 investigators from this group, by reviewing CG cases treated in their hospital settings between 1995 and 2019.

Inclusion criteria and collected data

Inclusion criteria were the following: patients with CG, defined by clinical diagnosis (firm, permanent swelling of lips with or without acute flares) with a compatible histology (inflammatory lymphocytic infiltrates and/or non-caseating epithelioid and giganto-cellular granulomas) on the basis of currently accepted criteria [6,14]. Indeed, it was previously reported that absence of granulomas does not exclude a diagnosis of CG if clinical features are compatible [6–8]. We included both idiopathic CG (Miescher's macrocheilitis, Melkersson-Rosenthal syndrome) as well as CG associated with a systemic condition (Crohn's disease, sarcoidosis), the latter being diagnosed on the basis of blood tests (including serum angiotensin convertase, C-Reactive Protein, blood cell count), CT-scan and/or endoscopic examinations when needed. Eligible patients should have been treated with one or several lines of systemic therapies, either alone or in combination, for at least one month, with available data regarding efficacy and duration of each line of systemic treatment. Any adjunction of systemic or intralesional corticosteroids during systemic therapy was also collected. Treatment effectiveness had been evaluated during patients' medical visits every 2 to 3 months. As there are no validated objective severity scores for CG, efficacy of systemic therapies was assessed retrospectively in patients' files on the basis of the physician's global assessment as previously described [6,18], as "complete response" (CR), "partial response" (PR) or "no response" (NR) to treatment. Best response (CR, PR or NR) was collected for each modality of treatment. Duration of therapy, time to response, duration of response and recurrences rates among responders were also collected. If a systemic treatment had been withdrawn and subsequently reintroduced, the efficacy of the second course was also reported to assess intra-individual reproducibility.

Outcomes.

Response rates (proportion of responders including CR and PR), complete response rates, time to response, duration of response and recurrence rates were assessed for each modality of treatment in the whole study population, and then according to the underlying disease (Miescher macrocheilitis, Melkerssen-Rosenthal syndrome, Crohn's disease, sarcoidosis).

Statistics.

Continuous data were described as median with first, third quartiles and ranges, and categorical data as numbers and percentages with their 95% confidence intervals (95%CI). Proportional analysis was assessed using the two-tailed Fisher's exact test. Statistical tests were performed using XL-Stat-Life software (Addinsoft, Paris, France). P-values lower than 0.05 were considered significant.

Results.

Characteristics of the study population.

Overall, 61 patients were included in the study. Median age at time of diagnosis was 45.0 years (Q1-Q3 26.0-59.0 years), and 41 (67.2%) were female. CG was either isolated (Miescher's disease) (n=38, 62.3%), part of a Melkersson-Rosenthal syndrome (n=9, 14.7%), associated with Crohn's disease (n=10, 16.5%) or sarcoidosis (n=4, 6.5%). No medical history of immunodepression or contact hypersensitivity reactions were recorded. The mucosal biopsy had evidenced non-caseating granulomas in 48 cases (78.7%) and non-specific lymphocytic inflammation only in 13 cases (21.3%). The median delay between diagnosis and introduction of a systemic drug was 10 months (Q1-Q3 4.0-15.0). Patients had been treated with one line (n=23, 37.7%), two lines (n=19, 31.2%), three lines (n=10, 16.4%), or four or more lines (n=9, 14.7%) of systemic therapies, which resulted in 136 courses of treatments with assessable efficacy (median duration of treatment 6.0 months, Q1-Q3 3.0-9.2). To note, 9 patients had experienced one (n=8) or two (n=1) reintroductions of a previously administered therapy; in such cases, only patients' response to the first course of therapy was included in the overall analysis of efficacy. The median follow up duration was 21 months (Q1-Q3, 7.0-62.0 months) and follow up status was available for 53 patients at 6 months (complete response at 6 months 18.9%, 95%CI 8.3-29.4), 35 patients at 1 year (complete response at 1 year 25.7%, 95%CI 11.2-40.2), 29 patients at 2 years (complete response at 2 years 44.8%, 95%CI 26.7-62.9) and 17 patients at 5 years (complete response at 5 years 41.2%, 95%CI 17.8-64.5).

Response to systemic therapies in the whole study population.

Overall, 33 distinct modalities of systemic therapies were identified, either as monotherapy (n=17) or combined therapy (n=16, including 12 dual combinations and 4 triple combinations). To note, 10 combinations included oral corticosteroids (**Figure 1**). Patients' response to the 136 courses of treatment are reported in **Figure 1**. Overall response (PR or CR) was reported after 100 courses of treatment (73.5%, 95%CI 66.1-80.9) but CR was only reported after 32 courses of treatment (23.5%, 95%CI 16.4-30.6). Overall, the median time to response was 3 months (Q1-Q3, 2-3 months) and the median duration of response was 7 months (Q1-Q3, 4.75-14.25). The proportion of responders (PR or CR) was significantly higher when using combined therapies (92.3%, 95%CI 82.1-100.0) compared to monotherapies (69.0%, 95%CI 60.4-77.7) (p=0.008). However, the proportion of complete responders did not differ between combined therapies (26.9%, 95%CI 9.9-43.9) and monotherapies (22.7% 95%CI 14.9-30.6) (p=0.6). Similarly, the duration of treatment and duration of response did not differ significantly between monotherapies and combined

therapies (data not shown). The proportion of responders was lower for earlier lines (first and second line) (67.0% 95%CI 57.3-76.7) compared to further lines of therapy (86.7%, 95%CI 76.7-96.6) (p=0.01) although the proportion of complete responders did not differ between earlier (25.3%, 95%CI 16.3-34.2) and further lines of therapy (20.0%, 95%CI 8.3-31.7) (p=0.40). After a first response, recurrence was observed in 35 out of 100 courses of treatment (median time to recurrence, 6 months, Q1-Q3 6.0-16.5), with no difference of recurrence rates between monotherapies (37.5%, 95%CI 18.1-56.9) and combined therapies (34.2%, 95%CI 23.5-44.9).

Regarding drugs category, we did not observe any significant difference in response rates between anti-bacterial agents (doxycycline, metronidazole, dapsone, clofazimine) (response rates 66.7%, 95%CI 45.1-79.2), immunomodulatory and/or immunosuppressive drugs (azathioprine, corticosteroids, colchicine, hydroxychloroquine, cyclosporine, methotrexate, thalidomide) (response rates 71.4, 95%CI 57.8-85.1) and biologics (infliximab, adalimumab, ustekinumab, rituximab) (response rates 75.0%, 95%CI 50.5-99.5) (p=0.8). Similarly, we did not observe any significant difference in complete response rates between anti-bacterial agents (CR rates 22.2%, 95%CI 11.1-33.3), immunomodulatory and/or immunosuppressive drugs (CR rates 23.8, 95%CI 10.9-36.7) and biologics (infliximab, adalimumab, ustekinumab, rituximab) (CR rates 25.0%, 95%CI 0.5-49.5%) (p=0.9). A detailed description of treatments which had been assessed in at least 3 patients (doxycycline, clofazimine, hydroxychloroquine, corticosteroids, metronidazole, dapsone, colchicine, infliximab, adalimumab, combined therapy of corticosteroids with either doxycycline or methotrexate) is provided in **Table 1**. Except from metronidazole, all of these therapies had allowed a response in at least half of patients (median duration of response 6.5 months, Q1-Q3 4.0-14.5 months). However, only three of these regimens (clofazimine, colchicine, and corticosteroids combined with doxycycline) had allowed complete responses in at least one third of patients (median duration of response among complete responders, 9 months, Q1-Q3 6-13 months) (**Table 1**).

Response to systemic therapies according to the underlying disease.

Patients' responses to systemic therapies according to their underlying condition are reported in **Figure 2** and **Figure 3.** The proportion of responders (partial and complete responses) did not differ significantly between patients with idiopathic CG (Miescher's macrocheilitis, Melkersson-Rosenthal syndrome) (77.5%, 95%CI 69.3-85.8) compared to those with secondary CG (Crohn's disease, sarcoidosis) (63.2%, 95%CI 47.8-78.5) (p=0.09). Similarly, the proportion of complete responders did not differ either between groups (24.5%, 95%CI 16.0-33.0 compared to 21.0%, 95%CI 8.1-34.0). Overall, the proportion of responders or

complete responders did not differ significantly according to the underlying disease (data not shown). The proportion of responders and complete responders among patients with Miescher's macrocheilitis was 74.7% (95%CI 65.1-84.3) and 21.5% (95%CI 12.5-30.6), respectively. All of the regimens which had been assessed in at least 3 patients with Miescher's macrocheilitis (doxycycline, clofazimine, hydroxychloroquine, oral corticosteroids, metronidazole, infliximab, combination of oral corticosteroids and doxycycline) had allowed responses in at least half of cases (**Figure 2**). To note, all patients had responded to oral corticosteroids (either alone or combined with doxycycline) or infliximab. On the other hand, only clofazimine, infliximab and oral corticosteroids combined with doxycycline had allowed complete responses in at least one third of patients (**Table 2**). Although assessed in only few cases, a complete response was also observed after treatment with rituximab (n=1), colchicine combined with oral corticosteroids (n=1), thalidomide combined with doxycycline (n=1) (**Figure 2**). The proportion of responders and complete responders among patients with Melkersson-Rosenthal syndrome was 89.5% (95%CI 75.7-100.0) and 36.8% (95%CI 15.1-58.5), respectively. All patients with a Melkersson-Rosenthal syndrome who had been treated with doxycycline (n=3) or clofazimine (n=3) had responded to treatment, though a complete response was observed in one case only for each drug (**Table 2** and **Figure 3A**). Although assessed in only few cases, a complete response was also observed after treatment with colchicine (n=1), thalidomide (n=1) and azathioprine (n=1) (**Figure 3A**). The proportion of responders and complete responders among patients with Crohn's disease was 60.0% (95%CI 42.5-77.5) and 16.7% (95%CI 3.3-30.0), respectively. At least two thirds of patients with Crohn's disease had responded to clofazimine (n=2), oral corticosteroids (n=3) or adalimumab (n= 3) although complete response was observed in one case only for each drug (**Table 2** and **Figure 3B).** To note, metronidazole which had been assessed in three patients with Crohn's disease. did not provide any efficacy on their CG (**Table 2** and **Figure 3B).** Although assessed in only few cases, a complete response was also observed after combination of vedolizumab and azathioprine (n=1), and triple combination of adalimumab, azathioprine and clofazimine (n=1) (**Figure 3B**). The proportion of responders and complete responders among patients with sarcoidosis was 75.0% (95%CI 45.0-100.0) and 37.5% (95%CI 3.9-71.0), respectively. Although assessed in only few cases, a complete response was observed after treatment with doxycycline (n=1), combination of hydroxychloroquine and oral corticosteroids (n=1), combination of methotrexate and oral corticosteroids (n=1) (**Figure 3C**).

Response after reintroduction of a systemic treatment

Nine patients had experienced one (n=8) or two (n=1) reintroductions of a previously administered therapy (**Figure 4).** In most cases (n=8), the efficacy remained similar after drug reintroduction (partial response, n=7, absence of response, n=1). In two cases, patients had experienced partial response after first course of treatment and achieved complete response after reintroduction (clofazimine for Crohn's disease and infliximab for Miescher's macrocheilitis) (**Figure 4**).

Discussion.

To our knowledge, we report the largest series assessing the efficacy of systemic treatments in patients with CG. The absence of validated strategy in this setting is illustrated by the wide heterogeneity of prescriptions in our series, with more than 30 distinct modalities of systemic therapy, either alone or combined. Most systemic therapies were at least partially efficient in 70% of cases, but the median duration of response reached only a few months and recurrence occurred in more than one third of cases. Complete response was only achieved in 20% of cases. Overall, this modest efficacy resulted in frequent drug rotation, with up to 3 lines of systemic therapies in one third of patients. On the other hand, we observed a progressive remitting behavior of the disease, as the proportion of complete responders slowly increased overtime: 18% at 6 months, 25% at 1 year, and 40% at 2 years and 5 years.

Previous reports of the efficacy of systemic drugs in CG, either primary or associated with other conditions, are reviewed in **Table 3**. These were mostly single case reports and small case series, with only 4 retrospective studies describing more than ten patients [18–21], including one large study assessing efficacy of azathioprine among 60 patients with primary and secondary CG [18]. Although such review carries the risk of reporting bias, we can estimate that the proportions of patients with overall response and complete response to systemic drugs in these case series reached 60% and 20% of cases, respectively (**Table 3**). Interestingly, these response rates are quite similar to our results, as overall response (PR or CR) and complete responses were observed after 70% and 20% of courses of systemic therapies, respectively. We did not observe any significant difference in response rates or complete response rates between the categories of anti-bacterial agents (doxycycline, metronidazole, dapsone, clofazimine), immunomodulatory and/or immunosuppressive drugs (azathioprine, corticosteroids, colchicine, hydroxychloroquine, cyclosporine, methotrexate, thalidomide) or biologics (infliximab, adalimumab, ustekinumab, rituximab). Regarding the efficacy of each individual drug, systemic corticosteroids were frequently prescribed and allowed high rates of response, as expected – however, regimens ranging from 0.1 to 1mg/kg/day allowed complete responses in only one third of patients. Besides, systemic

corticosteroids cannot be used in the long-term, and the median duration of treatment in our series was indeed quite short (4 months, Q1-Q3 3-6 months). Alternative options included systemic antibiotics, especially doxycycline which is frequently efficient on chronic skin inflammatory conditions thanks to its anti-inflammatory effects [24]. Doxycycline was frequently prescribed (100-200 mg daily) with an average efficacy, as responses and complete responses were observed in 65% and 20% of cases respectively, slightly higher than previously described (**Table 3**) [3,25–38]. Metronidazole, which has anaerobic antibacterial spectrum as well as immunomodulatory properties [39], has previously been suggested as a promising systemic therapy of CG, either primary or associated with Crohn's disease [19,25–27,40–46]. However, the regimens reported in our series (250-1000mg daily, median duration of treatment 3 months) provided disappointing results as they allowed responses in only one third of patients, without any case of complete response, even in the subset of patients with Crohn's disease. By contrast, we observed the highest rates of complete responses with clofazimine (50-200mg daily), a riminophenazine dye which exerts anti-microbial and anti-inflammatory properties - though the exact mechanisms of action have not been fully elucidated [47]. Our efficacy rates appeared higher than previous case reports [3,4,19–21,30,31,40,41,48–54] (**Table 3**). Long-term use of clofazimine is typically hampered by the occurrence of ichthyosis and pigmentation, which may account for the short duration of therapy in our series (median 5 months, Q1-Q3 3.0-10.0 months). On the other hand, clofazimine has even been used during several years in previous case series [20]. Dapsone (50-100mg/day), which is also an anti-leprosy drug with anti-inflammatory effects, did not provide any complete responses in our case series, by contrast with previous reports [19,21,28,29,32,38,43,46,48,49,55–60]. Immunomodulating agents such as hydroxychloroquine (200-600mg/day) or colchicine (1mg per day) had average efficacy, with overall responses in approximately two thirds of patients. Interestingly, colchicine, which had seldom been reported for treating CG [28,55] (**Table 3**) had however allowed a complete long-term response in one case from our series. Immunosuppressive drugs such as methotrexate (10-17.5mg/week), cyclosporine (4mg/kg/day) or azathioprine (1-2mg/kg/day) were rarely used in our series, and had only mostly allowed partial and transient, in line with previous reports (**Table 3**) [18–20,26,32,34,43,61–69]. To note, although assessed in only three patients from our series, two complete responses were observed with thalidomide (including one patient treated by combination of thalidomide and doxycycline). Similarly, thalidomide was found to provide complete responses in most of previously reported CG cases (**Table 3**) [21,34,48,49,55,61,70]. Thalidomide exerts various effects on the immune

system, including inhibition of neutrophils, prevention of lymphocyte proliferation and inhibition of pro-inflammatory cytokines (TNF alpha, IGN-gamma IL-8, IL-12) [71]. Thalidomide has been found to be effective in decreasing cutaneous sarcoidosis, by promoting granuloma differentiation to a Th1-type cellular immune response [72]. It has been hypothesized that the efficacy of thalidomide in OFG was related to its TNF-alpha inhibitory effect, by analogy with the efficacy of anti-TNF-alpha biological agents [22]. Indeed, we observed that infliximab and adalimumab had allowed response in nearly all treated patients in our case series, as previously reported (**Table3**) [3,19,20,26,27,30,31,33,38,42,44,48,62,63,66,67,73–77], although complete response rates reached only 25% of cases. On the other hand, duration of response to infliximab was the highest among all reported drugs (median duration of response 40.0 months, Q1-Q3 25.5-55.0). To note, ustekinumab, which has been reported in a single case report previously (**Table 3**) [34], did not provide any response among the two patients with Crohn's disease in our series.

When compared to monotherapies, combined therapies only provided a slight benefit. Although the proportion of responders was significantly higher when using combined therapies, the proportion of complete responders, duration of therapy and duration of response did not differ significantly. Overall, 10 out of 16 combinations included oral corticosteroids, and we can hypothesize that such strategy rather aimed to avoid side effects of long-term use of corticosteroids, though this specific issue was not assessed in our study.

Counterintuitively, long-lasting disease did not seem to be associated with a more refractory course. For instance, all cases of drug reintroduction led to a similar or even better response than the first course of therapy. Such observation may be related to a progressive remitting behavior of the disease. Although approximately half of the study population was lost to follow up after 1 year, we observed that 25% of patients were in complete remission at 1 year, and 40% at 2 years and 5 years. This was quite similar to a previous study including 49 OFG patients, which reported that 25% of patients had complete resolution of their disease within the first year of treatment and 50% after three years of treatment [6,14,40]. This remitting profile may also explain why the proportion of responders was lower for earlier lines (first and second line) when compared to further lines of therapy.

Our case series included both patients with idiopathic CG as well as those with systemic granulomatous disease (e.g. Crohn disease or sarcoidosis), in order to figure out whether these disorders may respond to therapy differently. Indeed, it has been previously reported that such conditions may respond preferentially to different therapies – for instance, azathioprine was found to be more efficient in the treatment of OFG with a concurrent diagnosis of Crohn's disease rather than in the treatment of OFG alone [18]. Aetiological mechanisms of primary OFG are poorly understood, and have been related to CD4 and CD8 T-cell activation with altered cytokine production [78]. There are close connections between CG and Melkersson-Rosenthal syndrome, which are included in the same spectrum of OFG, and with Crohn's disease which can be diagnosed several years after diagnosis of OFG [79,80]. In our series, the proportion of responders to systemic therapies did not differ significantly between patients with idiopathic CG (Miescher's macrocheilitis, Melkersson-Rosenthal syndrome) compared to those with secondary CG (Crohn's disease, sarcoidosis), or according to the underlying disease. However, given the small number of patients with secondary CG, we were not able to conclude whether efficacy of individual drugs differed according to the underlying condition. Overall, clofazimine, oral corticosteroids, and TNFalpha antagonists appeared to provide similar responses in all subsets of patients. To note, the mucosal biopsy had evidenced non-caseating granulomas in only 80% of cases, and non-specific lymphocytic inflammation in the remaining cases. However, it had previously been shown that histological assessment of OFG can be difficult. As such, non-caseating granulomas were identified in approximately 50% of mucosal biopsies in previous case series, whereas non-specific inflammatory infiltrates are observed in most specimens [6–8]. Overall, absence of granulomas does not exclude a diagnosis of CG if clinical features are compatible and further investigations had been adequately carried out for the diagnosis of a systemic condition.

We cannot exclude that our study population may be not representative of the majority of cases of CG. By including only patients who required a systemic therapy, we may have induced a selection bias in our study population who is likely to reflect the most severe, refractory cases of CG, as these patients had failed to respond to first-line topical or intralesional corticosteroids. Although our study population comprised young adults, which is quite similar to previous reports of patients with OFG, the proportion of females were higher than previously described [5,6,20,81]. Such sex-ratio may be related to a more severe course of disease among females, or such patients may experiment a more severe impact of the disease and seek for more efficient treatments. On the other hand, the long-term outcome of our cohort does not seem more severe than previously reported, as 25% and 40% of patients

were in complete remission at 1 year and 2 years respectively, which was quite similar to previously reported rates (25% of complete resolution within the first year of treatment and 50% after three years of treatment) [6,14,40].

Our study has some limitations. First, the small number of patients in each subset of disease, prevented us from proper comparisons of the efficiency of individual drugs according to the underlying disease. Second, retrospective assessment of efficacy was challenging, as objective severity scores are not available for CG. In previous case series, disease severity was similarly based on physician's global assessment [6,18] or using semi-quantitative scores such as absent/mild/moderate/severe swelling [14]. Despite the obvious relevance of patient's reported outcome such as quality of life [13] in such disorder, these data were not available either. Finally, there was a progressive remitting behavior of the disease overtime, which may have interfered with the observed efficacy of drugs.

Taken together, we report the largest series of systemic drugs among patients with CG, suggesting that most therapies allow partial and transient efficacy, which may be increased by combined therapies. The disease typically displays a remitting behavior, but only 40% of patients are in complete remission after 4 years. Clofazimine, corticosteroids and TNFalpha antagonists provided the highest rates of complete responses, with the latter allowing a long-term use. Doxycycline, colchicine and thalidomide appear may be considered before or as alternative options to TNFalpha antagonists.

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Tables

Table 1. Modalities and efficacy of systemic therapies in the whole study population*

Therapy	Number of patients	Drug dosage	Duration of therapy (months) (median, Q1-Q3)	Response rates** (%, 95%CI)	CR rates (%, 95%CI)	Duration of response** (months) (median, Q1-Q3)	Recurrence rates** (%, 95%CI)
Monotherapy							
doxycycline	21	100-200mg/day	4.0 (3.0-9.0)	66.7 (46.5-86.8)	19.0 (2.3-35.8)	8.0 (6.0-15.0)	28.6 (4.9-52.2)
CFZ	21	50-200mg/day	5.0 (3.0-10.0)	72.6 (58.0-94.4)	38.1 (17.3-58.9)	9.0 (4.75-14.25)	56.2 (31.9-80.6)
HCQ	18	200-600mg/day	6.0 (3.0-8.0)	50.0 (26.9-73.1)	16.7 (0-33.9)	6.0 (6.0-15.0)	22.2 (0-49.4)
CS	14	0.1-1mg/kg/day	4.0 (3.0-6.0)	92.9 (79.4-100)	28.6 (4.9-52.2)	6.0 (3.0-14.0)	23.1 (0.2-46.0)
MTZ	9	250-1000mg/day	3.0 (2.0-6.0)	33.3 (2.5-64.1)	0 (0-0)	10.0 (8.0-14.5)	33.3 (0-86.7)
dapsone	3	50-100mg/day	3.0 (2.0-7.5)	100 (100-100)	0 (0-0)	3.0 (2.0-7.5)	33.3 (0-86.7)
colchicine	3	1mg/day	4.0 (2.5-10.5)	66.7 (13.3-100).	33.3 (0-86.7)	10.5 (7.25-13.75)	0 (0-0)
IFX	4	5mg/kg/infusion	17.5 (4.75-35.0)	100 (100-100)	25.0 (0-67.4)	40.0 (25.5-55.0)	50.0 (1.0-98.9)
ADA	5	40mg/week	6.0 (5.0-8.0)	80.0 (77.9-100)	20.0 (0-55.1)	5.0 (4.75-6.25)	25.0 (0.0-67.5)
Combined therapy							
Cycline + CS	5	100-200mg/day 1mg/kg/day	5.0 (3.0-6.0)	100 (100-100)	40.0 (0-82.9)	6.0 (5.0-11.0)	60.0 (17.1-100.0)
MTX + CS	5	15mg/week 0.3-1mg/kg/day	4.0 (3.0-6.0)	100 (100-100)	0 (0-0)	4.0 (2.0-6.0)	20.0 (0.0-55.1)

only therapies which had been assessed in at least 3 patients are provided. ** assessed in patients with partial or complete responses.

CFZ, clofazimine; HCQ, hydroxychloroquine; CS, corticosteroids; MTZ, metronidazole; IFX, infliximab; ADA, adalimumab; MTX, methotrexate; CR, complete responses.

Table 2. Modalities and efficacy of systemic therapies, according to underlying disease*.

Therapy	Number of patients	Duration of therapy (months) (median, Q1-Q3)	Response rates** (%, 95%CI)	CR rates (%, 95%CI)	Duration of response** (months) (median, Q1-Q3)	Recurrence rates** (%, 95%CI)
Miescher's macrocheilitis (n=38 patients)						
doxycycline	15	4.0 (3.0-8.0)	66.7 (42.8-90.5)	20.0 (0-40.2)	6.5 (4.5-11.25)	20.0 (0.0-44.8)
CFZ	14	9.0 (7.0-11.5)	78.5 (57.1-100.0)	42.8 (16.9-68.8)	9.0 (7.0-11.5)	54.5 (25.1-84.0)
HCQ	14	6.0 (3.5-11.0)	50.0 (23.9-76.2)	21.0 (0-42.9)	12.0 (6.0-22.0)	14.3 (0.0-40.2)
CS	7	4.0 (3.5-10.0)	100.0 (100.0-100.0)	0 (0-0)	6.0 (3.5-11.0)	14.3 (0.0-40.2)
MTZ	6	4.0 (2.0-9.0)	50.0 (10.0-90.0)	0 (0-0)	10.0 (8.0-14.5)	33.3 (0.0-86.7)
IFX	3	5.0 (4.5-27.5)	100.0 (100.0-100.0)	33.3 (0-86.7)	50.0 (60.0-31.0)	66.7 (13.3-100.0)
Cycline CS	5	6.0 (4.0-7.0)	100 (100-100)	33.3 (0-86.7)	6.0 (3.5-8.5)	33.3 (0.0-86.7)
Melkersson-Rosenthal syndrome (n=9 patients)						
doxycycline	3	6.5 (7.0-11.5)	100 (100.0-100.0)	33.3 (0-86.7)	16.0 (14.0-17.50)	66.7 (13.3-100.0)
CFZ	3	3.0 (3.0-4.0)	100 (100.0-100.0)	33.3 (0-86.7)	3.0 (3.0-4.0)	66.7 (13.3-100.0)
HCQ	3	3.0 (2.0-5.5)	33.3 (0-86.7)	0 (0-0)	3.0 (3.0-3.0)	0 (0-0)
Crohn's disease (n=10 patients)						
CFZ	3	4.0 (2.5-14.0)	66.7 (13.2-100.0)	33.3 (0-86.7)	37.0 (30.5-43.5)	50.0 (0.0-100.0)
CS	4	3.50 (2.75-4.5)	75.0 (32.6-100.0)	25.0 (0-67.4)	10.5 (18.0-27.5)	66.7 (13.3-100.0)
MTZ	3	3.0 (2.5-3.0)	0 (0-0)	0 (0-0)	NA	NA
ADA	4	5.5 (4.75-7.0)	75.0 (32.6-100.0)	25.0 (0-67.4)	5.0 (4.5-7.5)	33.3 (0.0-86.7)

only therapies which had been assessed in at least 3 patients are provided. ** assessed in patients with partial or complete responses.

CFZ, clofazimine; HCQ, hydroxychloroquine; CS, corticosteroids; MTZ, metronidazole; IFX, infliximab; ADA, adalimumab; CR, complete responses; NA, not applicable.

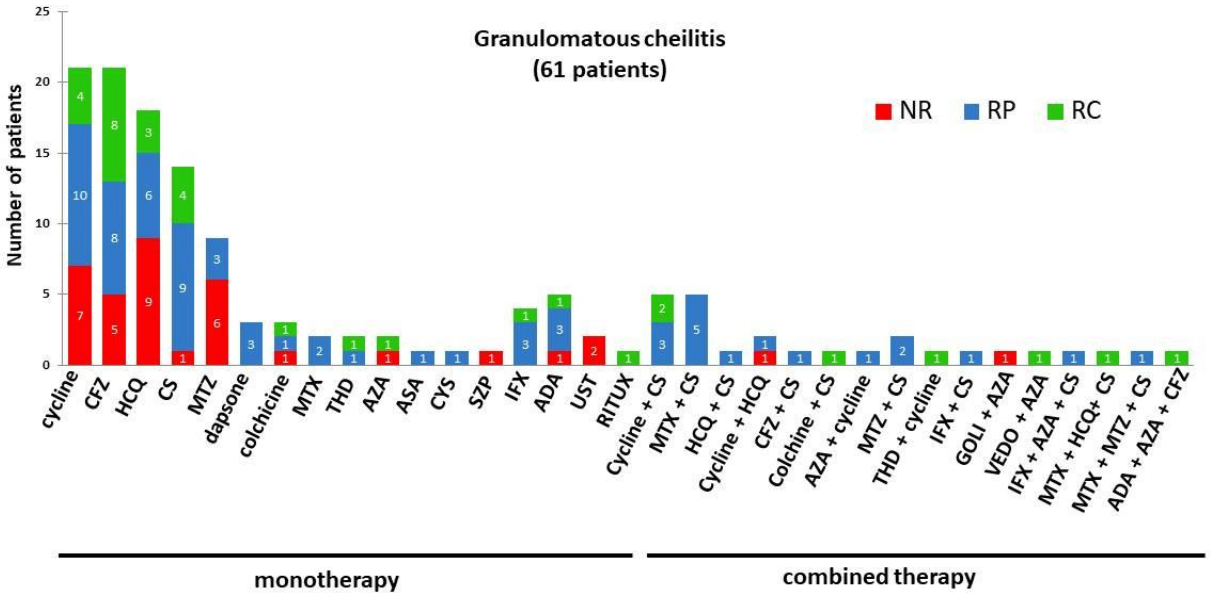
Table 3. Efficacy of systemic drugs in CG: literature review.

Drug	Reported cases with available response*	Complete Response		Partial Response		No Response	
		Number of cases / sample size of study (references)	CR rates among reports	Number of cases / sample size of study (references)	PR rates among reports	Number of cases / sample size of study (references)	NR rates among reports
Clofazimine	45	1/1 [50], 4/9 [20]	5 out of 45 **(11%)**	3/3 [51], 1/4 [40], 1/1 [41], 1/1 [52], 1/5 [19], 4/4 [54], 5/5 [21], 3/9 [20], 1/1 [48], 1/1 [4]	21 out of 45 **(47%)**	1/1 [30], 1/1 [3], 1/1 [53], 3/4 [40], 4/5 [19], 6/6 [31], 2/9 [20], 1/1 [49]	19 out of 45 **(42%)**
Metronidazole	25	2/2 [42], 5/13 [19], 1/1 [43], 1/1 [82], 1/1 [25]	10 out of 25 **(40%)**	1/1 [44], 1/1 [41], 1/1 [26], 1/1 [45], 3/13 [19], 1/1 [27]	8 out of 25 **(32%)**	1/1 [40], 5/13 [19], 1/1 [46]	7 out of 25 **(28%)**
Cycline	22	1/2 [28], 1/1 [25]	2 out of 22 (**9%**)	2/2 [29], 1/1 [30], 1/2 [28], 1/1 [26], 1/6 [31], 1/1 [27], 1/1 [32]	8 out of 22 (**36%**)	1/1 [33], 1/1 [34], 1/1 [35], 1/1 [3], 1/1 [36], 1/1 [38], 1/1 [37], 5/6 [31]	12 out of 22 (**55%**)
Dapsone	20	1/1 [38], 4/5 [56], 1/1 [58]	6 out of 20 (**30%**)	1/1 [29], 1/1 [60], 1/1 [28], 1/5 [56], 1/1 [21], 1/1 [57], 1/1 [32], 1/1 [49]	8 out of 20 (**40%**)	1/1 [59], 1/1 [19], 1/1 [43], 1/1 [46], 1/1 [55], 1/1 [48]	6 out of 20 (**30%**)
Macrolides	16	1/1 [35], 1/5 [41], 1/1 [83]	3 out of 16 (**19%**)	3/5 [64], 4/5 [41]	7 out of 16 (**44%**)	2/5 [64], 1/1 [30], 1/1 [35] 1/1 [36], 1/1 [53]	6 out of 16 (**37%**)
Azathioprine	77	1/1 [62], 1/3 [66], 2/2 [20] 1/2 [84], 1/1 [67]	6 out of 77 (**8%**)	22/60 [18], 2/2 [26], 2/3 [66] 1/1 [32], 1/2 [84]	28 out of 77 (**36%**)	1/1 [65], 1/1 [34], 38/60 [18], 1/1 [62], 1/1 [43], 1/1 [61]	43 out of 77 (**56%**)
Other thiopurines	3	1/1 [66]	1 out of 3 (33%)	1/2 [66]	1 out of 3 (33%)	1/2 [66]	1 out of 3 (33%)
SZP and other aminosalicylates	21	1/1 [85], 1/7 [86], 1/1 [84]	3 out of 21 (**14%**)	1/1 [28], 1/1 [26], 4/7 [86], 2/2 [67], 1/2 [40], 1/1 [45]	10 out of 21 (**48**%)	1/1 [65], 2/3 [40], 1/1 [46], 2/2 [55], 2/7 [86]	8 out of 21 (**38**%)
Methotrexate	11	1/5 [19], 1/1 [32]	2 out of 11 (**18**%)	1/1 [26], 1/5 [19], 1/1 [63]	3 out of 11 (**27**%)	1/1 [69], 3/5 [19], 1/1 [66], 1/1 [68]	6 out of 11 (**55**%)
Thalidomide	11	1/1 [34], 5/5 [55], 1/1 [48] 1/1 [70], 1/1 [61]	9 out of 11 (**82**%)	1/1 [21], 1/1 [49]	2 out of 11 (**18**%)	NA	NA
HCQ	10	1/1 [36], 1/2 [19], 1/1 [87]	3 out of 10 (**30**%)	1/1 [29], 1/2 [19], 1/1 [88]	3 out of 10 (**30**%)	3/3 [40], 1/1 [46]	4 out of 10 (**40**%)
Colchicine	2	NA	NA	1/1 [28]	1 out of 2 (**50**%)	1/1 [55]	1 out of 2 (**50**%)
MMF	1	1/1 [33]	1 out of 1 (**100**%)	NA	NA	NA	NA
Infliximab	29	1/1 [73], 1/1 [30], 1/2 [74], 1/1 [38], 1/1 [62], 2/9 [66], 1/1 [75], 2/2 [20], 1/11 [76], 1/1 [67]	12 out of 29 (**41**%)	1/1 [34], 2/2 [3], 1/2 [74] , 1/1 [26], 1/1 [45], 1/1 [77], 4/9 [66], 1/1 [46]	12 out of 29 (**41**%)	1/1 [19], 1/1 [43], 3/9 [66]	5 out of 29 (**18**%)
Adalimumab	10	2/4 [74], 1/1 [76], 1/1 [63]	4 out of 10 (**40**%)	1/1 [53], 1/4 [74], 1/1 [75], 1/1 [49]	4 out of 10 (**40**%)	1/1 [34], 1/4 [74]	2 out of 10 (**20**%)
Certolizumab	1	NA	NA	1/1 [74]	1 out of 1 (**100**%)	NA	NA
Ustekinumab	1	NA	NA	1/1 [34]	1 out of 1 (**100**%)	NA	NA
Omalizumab	1	NA	NA	1/1 [69]	1 out of 1 (**100**%)	NA	NA

***** Literature search conducted in Pubmed with "macrocheilia" OR "cheilitis granulomatosa" OR "granulomatous cheilitis" OR "Miescher cheilitis" AND "therapeutics" OR "treatments" between 1990 and 2019 (English language). To note, efficacy reports of systemic corticoids were the following: 9 complete response, 51 partial response and 20 with no response over 80 reports (data not shown**).** ***SZP, salazopyrine; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil.***

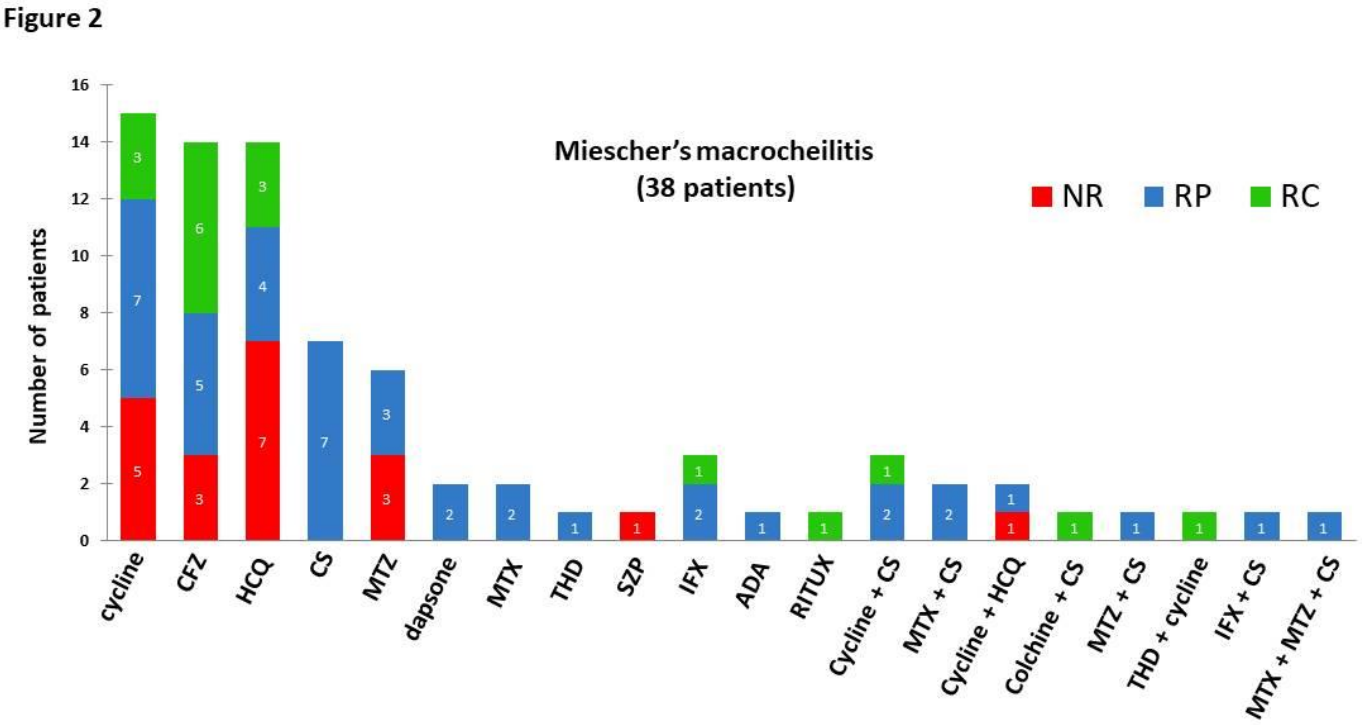
Figure 1. Efficacy of systemic therapies in the whole study population of CG (n=61 patients). Best response (non-responders, complete or partial responders) is indicated.

Figure 1



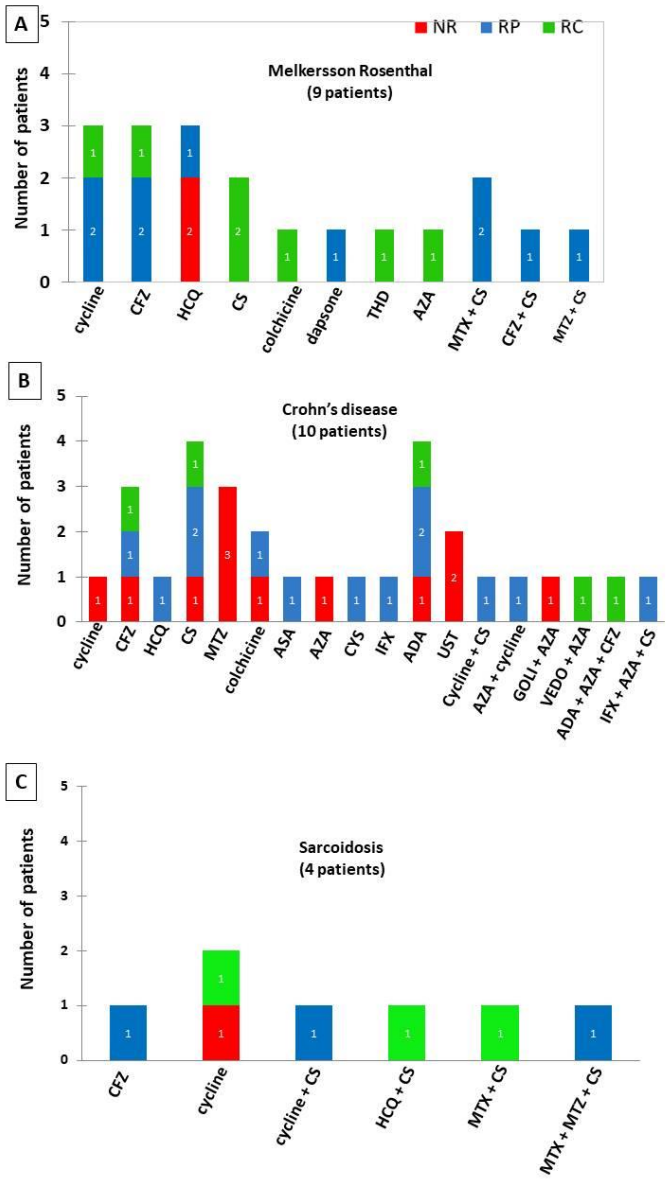
CFZ, clofazimine ; HCQ, hydroxychloroquin ; CS, corticosteroids ; MTZ, metronidazole ; MTX, methotrexate ; THD, thalidomide ; AZA, azathioprine ; ASA, 5-aminosalicylic acid; CYS, cyclosporine ; SZP, salazopyrine ; IFX, infliximab ; ADA, adalimumab ; UST, ustekinumab ; RITUX, rituximab ; GOLI, golimumab ; VEDO, vedolizumab

Figure 2. Efficacy of systemic therapies in patients with Miescher's macrocheilitis (n=38). Best response (non-responders, complete or partial responders) is indicated.



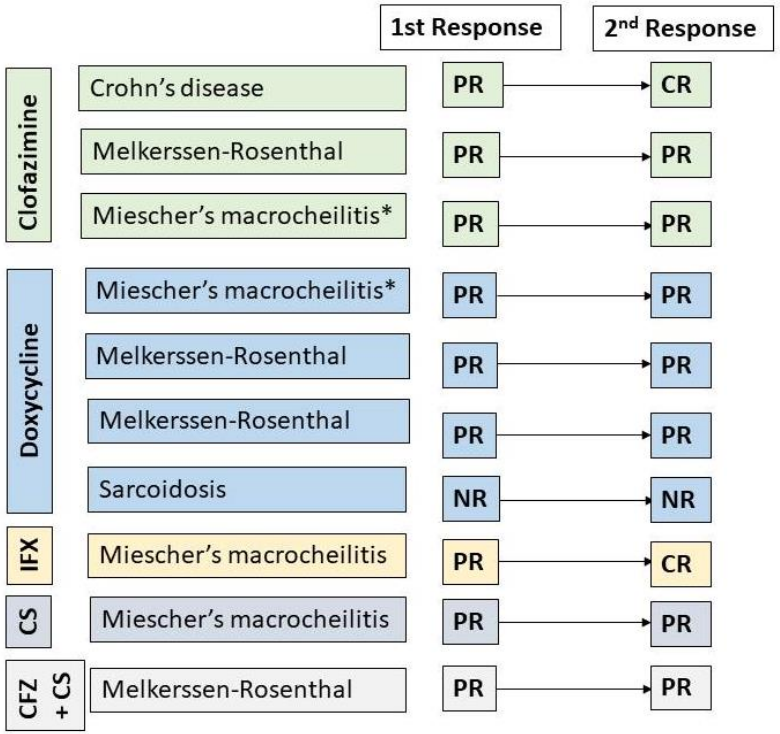
CFZ, clofazimine; HCQ, hydroxychloroquine ; CS, corticosteroids ; MTZ, metronidazole ; MTX, methotrexate ; THD, thalidomide ; SZP, salazopyrine ; IFX, infliximab ; ADA, adalimumab ; RITUX, rituximab

Figure 3. Efficacy of systemic therapies in patients with Melkersson Rosenthal syndrome (n=9, panel A), Crohn's disease (n=10, panel B) and sarcoidosis (n=4, panel C).



CFZ, clofazimine ; HCQ, hydroxychloroquine ; CS, corticosteroids ; MTZ, metronidazole ; MTX, methotrexate ; THD, thalidomide ; AZA, azathioprine ; ASA, 5-aminosalicylic acid ; CYS, cyclosporine ; IFX, infliximab ; ADA, adalimumab ; UST, ustekinumab ; GOLI, golimumab; VEDO, vedolizumab.

Figure 4. Efficacy of reintroduction of a previously administered systemic therapy. Nine patients are represented (* represents one patient who had two reintroductions).



CFZ, clofazimine ; CS, corticosteroids ; IFX, infliximab ; PR, partial response ; CR, complete response : NR, non-response

Annexe 1. Questionnaire de Recueil

Fiche de recueil: macrochéilite granulomateuse et traitements systémiques

- Caractéristiques démographiques : Sexe : Age au diagnostic :
- Date de diagnostic : ..../.....
- Diagnostic : ▫ Chéilite granulomateuse de Miescher / granulomatose oro-faciale primaire
  ▫ Maladie de Crohn ▫ Sarcoidose ▫ Syndrome de Melkersson Rosenthal

- Confirmation histologique: OUI / NON, *si NON : diagnostic clinique avec histologie non contributive ou absence d'histologie ?*
- Traitement chirurgical : OUI, date : ... /... NON

Lignes de traitements systémiques

RC, rémission complète. RP, rémission partielle. S, stabilité. P, progression.

1ere ligne :					Date de début :	Posologie initiale :	
Evolution	RC	RP	S	P	Récidive	Traitements associés (lesquels, posologie ?)	Modification de la posologie ? (laquelle ?)
M3							
M6							
M12							
M24							
M ?							
Date d'arrêt :					Motif d'arrêt :		
Commentaires libres* :							

2eme ligne :					Date de début :	Posologie initiale :	
Evolution	RC	RP	S	P	Récidive	Traitements associés (lesquels, posologie ?)	Modification de la posologie ? (laquelle ?)
M3							
M6							
M12							
M24							
M ?							
Date d'arrêt :					Motif d'arrêt :		
Commentaires libres* :							

3eme ligne :					Date de début :	Posologie initiale :	
Evolution	RC	RP	S	P	Récidive	Traitements associés (lesquels, posologie ?)	Modification de la posologie ? (laquelle ?)
M3							
M6							
M12							
M24							
M ?							
Date d'arrêt :					Motif d'arrêt :		
Commentaires libres* :							

4eme ligne :					Date de début :	Posologie initiale :	
Evolution	RC	RP	S	P	Récidive	Traitements associés (lesquels, posologie ?)	Modification de la posologie ? (laquelle ?)
M3							
M6							
M12							
M24							
M ?							
Date d'arrêt :					Motif d'arrêt :		
Commentaires libres* :							

* *Compléments utiles : périodes d'arrêts ? récidive liée à une décroissance de la posologie ? effets secondaires ?*

Vu, le Directeur de Thèse

Vu, le Doyen

De la Faculté de Médecine de Tours

Tours, le

JAOUEN Frédéric

41 pages – 3 tableaux – 4 figures – 1 annexe

Résumé :

Introduction. La macrochéilite granulomateuse est une entité inflammatoire rare, qui peut être isolée, associée au syndrome de Melkersson-Rosenthal ou à des maladies systémiques (maladie de Crohn, sarcoïdose). L'évolution est souvent chronique, entrecoupée de poussées inflammatoires. Bien que la corticothérapie, intra-lésionnelle ou systémique, soit efficace à court terme, son utilisation au long cours ne peut être préconisée. Il existe très peu de données sur l'efficacité des traitements systémiques dans la macrochéilite granulomateuse. Notre objectif était d'évaluer l'efficacité des traitements systémiques dans une série rétrospective de macrochéilites granulomateuses, en fonction de l'étiologie sous-jacente.

Matériel et méthodes. Il s'agissait d'une étude rétrospective des cas de macrochéilites granulomateuses, toutes étiologies confondues, traitées par au moins une ligne de traitement systémique entre 1995 et 2019 par les praticiens du réseau GEMUB (Groupe d'Etudes de la Muqueuse Buccale). L'efficacité était évaluée rétrospectivement et classée en « réponse complète », « réponse partielle » et « absence de réponse » ; le délai et la durée de réponses étaient également collectées.

Résultats. Parmi les 61 patients inclus, la macrochéilite correspondait à une forme idiopathique de Miescher (n=38, 62.3%), à un syndrome de Melkersson-Rosenthal (n=9, 14.7%), à une maladie de Crohn (n=10, 16.5%) ou une sarcoïdose (n=4, 6.5%). Le délai median entre le diagnostic et l'introduction d'un traitement systémique était de 10 mois (Q1-Q3 4.0-15.0). Les patients avaient été traités par une ligne (n=23, 37.7%), deux lignes (n=19, 31.2%), trois lignes (n=10, 16.4%), ou quatre lignes et plus (n=9, 14.7%) de traitements systémiques, correspondant à 136 séquences thérapeutiques évaluables (durée médiane de traitement 6.0 mois, Q1-Q3 3.0-9.2), réparties en 33 modalités de traitements (monothérapies, n=17 ; traitements combinés, n=16). La durée médiane de réponse était de 7 mois (Q1-Q3, 4.75-14.25). Toutes étiologies confondues, les monothérapies par doxycycline, clofazimine, hydroxychloroquine, corticoïdes, dapsone, colchicine, infliximab, adalimumab permettaient des réponses (partielles ou complètes) dans plus de 50% des cas, tandis la clofazimine, la colchicine et les corticoïdes oraux permettaient des réponses complètes dans plus de 30% des cas. En cas de macrochéilite de Miescher, seule la clofazimine, l'infliximab et la doxycycline permettaient des réponses complètes dans plus de 30% des cas. L'effectif des patients traités pour les autres étiologies étaient faibles, mais les traitements par doxycycline, clofazimine, corticostéroïdes et adalimumab étaient les plus fréquemment efficaces.

Discussion. Nous décrivons la série de plus large effectif sur l'efficacité des traitements systémiques dans cette pathologie rare. Bien que de nombreuses molécules ait permis une réponse partielle ou complète, celle-ci était en général de courte durée, motivant plusieurs lignes thérapeutiques successives. La clofazimine, les corticoïdes et les biologiques anti-TNF alpha étaient les traitements les plus efficaces.

Mots clés : Macrochéilites granulomateuses ; Granulomatose oro-faciale ; Syndrome de Melkersson-Rosenthal ; Traitements

Jury : Président du Jury : Professeur Loïc VAILLANT
Directeur de thèse : Pr Mahtab SAMIMI
Membres du Jury : Pr François MAILLOT, Dr Aline JOLY, Dr Adeline PERRINAUD

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