Impact of COVID-19 on leprosy reactions and of leprosy treatments on COVID-19 severity

Sir,

There is some uncertainty regarding the impact COVID-19 has on the course of dermatoses and how dermatologic treatments influence the disease's severity. Actually, leprosy reactions (types 1 and 2) and neuritis can be associated with infections, while thalidomide, corticosteroids, and clofazimine have been suggested as potential treatments for COVID-19.[1–3] In this study, we aimed to investigate the influence of COVID-19 on the clinical course of leprosy, and to explore the effects of leprosy treatments on COVID-19 severity.

A nationwide online self-reported survey was conducted in Brazil. Between May and October 2021, we recruited participants through 88,648 text messages, from a countrywide telephonic database. Additionally, patients with leprosy who reported COVID-19 infection, mainly from the Hospital of Tropical Diseases (Goiânia, Goiás) and Brasília University Hospital (Brasília, Federal District), were included. The subjects were asked to complete an electronic form requesting baseline demographic and clinical data related to COVID-19 and leprosy. The main outcomes were COVID-19 severity (treatment at home vs hospitalization), treatment duration (which classifies patients as pauci/multibacillary), current treatment (clofazimine, prednisone and/or thalidomide) and clinical course following COVID-19 infection (worsening or improvement of leprosy reactions and pain/sensitivity). The study was approved by the UNESP Institutional Review Board.

A total of 7828 respondents with COVID-19 were analysed; among those, 64 had leprosy (all from a group of leprosy patients attended by the authors), of whom 43 (67%) were men. Regarding age, 14 (22%) were <30, and 44 (69%) were between 30 and 60. Hospitalisation was needed for 10 (16%) leprosy patients, three of whom (5%) were admitted to the intensive care unit. Exacerbation of pre-existing leprosy lesions or reaction was reported by five (8%) patients, however, peripheral neurologic worsening (pain/exacerbated sensitivity) occurred in 11 (17%) of them. Among the non-leprosy respondents, 1121 (15.6%) needed hospitalisation, and 365 (4.7%) were admitted to the intensive care unit. When adjusted by sex and age, there were no differences between leprosy and non-leprosy patients for these outcomes ($P > 0.3$).

The main data regarding leprosy patients are displayed in Table 1. There was no difference in COVID-19 severity regarding the type of leprosy (pauci/multibacillary) nor the use of oral corticosteroids, clofazimine or thalidomide. However, patients who required hospitalisation were associated with neurological impairment, since 50% of them reported increased numbness or pain.

The use of clofazimine was associated with a lower frequency of neurological worsening since only 13% of the users reported increased numbness or pain. Meanwhile, neurological impairment occurred in 60% of those who reported increased skin lesions or reactions.

Reactions (type 1 or 2) are expected in 8–33% of leprosy patients during treatment. Neuritis and reactions (especially type 2) were expected to occur more often since the cytokine storm in COVID-19 shares some similarities with immunological response in leprosy.[1] A previous evaluation of 406 leprosy patients, of whom 16.9% were infected with COVID-19, found leprosy reaction frequency similar to leprosy control patients.[3]

Mycobacterium leprae directly induces IL23 secretion by Schwann cells, triggering a local TNFα-mediated response; both cytokines are involved in demyelinating processes in leprosy and are actively secreted in the inflammatory response induced by COVID-19.[1,3] Notwithstanding, the neurological symptoms reported by our patients might be due to a leprosy flare triggered by SARS-CoV-2 and direct viral pathogenicity cannot be neglected.[3]

Regarding the impact of leprosy treatments on COVID-19, there were reports with thalidomide 100 mg/day in association with corticosteroids.[2] Thalidomide accelerated the negative conversion of SARS-CoV-2 and decreased hospitalisation

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Table 1: COVID-19 severity (hospitalisation), and clinical course of the 64 leprosy patients according to specific systemic treatments

Variables	N (%)	COVID-19 severity**		Neurological impairment***	
		Odds ratio (CI 95%)*	*P*-value	Odds ratio (CI 95%)*	*P*-value
Leprosy type					
Paucibacillary	9 (14)	1 (–)	–	1 (–)	–
Multibacillary	55 (86)	1.2 (1.0–1.4)	0.32	1.6 (0.4–7.3)	0.52
Leprosy treatment					
Thalidomide	25 (39)	1.0 (0.2–4.9)	0.97	1.6 (0.6–4.6)	0.39
Clofazimine	16 (25)	2.3 (0.4–11.8)	0.33	0.2 (0.1–0.8)	*0.02*
Prednisone	31 (48)	0.7 (0.2–3.5)	0.71	0.8 (0.3–2.4)	0.72
Clinical impairment					
Skin lesions/reaction	5 (8)	1.4 (0.1–17.8)	0.97	12.4 (1.1–43.7)	*0.04*
Sensitivity/pain	11 (17)	20.6 (12.4–25.1)	*0.01*	–	–

*Logistic regression, adjusted by age ('no treatment with that drug' was the reference category); **COVID-19 severity: hospitalisation (n = 10) vs non hospitalisation (n = 54); correct classification 87.5%; R^2 (Nagelkerke) = 0.39; ***Neurological impairment: peripheral neurologic worsening (pain/exacerbated sensitivity) (n = 11) vs non-impaired (n = 53); correct classification 70.3%; R^2 (Nagelkerke) = 0.33 . P<0.05 was considered significant

days. Nevertheless, our series failed to demonstrate a protective effect of thalidomide on COVID-19 severity. Furthermore, there is some concern about the association of thalidomide and systemic corticosteroids due to the risk of venous thrombosis, a known complication of severe COVID.[1]

Despite the fact that clofazimine showed a protective effect against SARS-CoV-2 infection in laboratory models, a previous clinical study revealed no effect of clofazimine on the incidence or severity of COVID-19.[3] Since leprosy patients usually take 50 mg/day, it could be insufficient to inhibit SARS-CoV-2.[4]

Nevertheless, high dose clofazimine was suggested as a prophylactic for neuritis and nerve damage in leprosy, due to its anti-inflammatory properties.[5] It may explain the lower frequency of neurological impairment in our patients even at the recommended dose of clofazimine.

This survey has limitations regarding the self-response questionnaire as it was not suitable to evaluate death, the small number of leprosy patients, use of invasive vs non-invasive respiratory support, nor to access the dose of leprosy medications, vaccination status, or to differentiate type 1 from type 2 reactions. Prospective longitudinal studies are needed to explore these elements.

To conclude, leprosy reactions did not increase following COVID-19, nor did leprosy treatments (thalidomide, corticosteroids and clofazimine) influence COVID-19 severity. Despite neurological symptoms in leprosy patients being exacerbated after severe COVID-19, these were less expressive in those who used clofazimine.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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