Received: 11 May 2020 | Revised: 13 May 2020 | Accepted: 15 May 2020

DOI: 10.1111/dth.13631

SHORT PAPER

DERMATOLOGIC THERAPY WILEY

Management of leprosy patients in the era of COVID-19

Ayman Abdelmaksoud[1] | Sunil Kumar Gupta[2]

[1]Mansoura Dermatology, Venerology and Leprology Hospital, Mansoura, Egypt

[2]Department of Dermatology, Venereology and Leprosy, AIIMS, Gorakhpur, India

Correspondence
Ayman Abdelmaksoud, Mansoura Dermatology, Venerology and Leprology Hospital, Mansoura, Egypt, 5-Amien Alsamanoudy Street, from AbdelsalamAaref Street, Mansoura, Egypt.
Email: behcet.behcet@yahoo.com

Dear Editor,

Leprosy or Hansen's disease (HD), a chronic granulomatous infection caused by the intracellular parasite *Mycobacterium leprae* or *Mycobacterium lepromatosis*, has affected humans for more than 4000 years with high degree of stigmatization even now. Leprosy is dominantly a disease of peripheral nerves, skin, and mucosa. Upper respiratory tract impairment has been reported in the majority of leprosy patients as *M. leprae* spread through droplet infection. Idris et al noted that *M. leprae* invasion into microvessel endothelial cells occurs before invading the Schwann cells, and the most important region for *M. leprae* to invade microvessel endothelial cells is identical to the region involved in the invasion into nasal mucosa epithelial cells.[1]

As the nasal mucosa is considered to be the invasion pathway of *M. leprae*, it may infect the olfactory receptors and olfactory bulb. This impairment of the olfactory receptors and olfactory bulb develops in the early stages of the disease. Olfactory dysfunction and a significant reduction in olfactory bulb volume were observed in all leprosy patients studied by Veyseller et al who were severely hyposmic or anosmic.[2] Similarly, large number of pauci-symptomatic, young-aged COVID-19 patients presented with anosmia or hyposmia due to neurotropism propensity of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and related microvascular injury with increased risk of acute respiratory distress syndrome.[3]

Treatment of leprosy is based on the combination of a three-drug regimen of rifampicin, dapsone and clofazimine (multidrug therapy [MDT]). Dapsone-induced esinophilic pneumonia has been reported in leprosy patients.[4] Alternate antileprosy regimen has been studied by Narang et al[5] with promising results in clinically "nonresponsive" patients to MDT of WHO. This regimen consisted of minocycline, clofazimine, and ofloxacin (24 months). Doxycycline can be used alternatively to minocycline by Narang et al.[5] in the regimen due to similar chemical structures. Low-dose doxycycline has been shown to be more effective than high doses to prevent induction of pro-inflammatory cytokines (such as interleukin 6 [IL-6]) and hence suggested low in association with hydroxychloroquine as a promising prophylactic and therapeutic strategy for the early phase of COVID-19.[6]

Severe "cytokine storm," with markedly higher levels of pro-inflammatory cytokines including interferons, tumor necrosis factors, ILs, for example, IL-6, and chemokines, has been considered in severe COVID-19 patients.[7] Indeed, "cytokine storm" could be expected in leprosy reactions that may be triggered by infections, including respiratory tract infections. Though it is unclear if elevated IL-6 levels are detrimental or beneficial in COVID-19 pneumonia, IL-6R monoclonal antibody (tocilizumab)-directed COVID-19 therapy has been used in a clinical trial in China.[7] Borderline tuberculoid leprosy has been reported after use of an IL-6 inhibitor (tocilizumab) in a rheumatoid arthritis patient.[8] Thus, tocilizumab should be taken cautiously in leprosy-endemic areas, until further research.

Systemic steroid, prednisolone is widely used for the treatment of leprosy reactions, particularly for erythema nodosum leprosum (ENL), a severe multisystem immune-mediated complication of multibacillary leprosy with extracutaneous manifestations for example, fever, arthralgia, malaise. Prolonged, high-dose treatment with prednisolone (for over 12-14 weeks) increases the risk for prednisolone-induced immunosupression. Systemic corticosteroids (predniso(lo)one ≥20 mg) significantly increase risk of SARS-CoV-2 infection.[9] Other suitable ancillary treatments or alternatives to corticosteroids are hence warranted.

Apremilast is an orally effective, selective phosphodiesterase-4 (PDE-4) inhibitor with a potent anti-inflammatory, immunomodulatory actions, and is clinically effective in inflammatory conditions like chronic plaque psoriasis. PDE-4 inhibitor is not immunosuppressive and can be used safely in COVID-19 patients.[9] Recently, apremilast confirmed its safety in very critical psoriasis patients with severe

TABLE 1 Suggested treatment of leprosy and leprosy reactions in the era of COVID-19

Drug used/suggested	Leprosy	Leprosy reactions	COVID-19 remarks	References
Multi-drug therapy (MDT)	• MDT is the first line of therapy for leprosy. • -Alternate anti-leprosy therapy for "nonresponders"	• Lessen risk of reactions[a]	• Dapsone-induced pneumonia may occur	4,5
Systemic steroids	• Not required	• Avoid prolonged, high doses[b] • For controlled cases, keep the dose of predniso(lo)one ≤20 mg/d	• Low-dose corticosteroids predniso(lo)one ≤20 mg is advised	9
Methotrexate	• Not required	• Weekly doses ranging from 7.5 to 20 mg, according to the severity of the case, with low-dose corticosteroids	• Low-dose methotrexate (≤10 mg/wk) is advised for higher risk patients[c]	9,12
Cyclosporine	• Not required	• Daily dose of 5-7.5 mg/kg, according to the severity of the case	• Low-dose cyclosporin to ≤1 mg/kg/d is advised for higher risk patients[c] • No concern with higher doses • Has antiviral activity	9,14,15
Doxycycline	• Alternative to minocycline for MDT nonresponders	• May be considered as a neuroprotective agent	• Low-dose doxycycline with hydroxychloroquin for the early phase of the disease	6
Apremilast	• Not required	• Monotherapy or with low-dose corticosteroids	• Safely tried in hospitalized COVID-19 patient with psoriasis	5,10
Oral metronidazole and topical metronidazole gel 1%	• Not required	• For trophic ulcers secondary to chronic neuritis (400 mg, thrice/d for 1 week and topical metronidazole gel 1% for 3 weeks)	• Oral metronidazole has immunomodulatory properties	16,17

[a]Reactions may occur during or after full-course of MDT.
[b]Except for sever acute reactions.
[c]High-risk patients, for example, elderly, diabetic, those with cardiovascular or pulmonary diseases, those with malignancies.

COVID-19.[10] Chronic recalcitrant steroid-dependent ENL showed dramatic response to apremilast in two patients. Apremilast with low-dose corticosteroids may be also considered.[11] Perez-Molina et al noted that methotrexate at weekly doses ranging from 7.5 to 20 mg (median 15 mg/wk), with low-dose corticosteroids, was effective and safe as a corticosteroid-sparing agent.[12] Cyclosporin monotherapy may be an effective alternative treatment in prednisolone-resistant or dependent cases of type-1 reaction in a dose range of 5 to 7.5 mg/kg/d.[13] Experts suggested a possible lower dose of methotrexate to ≤10 mg/wk, cyclosporin to ≤1 mg/kg/d for higher risk patients of severe COVID-19 disease, for example, elderly.[9] Others reported no reason for concern with higher doses as cyclosporin has a selective antiviral activity and could confer protection upstream of the cytokine storm in COVID-19-infected patients.[14,15]

Oral metronidazole 400 mg, thrice per day for 1 week and topical metronidazole gel 1% for 3 weeks were found to be very effective in 20 leprosy cases with poorly controlled trophic ulcers.[16] Metronidazole, owing to its immunomodulatory properties, could serve as a potential candidate to counteract majority of the immunopathological features of COVID-19 infection.[17]

Taking together with proper skin care, nasal lubricant, social distancing (quarterly evaluation, except for acute leprosy reactions), we provide an updated, simplified guide for leprologists to manage their patients in the era of COVID-19 pandemic. We summarized related literature data, in addition to our experience in Table 1.

ORCID

Ayman Abdelmaksoud https://orcid.org/0000-0003-4848-959X
Sunil Kumar Gupta https://orcid.org/0000-0001-6810-6483

REFERENCES

1. Idris I, Abdurrahman AH, Fatulrachman, et al. Invasion of human microvascular endothelial cells by *Mycobacterium leprae* through Mce1A protein. *J Dermatol*. 2019;46(10):853-858.
2. Veyseller B, Aksoy F, Yildirim YS, et al. Olfactory dysfunction and olfactory bulb volume reduction in patients with leprosy. *Indian J Otolaryngol Head Neck Surg*. 2012;64(3):261-265.
3. Garavello W, Galluzzi F. Olfactory dysfunction in COVID-19. *Otolaryngol Head Neck Surg*. 2020 May 5. [Online ahead of print]. https://doi.org/10.1177/0194599820925403.
4. Kaur J, Khandpur S, Seith A, Khanna N. Dapsone-induced eosinophilic pneumonitis in a leprosy patient. *Indian J Lepr*. 2005;3:267-271.

5. Narang T, Bishnoi A, Dogra S, Saikia UN, Kavita. Alternate anti-leprosy regimen for multidrug therapy refractory leprosy: a retrospective study from a Tertiary Care Center in North India. *Am J Trop Med Hyg*. 2019;100(1):24-30.
6. Conforti C, Giuffrida R, Zalaudek I, di Meo N. Doxycycline, a widely used antibiotic in dermatology with a possible anti-inflammatory action against IL-6 in COVID-19 outbreak. *Dermatol Ther*. 2020;20:e13437. https://doi.org/10.1111/dth.13437.
7. Zhang Y, Zhong Y, Pan L, Dong J. Treat 2019 novel coronavirus (COVID-19) with IL-6 inhibitor: are we already that far? *Drug Discov Ther*. 2020;14(2):100-102.
8. Nambiar PH, Katikaneni M, Al Nahlawi B, Hayat SQ. Leprosy after interleukin 6 inhibitor therapy in a patient with rheumatoid arthritis. *Lancet Infect Dis*. 2019;19(7):787.
9. Wang C, Rademaker M, Baker C, Foley P. COVID-19 and the use of immunomodulatory and biologic agents for severe cutaneous disease: an Australian/New Zealand consensus statement. *Australas J Dermatol*. 2020 Apr 7. [Online ahead of print]. https://doi.org/10.1111/ajd.13313.
10. Mugheddu C, Pizzatti L, Sanna S, Atzori L, Rongioletti F. COVID-19 pulmonary infection in erythrodermic psoriatic patient with oligodendroglioma: safety and compatibility of apremilast with critical intensive care management. *J Eur Acad Dermatol Venereol*. 2020 May 9. [Online ahead of print]. https://doi.org/10.1111/jdv.16625.
11. Narang T, Kaushik A, Dogra S. Apremilast in chronic recalcitrant erythema nodosum leprosum: a report of two cases. *Br J Dermatol*. 2020;182(4):1034-1037.
12. Perez-Molina JA, Arce-Garcia O, Chamorro-Tojeiro S, et al. Use of methotrexate for leprosy reactions. Experience of a referral center and systematic review of the literature. *Travel Med Infect Dis*. 2020 Apr 14;101670. [Online ahead of print]. https://doi.org/10.1016/j.tmaid.2020.101670.
13. Lambert SM, Alembo DT, Nigusse SD, Yamuah LK, Walker SL, Lockwood DNJ. A randomized controlled double blind trial of ciclosporin versus prednisolone in the management of leprosy patients with new type 1 reaction, in Ethiopia. *PLoS Negl Trop Dis*. 2016;10(4):e0004502.
14. Rudnicka L, Goldust M, Glowacka P, et al. Cyclosporine therapy during the COVID-19 pandemic is not a reason for concern. *J Am Acad Dermatol*. 2020 May 3. https://doi.org/10.1016/j.jaad.2020.04.153.
15. Sanchez-Pernaute O, Romero-Bueno FI, Selva-O'Callaghan A. Why choose cyclosporin a as first-line therapy in COVID-19 pneumonia. *Reumatol Clin*. 2020 Apr 16. [Online ahead of print]. https://doi.org/10.1016/j.reuma.2020.03.001.
16. Mishra S, Singh PC, Mishra M. Metronidazole in management of trophic ulcers in leprosy. *Indian J Dermatol Venereol Leprol*. 1995;61(1):19-20.
17. Gharebaghi R, Heidary F, Moradi M, et al. Metronidazole; a potential novel addition to the COVID-19 treatment regimen. *Arch Acad Emerg Med*. 2020;8(1):e40.