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Editorial

Repurposing of Drugs for Non-responding Erythema Nodosum Leprosum Cases - A Perspective

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Dear Editor,

Leprosy (Hansen's disease) caused by Mycobacterium lepra is a debilitating tropical disease having maximal stigma till date. Efforts have been made for many decades to keep disease incidence under control. In 2019, 202,185 new cases of leprosy were reported around the world, with 14,981 (7.4%) of those found in children under the age of 15.[1-3] Globally in 2020, 1, 28,405 new leprosy patients were diagnosed. New paediatric cases were 8661 diagnosed with leprosy and 7216 patients with grade 2 disability by WHO region.[4]

Current treatment guidelines: The current treatment guidelines includes 3-drug regimen with rifampicin, dapsone and Clofazimine for all leprosy patients, with duration of treatment of 6 months for Paucibacillary (PB) leprosy and of 12 months for Multibacillary (MB) leprosy. The dosage and frequency in adult were 600 mg once a month Rifampicin, Clofazimine 300 mg once a month and 50 mg daily, dapsone 100 mg daily; for Children (10–14 years) it is 450 mg once a month Rifampicin, Clofazimine 150 mg once a month and 50 mg on alternate days, dapsone 50 mg daily; in Children less than 10 years or < 40 kg 10 mg/kg once month Rifampicin, 100 mg once a month, 50 mg twice weekly Clofazimine, 2 mg/kg daily Dapsone. Because no MDT combination blister packs are available for children under 40 kg, they must be treated with single formulation drugs. It would be able to follow the recommendations in the Operational Manual, Global Leprosy Strategy 2016–2020 on how to partially use (MB-Child) blister packs for treatment for children weighing 20 to 40 kg.[5]

Current ENL reaction management: The treatment of ENL depends upon the severity of reactions like mild, moderate and severe. The drugs currently being used is steroids in case of severe reactions and neuritis, Clofazimine in case of steroid dependent cases for 12 months and finally thalidomide in all treatment failure cases.[5]

Other options: Researchers had already come a long way in terms of effective medical treatment of the infection through multidrug therapy, as well as better understanding and treatment of leprosy complications. However, another significant challenge of leprosy has been *Mycobacterium leprae* unique properties and interaction with the host immune system. This has impacted the successful implementation vaccines and accurate diagnostic tests. While multidrug therapy has reduced the prevalence of leprosy, but we have continued to struggle to reduce the incidence of leprosy by interrupting *M. leprae* transmission through preventive strategies.[6]

It would be recommendable to promote drug repurposing (*in-silico* studies/molecular docking) in leprosy management rather than standing in line for newer drugs for longer periods of time. Drug repurposing, also known as drug repositioning, reprofiling, or re tasking, is a strategy for developing novel applications for approved or investigational drugs that fall outside the scope of the original medical indication.[7] One of most successful examples of drug repurposing to date has been based on serendipity, such as the repurposing of thalidomide for Erythema nodosum leprosum (ENL)[7]. However, it was discovered by chance to be effective in the treatment of ENL[7] first (in 1964). Only 10% of patients in an Indian cohort study had a single episode, while 62.5% had chronic ENL.[8]

The prime targets in this case should be mental stressors and inflammatory mediators. In the pathology of an ENL reaction, several serological markers have been identified. This includes tumour necrosis factor alpha (TNF-), interleukins, and cytokines (IL-6, IL-7, and IL-17F). Many *in vitro* and *in vivo* studies have shown that metformin has anti-inflammatory properties as well as an inhibitory role on tumour necrosis factor alpha. Metformin reported to inhibit the production of inflammatory cytokines like IL-6, IL-1β, and TNF-α in a dose-dependent manner, and also protein and messenger RNA expression. In addition to its inhibitory properties, it up regulates the protein expression of anti-inflammatory cytokines such as IL-4 and IL-10, which is maintained throughout.[8-9] As a result, in a dose-dependent manner, metformin can be one of the choices to be used in type 2 lepra reaction with dual benefit. In ENL, prednisolone and thalidomide have been used to reduce the severity of clinical manifestations and provide remission. The plan for alternative drugs is justifiable due to its unfavorable side effects. Metformin being in market for several decades and found to be safe in most of the age groups and can be used for a longer period of time in this regard. Tynan *et al*., explored the effectiveness of five different SSRIs (citalopram, sertraline, fluoxetine, fluvoxamine, and paroxetine) as well as one other group of SNRI drugs in suppressing microglial inflammation in response to inflammatory stimulus and inhibiting TNF-α.[9-10] As per recent evidence, SSRIs[10-12] may be a beneficial clinical approach to treat both mental stressors and reaction inflammations. SARS-CoV-2 infection is more likely in leprosy patients who are on systemic corticosteroids. As a result, other appropriate alternative treatments to corticosteroids are needed. Apremilast, an orally active, selective phosphodiesterase-4 (PDE-4) inhibitor with potent anti-inflammatory and immunomodulatory

properties, evidenced a dramatic response in two steroid-dependent ENL patients. IL-6 expression was found to be elevated in COVID-19 patients with leprosy. Single nucleotide polymorphisms in IL-6 genes have been linked to leprosy reactions in clinical studies.[13] Furthermore, one of the markers of neuropathic pain in leprosy was found to be IL-6 and patients with SARS-CoV-2/leprosy co-infections may be predisposed to silent neuropathy.[14] The mycobacterium indicus pranii (MIP) vaccine has also been tried for recurrent ENL.

These interesting finding provides us insight towards the need of usage of monoclonal antibodies against IL-6 receptors to prevent neuritis by tocilizumab etc. Currently also leprosy patients with COVID, due to lack of effective drugs the World Health Organization (WHO) and other health agencies have chosen to reassess the efficacy of licensed and experimental drugs to treat emerging health problems. A fact, we conclude that repurposing drugs in leprosy represents a significant opportunity from the perspective of unmet drug availabilities.

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