Viewpoint

Fixed duration multidrug therapy (12 months) in leprosy patients with high bacillary load – Need to look beyond

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Fixed duration multidrug therapy (FDT–12 months) is recommended by the WHO for multibacillary (MB) Hansen's disease (HD). It comprises a combination of rifampicin, clofazimine and dapsone, which has proven its effectiveness as judged by continuous decline in the bacteriological index (BI) and relatively low relapse rates among patients who start treatment with a low or negative initial bacteriological index. Since its introduction, more than 16 million patients have been treated and a large number of disabilities/morbidities prevented. While most patients go through the course of therapy and post-RFT (release from treatment) period without any serious events, highly bacillated patients tend to experience problems, such as painful neuritis of erythema nodosum leprosum (ENL), worsening of nerve function leading to the development of deformities and disabilities, delayed regression of cutaneous lesions, relapses/recurrences. Recurrences in highly bacillated patients can lead to dissemination of bacilli. This poses a risk to their contacts, especially those who are genomically susceptible to infection or reinfection. We have highlighted several concerns with fixed duration (12 months) multidrug treatment (MDT) for highly bacillated Hansen's disease patients and concluded with a few recommendations to mitigate these challenges.

Relapses/Recurrences

As there is no clear definition for cure in Hansen's disease, a low relapse/recurrence rate is considered one of the main indicators of the efficacy of FDT. Recurrence may be due to endogenous relapse or exogenous reinfection. Although the relapse/recurrence rate following FDT has been reported as low/acceptable, however in the last 4 years before the COVID-19 pandemic, a 29.5% increase from 2,743 cases in 2016 to 3,893 relapse cases in 2019 were reported to WHO. Besides, cases requiring "retreatment" increased from 11,881 cases in 2016 to 15,517 in 2019, an increase of 23.4%.[1,2] There are wide variations in the observed relapse rates, mostly because of the lack of a universally accepted definition of relapse. In a multicentric study on the quality of routine data collection on relapses, the overall rate of relapse per new patient treated varied from 0 to 29.4% in individual projects.[2,3] These figures may still be an underrepresentation of the problem in the field because in the absence of repeated smear microscopy many recurrent cases may go undetected or have delayed detection.

Current literature concerning the duration of multidrug treatment on relapse rates is conflicting and apparently related to the wide range of initial bacteriological index among study subjects. While some studies have observed low relapse rates irrespective of the duration of multidrug treatment,[3–7] the U-MDT study from Brazil showed seven times more relapses in the 6-month regimen (U-MDT) in comparison to 12 months of treatment (FD-MDT).[8] Studies on multibacillary patients reveal an even more worrying picture, reporting cumulative recurrent frequencies of relapse, ranging from 17% to 39%.[9–11] When relatively short durations of treatment are compared, such as 6 months versus 1 year or 2 years,

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it is unlikely that the risk of reinfection will vary much between groups. When the 12-month FDT is compared to 'treatment till smear negativity' in highly bacillated patients, the differing risk of recurrence/reinfection emerges more clearly.[10] Some experts believe that "some of the apparent relapses due to reinfection would not be prevented with longer MDT."[5] Taking this statement as partially correct, we believe that antimicrobials need to be given for a longer period for patients with high bacterial load, particularly polar lepromatous leprosy and Histoid leprosy, to reduce the infectious pool and the duration of infectivity.

Reactions

Both type 1 and 2 erythema nodosum leprosum reactions appear to be associated with the presence/persistence of *M. leprae* and/or their antigens, Th1 and Th2 type of immune responses and the release of related cytokines.[12] After FDT, viable lepra bacilli are still demonstrable in skin and nerves, especially in patients with a high initial bacteriological index.[13] Type 1 and type 2 reactions have been observed up to 5 years and 8–10 years, respectively, after successful completion of therapy.[14] Prolonged antimicrobial protection of patients is relevant in killing bacilli. Incidence of reactions has been observed to be closely related to the duration of therapy; the longer the duration, the lesser the number of reactions.[12] Where anti-inflammatory or immunomodulatory drugs did not help, antimicrobial treatment has been reported to produce dramatic relief in patients with chronic/refractory erythema nodosum leprosum.[15,16] Immunotherapy is another intervention that demonstrated reduction in incidence of type 2 reactions among leprosy patients.[17,18] The risk of painful erythema nodosum leprosum neuritis appears to differ according to the duration of multidrug treatment. A report compared 63 lepromatous leprosy (LL) patients given 12 months of fixed duration multidrug treatment to 134 LL patients given 24 months of fixed duration multidrug treatment. While there was a higher occurrence and intensity of ENL in the group receiving one year of MDT, the difference was not statistically significant. Nevertheless, it was observed that the duration of ENL and neuritis was longer in the 12-month group.[12]

Persistence and progression of skin lesions and disability despite completion of treatment

Persistent or slowly regressing unhealed or active skin lesions have been reported in up to 20% of patients, even 5 years after release from treatment.[8,19] Persistence of *M. leprae* in the eye and ocular involvement as part of erythema nodosum leprosum can result in visual impairment and complete blindness. Some experts suggest treatment for more than 2 years when there is ocular involvement.[20] Involvement of bones, joints, testes, liver, lymph nodes, etc. and persistence of bacilli in some of these sites may add to the morbidity.[21]

Individuals with Hansen's disease continue to suffer morbidities from repeated reactions with progression of nerve function impairment (NFI) occurring in more than 18% of patients and worsening of disabilities, which may be as frequent as 25% in smear positive cases.[8] The risk of progression in disability continues for many years after release from treatment.[22,23] A survival analysis of disability progression observed that 40% of the patients who had a disability at diagnosis worsened within 10 years of multidrug treatment.[23] Among those with no disability at diagnosis, 16.7% of MDT treated patients became disabled within a mean of 38.5 months.[23]

Antimicrobial resistance

Increasing antimicrobial resistance (AMR) is another major concern, especially for infectious diseases like Hansen's disease. The first study from WHO reporting global data on antimicrobial resistance in Hansen's disease used 1,932 samples (1,143 relapses and 789 new cases) from multibacillary cases at sentinel sites of 19 countries from 2009 to 2015.[24] These samples were studied for resistance to rifampicin, dapsone and ofloxacin. Rifampicin resistance was observed among relapse (58/1,143, 5.1%) and among new (16/789, 2.0%) cases in 12 countries, mainly India, Brazil and Colombia reporting more than five rifampicin-resistant cases. In addition, analysing data only among new case samples in this study, the percentage of detected antimicrobial resistance reached alarmingly higher levels of rifampicin resistance ranging from 8.2% in India to 15.6% in Brazil.[24,25] A recent meta-analysis of 32 papers describing the resistance of *M. leprae* to rifampicin reported pooled cumulative incidences of 10% in new cases and 20% in relapsed cases and this increased to 42% in non-responsive and intractable cases.[25] This is alarming since rifampicin is the only potent bactericidal drug in WHO multidrug treatment.

Failure to reduce disease incidence

The incidence rate of Hansen's disease has not markedly declined in endemic countries and provinces that transitioned directly from dapsone monotherapy to FDT.[26,27] This was true even in areas with a well-run Hansen's disease control programme.[28] In addition, the proportion of multibacillary cases has been steadily increasing over the past years. Only those provinces where multidrug treatment till smear negativity was administered before the introduction of FDT showed a decline in incidence rates (e.g. Tamil Nadu in India) with some districts such as Coimbatore (Tamil Nadu, India) even aspiring for the official declaration of Hansen's disease–free status. Evidence from several studies indicates that prolonged dapsone monotherapy achieved higher reduction in new case detection rate as compared to FD-MDT, reiterating the importance of prolonged duration of treatment, particularly in highly bacillated patients.[29-32]

Persister bacilli

Persisters are a population of dormant *M. leprae* that can survive antibiotic treatment and remain dormant within the body, potentially leading to relapse or drug resistance in Hansen's disease patients. Managing persisters in Hansen's disease requires the development of novel treatment

strategies that specifically target these subpopulations of bacteria, such as the use of new combination therapy and immune modulation. In the study conducted by Gupta *et al*., it was observed that viable bacilli persisted in up to 29.4% of patients even after a year of receiving multidrug treatment alone. However, when multidrug treatment was administered in conjunction with minocycline and ofloxacin, such persistence was not observed.[13] In addition, the development of more sensitive diagnostic tools that can detect low levels of *M. leprae* in tissues and blood would enable more effective management of persisters in Hansen's disease.

Other challenges

The efficacy of a drug is based on the regularity of treatment to maintain optimum drug levels above the minimum inhibitory concentration. Irregularity of treatment is likely to compromise the observed efficacy of even the most potent regimen. Default rates of up to 34% in treatment adherence have been reported in India.[33] In another study from India, metabolites of dapsone were found only in 50% of the patients on treatment.[34] Poor adherence may also promote relapses, reinfection and drug resistance. Home visits by peripheral health workers or local volunteers to supervise treatment and SMS reminders are approaches that have helped improve adherence to treatment in TB and could prove helpful in Hansen's disease as well.

The decline in expertise to diagnose and treat Hansen's disease introduces a further challenge, leading to an increase in undiagnosed highly bacillated patients shedding bacilli. This, combined with lack of public awareness, caused a delay in diagnosis of 1–10 years for 25.5% of the patients, while 42.6% reported being misdiagnosed.[35] The unavailability of reliable skin smear microscopy in many places hinders the diagnosis of LL which often shows no skin patches or nerve thickening. Also, periodic skin smears can help diagnose recurrence of the disease even when signs of recurrence are subtle or disguised by the sequelae of previous infection. Where smear microscopy is available, the clearance of bacilli from tissues can be monitored as a way of distinguishing "slow responder" multibacillary patients from others. Prolonged anti-microbial protection may be considered in this subgroup of patients, while always considering the possibility of drug resistance.

Conclusion

Patients with high bacillary load suffer repeated reactions, progressive nerve function impairment and worsening of disabilities.[36] They also experience endogenous relapse and exogenous reinfection.[9] This ensures transmission even in well-run control programmes. Choosing one or a combination of the following options in highly bacillated patients is likely to help protect patients as well as the general population [Box 1].

Despite FDT serving most patients well, it apparently does not suffice for the highly bacillated patients. Similar concerns have been noted by others.[37] Both past WHO service and consultations leading up to the Indian National Strategic Plan and Roadmap for Leprosy 2023–2027 have taken cognizance of the issue of disease activity and drug resistance in leprosy cases after completion of multidrug treatment and suggest alternate drugs should be made available in these scenarios.[38] "Looking beyond FDT," in this small but very important group of patients, will help evolve more effective anti-microbial treatment for them, reducing the development of reactions and neuritis. Evidence indicates that prolongation of multidrug treatment in highly bacilliferous patients is also crucial for reducing reinfection and subsequent transmission.

Box 1: Suggestions for the management of highly bacillated patients

- *Prolonging antimicrobial therapy*. WHO operational guidelines state that "it may be advisable to treat an MB patient with high BI for more than 12 months, taking careful consideration of the clinical and bacteriological evidence".[38]
- *Adding immunotherapy* (BCG/MIP/LepVax vaccines) as an adjunct to FDT.
- *Increasing the frequency/dosage of rifampicin* which might reduce the incidence of "endogenous" relapse due to persisters by analogy with tuberculosis.
- *Adding more potent bactericidal drug* (e.g. rifapentine, minocycline, moxifloxacin) to kill bacilli more rapidly.
- *In high endemic areas, post-MDT chemoprophylaxis for highly bacillated patients will be with a fully supervised regimen* like ROM, PMM, etc.
- *Increasing the availability of reliable slit skin smear microscopy services*.
- *Ensuring adherence to treatment* using new technologies, like serology and molecular biology, to follow the patients in the field.
- Devising *validated diagnostic criteria for relapse* and inclusion of the same in long-term clinical trials comparing alternative MDT regimens.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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