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Editorial

Priority Setting for Research cum Interventions in Drug Resistance in Leprosy

Like other microbes, *Mycobacterium leprae* is also known to harbor mutants responsible for drug resistance and it can also become resistant to various drugs by other mechanisms. Further, there is very little information about *M. lepromatosis* regarding these aspects. Following use of dapsone monotherapy in leprosy, and possibly due to chemoprophylaxis with dapsone and acedapsone an increasing resistance was reported to sulphones in 1960s and 1970s. Proportion of dapsone resistance was more in bacilliferous multibacillary cases and those who were treated with lower dosage of sulphones. Similar problem was observed in cases treated with monotherapy of rifampicin.

Designing of multi-drug treatment (MDT) in 1982 by WHO was essentially to tackle the major problems of drug resistance, relapses and the hope of faster termination/reduction in the transmission of disease. After recommendation of MDT regimens in 1982, this strategy was adopted by almost all member countries, India decided to implement this strategy in 1983. By 1995 most leprosy patients were getting treated with MDT with significant reduction in numbers, much lower relapse rates than in the dapsone monotherapy period and also, reduction in dapsone resistance rates. Some hospital-based studies using mouse foot pad showed more than 85% reduction in sulphone resistance in relapse cases and those with persisting BI after FDT. Population based studies from South India also observed similar trends i.e. about 5% sulphone resistance in post-MDT era, very low or no rifampicin resistance in the reported cases.

With the establishment of molecular markers for detecting drug resistance specially to dapsone, rifampicin and quinolones, WHO catalysed and initiated the establishment of global network for drug resistance surveillance in leprosy in 2008, which was supported by ILEP and the Nippon Foundation. Guidelines to carry out this surveillance were released in 2009. International Reference Labs in France and USA have been providing the quality assurance for these studies. These guidelines have been updated in 2017. Resistance to rifampicin, dapsone and ofloxacin has been reported from most of the countries reporting leprosy cases in their programmes which include Brazil, China, Colombia, Malaysia, Korea, Myanmar, Indonesia, Philippines, Japan, India and USA. Highest resistance rate has been reported from the Western Pacific region. 2010 onwards several publications have resulted from this global effort: Dapsone resistance rates have varied from 1.7% to 10% whereas rifampicin resistance has mostly ranged from 1% to 5% (around 1-2% in fresh untreated cases) in these reports. Isolated cases of multi-drug resistance (MDR) have also been reported. A study from eastern India observed no mutations to *folP*1 and *rpo*B but very high resistance to quinolones. While widespread use of MDT has stablished the situation of resistance to dapsone and rifampicin, an alarming increase in resistance to quinolones (mutations in *gyr*A) has been observed in several reports from India. It has been observed that ofloxacin resistance was nearly same in treatment naïve and earlier treated relapsed/ poor responders - this is possibly due to extensive use of these antibiotics for other infections.

Mutations observed in drug resistance determining region of genes like *rpo*B, *fol*P1, *gyr*A considered relevant for resistance to these drugs have been mapped and published. Some mutations outside these regions have also been considered relevant. Various techniques for mutation detection (PCR amplification and Sanger sequencing; DNA array technology, RT-PCR HRM; Genotype Leprae-DR; NGS-whole genome sequencing) have been described and can be used as per their availability.

WHO has also provided guidance and published the guidelines to treat drug resistant leprosy cases (Eight meeting of Expert Committee, Geneva 2010; also available in WHO 2017 Guide for surveillance of AMR in leprosy). For dapsone resistance- standard MB-MDT is recommended. For rifampicin resistance, a regimen comprising of ofloxacin, minocycline and clofazimine for 6 months daily, followed by either ofloxacin/ minocycline and clofazimine daily, for further 18 months is recommended. Very little published experience on the use of these regimens/ other regimens recommended by other academic researchers is in the public domain.

In India, National Leprosy Eradication Programme of India - NLEP (2023) has published National Guidelines for surveillance of antimicrobial resistance in leprosy, and these update the guidelines that were being followed since 2009. Surveillance data of cases from 4/5 sentinel sites from India during 2018-2020, showed that 3.1% of the cases studied were having resistance for dapsone; 4% against rifampicin; 0.6% against quinolones. During the same period (2018-2020), Brazil reported overall 1.4% drug resistance with less than 1% for dapsone and rifampicin. In another study from north India, almost equal resistance has been observed in both relapse cases as well as chronic recurrent ENL cases. Resistance to these anti- microbial drugs has also observed in smear negative specimens.

Varying rates of resistance in fresh untreated cases indicate transmission of drug resistance. However, that can be accepted as a probability and needs to be proven by molecular typing of strains. This was done in a recent study from Brazil showing intrafamilial transmission by VNTR analysis.

Future

It is clear that MDT has succeeded in reducing and containing the drug resistance in leprosy. Currently, number wise drug resistance in leprosy does not seem to be a significant problem with approximately 95% expected success rate with present MDT. However, that should not slow the efforts. Some points deserve focus:

(i) Published data shows that coverage and effectiveness of drug resistance surveillance network need to be reviewed and strengthened especially in India, Indonesia & other countries of Western Pacific.

(ii) The data on the usefulness of regimens recommended / tried to treat rifampicin (alone or in combination with dapsone/ quinolone) resistance needs to be reviewed as ofloxacin containing regimen(s) may have limitations in India / countries with high percentage of quinolone resistance. Immunotherapy (MIP/BCG) as adjunct to MDT is expected to eliminate all persisting bacilli- sensitive and or resistant, its usage will certainly help in preventing/ treating drug resistant leprosy.

(iii) Access to molecular detection of drug resistance should be expanded so that needy patients get the services and are properly treated – important for the patients and prevention for future.

(iv) Scope of drug resistance surveillance deserves to be expanded to smear negative patients especially with chronic/ recurrent ENL.

(v) Mouse foot pad labs deserve special support and expansion to address the need to detect CLF resistance, correlation with new mutations/ mechanisms.

(vi) Repurposing of existing drugs to treat drug resistant/ unresponsive patients appears be an attractive idea, bedaquiline is already being tried as an option.

(vii) *Mycobacterium lepromatosis* merits studies in relation to drug resistance.

(viii) Research on drug resistance in leprosy needs concerted efforts, establishment of research consortium and academic forum. Less than 20 publications and only about dozen original articles in last 10 years among more than one thousand articles on this subject in PubMed shows dwindling interest in research on drug resistance in leprosy! Situation must change.

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