Indian J Med Res 144, October 2016, pp 499-501
DOI: 10.4103/0971-5916.200884

Quick Response Code:

Commentary

Uniform multidrug therapy for leprosy – time for a rethink?

Uniform multidrug therapy (U-MDT) is a single regimen for all cases of leprosy, lasting for six months. It was first discussed as a serious proposition at the WHO Technical Advisory Group in 2002 and an Editorial in 2003 laid out several criticisms of the concept[1]. The main criticism was that it added an unnecessary drug to the current paucibacillary (PB) treatment, while undertreating multibacillary (MB) cases, especially those with a high bacteriological index. Important considerations when discussing MB cases were that very little evidence was available at that time concerning the efficacy of 12 months treatment (introduced in 1998), or about the level of rifampicin resistance that could potentially be developing undetected in leprosy patients on MDT. If significant rifampicin resistance was developing, it would be unwise to attempt further shortening of the regimen.

Relapse after MDT

Turning first to MB cases, 12-month MDT has been shown to be robust[2] and rifampicin resistance, while not yet studied in large numbers of cases, is not a cause of major concern[3]. The ultimate test of efficacy of drug regimens for leprosy is the relapse rate, and in this era of evidence-based medicine, we should be willing to trust the evidence, especially when it can be triangulated with information from several independent sources. In this issue Manickam and colleagues[4] have presented the results of an open trial of U-MDT in India and P. R. China, sponsored by the WHO. Amongst 1298 MB patients, the relapse rate was 0.074 per 100 person years (PY), with a cumulative rate of 0.37 per cent at five years. This is well below the target of <5 per cent relapse at five years and compares favourably with the one- and two-year MDT regimens. The regimen was fully acceptable to patients and compliance was very high. The limitations of this study are important: there was no control group, no laboratory tests of initial bacillary load were done, the intended sample size of 2500 MB cases was not reached and perhaps most importantly, the follow up of five years could be regarded as too short, with most relapses expected to occur after that period.

On the other hand, the low relapse rate has been corroborated by other studies, in which some of these limitations were dealt with. A randomized controlled trial in Brazil included 613 MB patients, with 323 in the U-MDT arm; so far, two relapses have been reported, but follow up is still ongoing[5]. In Bangladesh, a controlled (but not randomized) trial of U-MDT versus 12-month MDT included 918 MB cases in the U-MDT arm, with no relapses during an average follow up period of seven years; 25 per cent of patients had completed nine years of follow up[6].

MB relapse after treatment for leprosy may be difficult to confirm, especially when skin smears and other laboratory tests are not available, so in many cases, the diagnosis is based simply on a strong clinical suspicion, as in the Indian trial (in the Chinese centres of the same trial, skin smears were done); there can be confusion with reactions, especially in the first 3-5 years after treatment. Relapse seems to occur in two phases: in the first 1-3 years, a high relapse rate seems to indicate inadequate treatment, whereas two alternative mechanisms are proposed for later relapses. 'Persisters' are thought to be dormant bacilli that remain viable after an adequate course of antibiotics to which they remain sensitive; these can subsequently be grown in the mouse footpad and have been assumed to be the main cause of late relapse. Persisters were first described in the dapsone era but are apparently still alive and well[7]. Reinfection is an alternative mechanism for a late clinical relapse, and there is recent evidence that this may be more common than was previously thought[8].

This reasoning suggests that based on the three studies of U-MDT already mentioned, treatment with

U-MDT may be regarded as adequate (low early relapse rate). Late relapses may occur, but these are more dependent on the unpredictable behaviour of persisters and possible reinfection than on the regimen being used.

Other Considerations

Turning to PB cases, the addition of clofazimine, which causes skin discolouration is a potential problem. The Indian trial[4] reported 100 per cent acceptance of the additional drug, but in Brazil, 6.9 per cent of patients wanted to stop clofazimine (note that the Brazilian trial was in MB patients who would get clofazimine anyway, but it illustrates a likely problem in PB patients)[9]. One argument to justify adding clofazimine to the PB treatment regimen is that some MB cases are misclassified as PB and may be inadequately treated; U-MDT removes that risk.

One argument that is often used against further shortening of MDT is that serious complications of leprosy appear during the first 3-5 years after diagnosis, in a large number of cases. Having patients attend a treatment clinic every month allows closer monitoring of these potentially disabling events. In the Indian trial, around 150 cases of type 1 reaction and/or neuritis occurred and 24 patients developed type 2 reactions. The timing of these events has not been spelt out in detail, but many will have occurred after six months of MDT[4]. In Brazil, 38.6 per cent of patients had a reaction before the end of U-MDT, but 35 per cent had their first reaction after the end of U-MDT[9].

Reactions and neuritis are a more serious problem than relapse, both in terms of the proportion of patients affected and in terms of the future consequences. Relapse is easily treated with a further course of MDT although if possible, samples should be taken to test for drug resistance. In the presence of proven rifampicin resistance, an adequate alternative regimen is available[3].

Efforts to diagnose nerve damage as early as possible need to be rethought, as monitoring nerve function by health workers is less than ideal in most leprosy control programmes, even if patients are regularly attending to collect MDT. Just as self-care, with the necessary supportive services in the background, is gradually being seen as the only way to effectively manage residual disability in the vast majority of cases, innovative methods of self-assessment are needed so that people affected by leprosy can identify new problems as they arise. Empowerment of those affected is an essential element in this process[10].

U-MDT has the potential to reduce the burden of clinic attendance on those affected, which will be a help to many. At a stroke, it will cause prevalence (which is directly related to the duration of treatment) to fall below 1 in 10,000 almost everywhere, which will be satisfying for those who are still focusing their attention on this mirage. While there is resistance to this change from many quarters including physicians involved in the care of those affected by leprosy, we need to look again at the real goal of leprosy control, which is to minimize disability caused by leprosy, through early case detection, adequate chemotherapy and appropriate management of complications. Whether or not U-MDT becomes the officially recommended treatment for leprosy, let us direct our attention more intentionally towards the better management of serious complications: relapse is a minor complication, but reactions and neuritis are much more important.

Paul R. Saunderson
American Leprosy Missions,
1 ALM Way, Greenville,
South Carolina 29601, USA
psaunderson@leprosy.org

Received August 26, 2016

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