Multidrug resistant tuberculosis: A challenge in clinical orthopedics

With the availability of effective and safe anti tubercular drugs from 1950s to 1980s, the medical fraternity developed a sense of euphoria regarding the control of tuberculous infections. Unfortunately, however, the optimism was short lived because of many factors. With 36 million HIV positive cases worldwide, increasing number of human beings get infected with typical and atypical mycobacteria, abuse of broad spectrum antibiotics (many of which have potential anti tubercular action), longevity of the human race with concomitant immune compromising morbidities (diabetes, use of immosuppressive drugs in organ transplantations, rheumatoid disorders and malignancies) the incidence of multidrug resistant tuberculosis (MDR-TB) is increasing worldwide. Currently available first line chemotherapeutic agents have been in clinical use for >30 years, and the infective mycobacterium is getting used to these drugs.

The population with AIDS and immune compromised states are likely to get infected with atypical tuberculous bacilli and many of these strains show resistance to a large number of available anti tubercular drugs. Failure of compliance of standard anti tubercular drugs is another cause of development of resistance. According to WHO estimates it is only 25% of cases who complete the full course of therapy, 75% of defaulters again harbor mycobacteria with acquired resistance. Patients infected with resistant mycobacterium (primary or acquired) are a potential source of spread of MDR strain to other members of society. The real extent and existence of MDR-TB is unknown because of technical problems regarding surveillance and reporting, especially from high disease burden areas. Broadly speaking the resistance in 1st time treated patients is 5-10% and 10-15% in previously treated patients.

DEFINING MULTIDRUG RESISTANT TUBERCULOSIS

Strictly speaking MDR-TB is a bacteriological diagnosis. It is defined if the infecting organism is resistant to isoniazid and rifampicin (with or without resistance to other anti TB drugs). More recently (in 21st century) another complication of MDR has been recognized as extensively drug (XDR)-TB that is, the MDR strains that are resistant to fluoroquinolones plus one of the injectables such as kanamycin, amikacin, and capreomycin. Unfortunately unlike pulmonary TB, in skeletal tuberculous infection (a paucibacillary disease) one is unable to harvest the infecting mycobacterium in approximately 80% of specimens. In clinical orthopedics if the disease is not showing evidence of progressive healing within 4-5 months of the institution of multiple anti tubercular drug therapy one should consider such cases as resistant or therapeutically refractory cases. Also when the destructive process increases, sinuses and ulcers continue to discharge, new cold abscesses appear, there is an increase in size of existing cold abscess and additional active tubercular foci develop, it is either resistant or therapeutically refractory case.

THERAPEUTICS

A favorable clinical response is clinically judged by improvement in general health, body weight, fever, pain and laboratory findings. Imaging modalities (X-rays and magnetic resonance imaging [MRIs]) however lag behind the biological healing process. Imaging modalities do not differentiate between the granulation tissues of active inflammation and that of the repair process. X-rays and MRIs done up to 5 months of treatment may show images of “deterioration”. However, if X-rays and MRIs show deteriorating picture even after 5-6 months of effective drugs one should obtain the tissue for culture and consider the possibilities of a “therapeutically refractory tuberculous infection” or an alternative pathology. By the time, a patient is clinically suspected to be a resistant case he has already had the first line drugs (isoniazid, rifampicin, pyrazinamide, ethambutal, streptomycin) for many months. One has to resort to “the second line” or potential anti TB drugs [Table 1]. We have been using a combination of minimum of three first line drugs and at least two second line drugs in MDR-TB. Most of the second line drugs are more costly and more toxic. At least in initial stages patient must be kept under close observation for intolerance and toxic effects. Throughout the treatment attention must be paid to supportive therapy, nutrition and control of medical comorbidities. Operative debridement, drainage

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| Website:                  | www.ijoonline.com |
| DOI:                      | 10.4103/0019-5413.132487 |
and decompression (in tuberculous paraplegia) may be undertaken for absolute indications. The patient and his family must be warned about postoperative spread of disease and complications. Despite the best of efforts mortality at the end of 5 years is 50% for MDR and nearly 100% for XDR-TB. The recommended duration of treatment is at least 18 months after sputum culture conversion in pulmonary cases.6

**IMMUNITY AND TUBERCULOSIS**

The immune response of healthy human beings against tubercular bacilli has been very effective due to which only 5% of infected persons develop clinically evident primary (pulmonary) disease and only a further 5% or so develop postprimary disease later in life.5 Immunomodulation in conjunction with multidrug therapy may be of help in MDR-TB. Attempts are underway for the development of effective immunopotentiating techniques. Immunomodulatory therapies should be rational and attractive however currently most of the efforts are like preclinical trials.7,9 Pending such advances the following modality has been used by us as an adjunct to anti TB drugs.10,11 Levamisol (150) mg is given at night for 3 consecutive days at weekly intervals for a total of 45 tablets. Four injections are administered once a month. The first and second are 0.1 ml intradermal Bacillus Calmette-Guerin (BCG) injections and the third and fourth are intramuscular diphtheria + pertussis + tetanus vaccine injections. Clinically a favorable response was observed in 85% of patients.5,11 The helper subset of T lymphocytes is central to cell mediated immunity against tuberculous infection. These cells carry CD4+ antigens on their surface (CD4 + lymphocytes). In patients who were considered therapeutically refractory CD4+ count was found to be lowered.11 The above mentioned immunomodulation regime in conjunction with second line drugs demonstrated upgradation of CD4+ count after 4-6 months of therapy.5,11 BCG vaccination has been known to provide some degree of immune protection for various mycobacterial infections.12,13 Direct BCG vaccination without tuberculin testing is considered safe and acceptable to the persons being vaccinated. Booster BCG vaccination in patients activates macrophages to be more effective killer cells against mycobacteria.14 Though, the mechanism of influence on immune response after mycobacterial vaccination remains speculative however it is considered that macrophages get activated to become more effective killer cells against mycobacteria, probably it switches off the tissue - necrotizing aspects of Koch5 phenomenon and replaces an inappropriate immune reaction by an appropriate one against mycobacterial infections.

**RECURRENCE**

Tuberculous infection may recur at any time during the life span of patient. Approximately, 2-5% of patients report back with reactivation within about 20 years after the apparent clinical healing of the first lesion.2 The causes of reactivation include prolonged use of systemic cortisone therapy, immunosuppressive drugs, malnutrition, development of diabetes or an immune deficiency state and any surgical procedure or injury to the previously infected area. Dormant tuberculous bacilli, persistent in macrophages and tissues for years, may start to replicate under such circumstances or reinfection with a different type of mycobacterium may take place. Such patients require to be treated by newer chemotherapeutic agents, or drugs which were not used earlier or used for the short duration or used in the remotest past. The duration of drug therapy recommended is 12-18 months.6
With the perpetuation of endemic state of TB in the developing world and currently about 10% annual increase in its incidence in the affluent countries, the challenge of tuberculous infection and that of MDR-TB is far from contained. Attempts are being made to develop recombinant BCGs for more effective methods or including strong cell mediated immunity for clinical use.\textsuperscript{15}

INH must form part of any multidrug therapy. Thioacetazone is contraindicated in HIV positive patients because of risk of severe skin reactions. Avoid more than one hepatotoxic drug in patients where surgical intervention is anticipated.

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\textbf{How to cite this article:} Tuli SM. Multidrug resistant tuberculosis: A challenge in clinical orthopedics. Indian J Orthop 2014;48:235-7.

\textbf{Source of Support:} Nil, \textbf{Conflict of Interest:} None.