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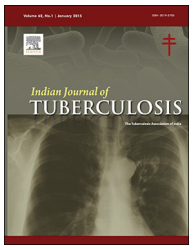

Original Article

Immunotherapy for non-responders among patients of spinal tuberculosis

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ABSTRACT

Background: Combined chemo- and immunotherapy are the major advancement in the treatment of tuberculosis. Immunotherapy supposedly increases cure rate while reducing the duration of treatment and tissue damage. Non-responders are those patients of tuberculosis who do not respond to anti-tubercular therapy (ATT) in the desired manner despite the mycobacteria showing sensitivity to the given drugs. The role of immunotherapy in the treatment of this particular subset of patients has been investigated scarcely.

Methods: The present study included a retrospective review of prospectively collected clinico-radiological data of 14 non-responder patients who were taking ATT for spinal tuberculosis for a mean duration of 10.3 months. An immunotherapeutic regime comprising of single intramuscular injection of vitamin D 600,000 IU, 3 days course of oral albendazole 200 mg daily, salmonella vaccine 0.5 ml intramuscular and influenza vaccine 0.5 ml intramuscular were added to ATT. The vaccines and the course of oral albendazole were repeated after a month.

Results: Before immunotherapy, seven patients were partially dependent while other seven were completely dependent on others for activities of daily living. All except one patient after treatment became independent till last follow-up (p value <0.01). Post immunotherapy, ATT was continued for mean duration of 4.9 months with mean follow-up of 22.4 months. All patients showed good clinical response within 2–6 weeks after the initiation of immunotherapy.

Conclusions: The crux to success of the immunotherapy regime is its potential to restore the existing Th1 Th2 imbalance and to provide substitute to the anergic and dysfunctional immune cells.

1. Introduction

Tuberculosis is an immunological disease with infective transmission. Unlike other microbial infections, which destroy host cells either by direct contact or through release of endotoxins or exotoxins, mycobacteria invokes tissue destruction through inappropriate immune reaction to its antigens. Most efforts to fight against the challenging disease have been directed toward merely killing of the infective pathogen, while

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the immune component of the disease, somehow, has never received the attention it deserves. Various immunotherapeutic agents have targeted the existing host anti-tubercular immune response with an aim to either kill the bacilli or contain it. These include (1) antigenic stimulation with BCG or M. vaccae or RUTI vaccinations to augment Th1 response,[1–3] (2) biological therapy to enhance the Th1 protective response with many different cytokines like interleukin 2 and IFN γ etc.,[4,5] and (3) anti-Mycobacterial antibodies.[6] There have been recent reports about immune response modifier like corticosteroids, thalidomide, or anti TNF-α, etc., reducing systemic inflammation.[7–10]

In endemic areas, majority of extrapulmonary and skeletal tuberculosis patients receive ATT on mere clinico-radiological correlation and without any bacteriological or histopathological confirmation. It is not uncommon to see patients who, despite receiving ATT for months or even years, fail to show clinical improvement and rather show signs of worsening. Many of these patients, during the course of their treatment, turn out to be suffering from multidrug-resistant (MDR) tuberculosis. However, a significant number of such patients who have shown to harbor Mycobacteria (Mtb) sensitive to ATT pose a real challenge. These non-responders may form significant number of patients from the endemic areas like Asian sub-continent and have forced many physicians to question efficacy of short-term chemotherapy making all their patients to continue the medication for 18 or even 24 months.

A review of literature showed very scarce attention to such non-responders, which contribute significantly to the quantum of tubercular patients in the developing world. We could find just one study, which used immunotherapy in the form of oral levamisole, intradermal BCG, and intramuscular diphtheria tetanus (DT) vaccine for such non-responders with good results.[11] We evaluated the role of intramuscular salmonella and influenza vaccines, injectable vitamin D, and a course of antihelminthic drugs as an adjunct immunotherapy for the non-responding cases suffering from spinal tuberculosis.

2. Material and methods

This study is a retrospective review of prospectively collected clinico-radiological data of 14 consecutive non-responding cases of spinal tuberculosis who were diagnosed and treated at our government-based, tertiary-level, teaching referral center from 2009 to 2013. The non-responding cases of spinal tuberculosis of >12 years of age of either gender were considered for proposed immunotherapy. The cases with chronic illnesses like uncontrolled diabetes, renal or hepatic disorders, and HIV infection were excluded from the study including patients harboring MDR strains of Mtb. A written informed consent was obtained from all the patients before starting immunotherapy. All patients were broadly divided into three groups on the basis of clinical scenarios: (1) non-responders based on the clinical/hematological/radiological parameters despite sufficient duration of ATT of 6 months or more (6 patients), (2) non-responders with worsening of the disease despite continued ATT for 3 months or more (5 patients), and (3) non-responders despite an added surgical debridement and continued ATT post-operatively for 3 months or more (3 patients).

The patients were initially evaluated with detailed clinical and neurological examinations. The clinical parameters to dictate clinical improvement or deterioration included constitutional symptoms like fever, loss of appetite and loss of weight, local pain, and tenderness, limitation of movements, and change in quantity of discharge or size of abscess, or progression of the neurological deficit if any. The relevant hematological (total and differential leukocyte counts, hemoglobin, and erythrocyte sedimentation rate) and radiological investigations (spine radiographs, chest radiographs, contrast-enhanced magnetic resonance imaging, and computed tomography) were performed on in-patient/out-patient basis. The additional investigations performed were pus for microscopic examination, culture for acid-fast bacilli, polymerase chain reaction (PCR) and nucleic acid amplification test (NAAT), and a work-up for possible drug resistance.

The ATT regimen (category I) included an initial intensive phase consisting of four drugs: Isoniazid (H) 5–10 mg/kg/d; Rifampicin (R) 10–20 mg/kg/d; Pyrazinamide (Z) 25–35 mg/kg/d; and Ethambutol (E) 15–25 mg/kg/d along with Pyridoxine 10 mg for 2 months, three drugs HRE for 3 months, followed by maintenance phase of 4 months of two drugs HR. However, all patients had varied therapeutic profiles both in terms of duration of ATT and even the regimen at the time of start of immunotherapy. Three patients were on category II ATT of five drugs including intramuscular injection of Streptomycin 1 g daily for 90 days, five patients were on repeat intensive phase of four drugs after completing one full category I regimen, four patients were on three drugs phase of category I regime while two patients were on two drugs maintenance phase. The immunotherapy regimen comprised of antihelminthic drug albendazole 200 mg oral once daily for 3 days, single dose intramuscular injection of 6,00,000 IU of vitamin D, intramuscular Salmonella typhi purified Vi-capsular polysaccharide vaccine 0.5 ml (Typbar TCV, Bharat Biotech International Ltd., India), and intramuscular Influenza vaccine 0.5 ml (Influvac, Abbott India Limited, India). The vaccines and the course of albendazole were repeated after a month. All outdoor patients were seen monthly to assess clinical response and early detection of complications (drug-related side-effects, reactivation of disease process, and worsening of neurology). Response to therapy was seen clinically by improvement in back pain, constitutional symptoms, and neurological deficit, biochemically by serial ESR. Radiographs were obtained every 6 weeks.

Statistical analysis: Wilcoxon matched-pairs signed-ranks test was performed, using InStat software for Windows (GraphPad version 3.00, SanDiego, California, USA), to statistically evaluate the significance of clinical outcome. The resulting p value of <0.05 was accepted as statistically significant differences of the median of paired observations.

3. Results

The study included 14 cases with demographic and clinical profile as given in Table 1. The most common presenting symptom was persistent pain in the back (14 patients), fever (8 patients), and weakness of the lower limbs (7 patients). Tenderness (nine patients) and spastic paraplegia/quadriplegia