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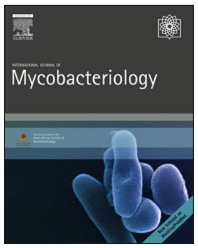

Host-directed therapies for multidrug resistant tuberculosis

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ABSTRACT

Tuberculosis (TB) causes 1.3 million deaths annually. There are 0.5 million cases of multidrug resistant TB (MDR-TB) and the number of cases is rising globally. The current status quo of the lengthy treatment duration and poor treatment outcomes associated with MDR/extensively drug-resistant TB, and those with comorbidity of TB with human immunodeficiency virus and noncommunicable diseases in sub-Saharan Africa is unacceptable. The TB drug pipeline remains sparse. New innovations for shortening the duration of therapy and improving treatment outcomes (cure and long-term functional disability due to lung damage) are urgently required. A wide range of host-directed therapies (HDT) are now available which require evaluation as adjuncts to current TB drug treatment. Examples are:

(1) Repurposed drugs:
- Analgesics/nonsteroidal anti-inflammatory drugs (cyclooxygenase-2 inhibitors, e.g., ibupofen).
- Cholesterol-lowering drugs (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, e.g., simvastatin).
- Asthma drugs (leukotriene synthesis inhibitors, e.g., zileuton).
- Diabetes drugs (reactive oxygen species removal and increased CD8+ T-cell responses (e.g., metformin).
- Anticonvulsants (inhibition of histone deacylation, e.g., valproic acid).

(2) Cellular therapy: using the patient's own bone marrow-derived stromal cells.
(3) Immune therapies: for example, anti-interleukin-6/interleulin-6 receptor monoclonal antibody.
(4) Therapeutic vaccines: protein vaccines (e.g., granulysin), DNA vaccines, environmental mycobacteria vaccines (e.g., *Mycobacterium vaccae*, *Mycobacterium indicus pranii*).
(5) Micronutrients: for example, Vitamin D, zinc, probiotics, and so forth.

The Host-directed Therapies Network consortium of 64 partners was launched in Cape Town after a meeting hosted by the South African Medical Research Council in April 2015. This network (which is open to anyone interested) plans to take forward a wide range of HDTs in randomized, placebo-controlled clinical trials as adjuncts to current TB treatment regimens with the aims of:

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(1) Shortening the duration of treatment for drug-sensitive TB and MDR-TB.
(2) Improving treatment outcomes (mortality/morbidity) for MDR/extensively drug-resistant TB patients.
(3) Improving lung function and preventing lung damage so that the patient can return to gainful employment after treatment.
(4) Improving treatment outcomes for clinical presentations associated with tissue injury:
    (i) Miliary TB (including TB meningitis and TB pericarditis).
    (ii) Immune reconstitution inflammatory syndrome.

(5) Improving treatment outcome of TB and/or human immunodeficiency virus-positive individuals with comorbidities such as noncommunicable diseases (e.g., diabetes, liver disease, and cardiac disease), and cancers.

Conflicts of interest

The authors have nothing to disclose.