Nonsteroidal Antiinflammatory Drugs for Adjunctive Tuberculosis Treatment

Juraj Ivanyi1 and Alimuddin Zumla2

1Department of Clinical and Diagnostic Sciences, Kings College London at Guy’s Hospital Campus, and 2Centre for Clinical Microbiology, Department of Infection, Division of Infection and Immunity, University College London, United Kingdom

(See the brief report by Vilaplana et al on pages 199–202.)

Keywords. Tuberculosis; adjunctive treatment; non-steroidal anti-inflammatory drugs; Ibuprofen; prostaglandin inhibitors.

Tuberculosis continues to cause 1.4 million deaths annually despite effective treatment being available since the 1970s. The standard 4-drug tuberculosis treatment regimen involving isoniazid, rifampicin, pyrazinamide, and ethambutol achieves 90% cure rates in programmatic settings [1]. Mycobacterium tuberculosis bacilli are difficult to eradicate since they exist in a spectrum of replication states, from metabolically active, “rapid” replicators to nearly “dormant” nonreplicating persisters. Thus, treatment is required for a duration of at least 6 months in 2 phases: a 2-month intensive phase involving all 4 drugs and a 4-month continuation phase involving rifampicin and isoniazid. Major challenges for tuberculosis control programs include poor compliance, resulting in the emergence of multidrug-resistant M. tuberculosis strains, which require the use of more toxic second-line drugs for at least 24 months [1]; problems also arise from failures in drug supply and from drug intolerance. Shortening of the tuberculosis treatment period for both drug-susceptible and drug-resistant tuberculosis would greatly improve tuberculosis management and infection control.

Immunotherapy has been considered as a possible approach toward shortening the duration of chemotherapy, with a wide range of cytokines or their inhibitors and chemical or biological immunomodulatory compounds being explored [2]. However, the factors that determine the replication rate of M. tuberculosis and synergize or antagonize the effectiveness of mycobactericidal drugs remain poorly understood. Efforts at developing new drugs that act on replicating populations of M. tuberculosis, which thrive under metabolically active, rapid replicators to nonreplicating persisters, which require the cyclosporine-sensitive and genetically in- 

EDITORIAL COMMENTARY

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DOI: 10.1093/infdis/jit153

The Journal of Infectious Diseases 2013;208:185–8

Received and accepted 13 February 2013; electronically published 5 April 2013.

Correspondence: Juraj Ivanyi, MD, PhD, Clinical and Diagnostic Sciences Department, Hodgkin Bldg, 2nd Fl, Guy’s Campus of Kings College London, London SE1 1UL United Kingdom (juraj.ivanyi@kcl.ac.uk).

Tuberculosis, adjunctive treatment, non-steroidal anti-inflammatory drugs, Ibuprofen, prostaglandin inhibitors.
to prostaglandin H₂ and prostacyclin (which lead to release of mediators of pain, inflammation, and fever) and to thromboxane A₂ (which stimulates platelet aggregation and vasconstriction). Ibuprofen is listed as a core medicine by the World Health Organization [12] and is a widely used analgesic and anti-inflammatory drug that inhibits both COX-1 and COX-2 cyclooxygenases. COX-1 inhibition is responsible for unwanted side effects, such as gastrointestinal ulceration and bleeding. However, even selective COX-2–inhibitory NSAIDs carry a cardiovascular risk, leading to hypertension and myocardial infarction due to COX-2 inhibition in vascular endothelial and smooth muscle cells [13].

The results obtained by Vilaplana et al are highly relevant for further consideration of evaluation of the use of ibuprofen in humans for the adjunctive treatment of drug-susceptible and drug-resistant tuberculosis. The rationale for use of adjunctive antiinflammatory therapy for tuberculosis is to alleviate the excessive and harmful host inflammatory responses that lead to pathological lung lesions. Induced by antigenic and immunomodulatory glycolipid stimuli, these “decoys” [14] trigger host reactions, which are protective in the majority of infected individuals but become pathogenic in a minority of infected subjects. The lungs are the route of entry of M. tuberculosis infection and permit the pathogen to evade protective systemic host defense, persist in a latent state, and form pathological lesions, which are essential for efficient transmission of M. tuberculosis from the granuloma lung lesion into the alveoli and aerosols. Antiinflammatory therapy is, thus, targeted toward lung granulomatous lesions generated by an influx of a range of immune cells such as monocytes, lymphocytes, and neutrophils (PMNs) [15]. All these cell types produce prostaglandins and, therefore, can be targets for the action of COX-1 and COX-2 cyclooxygenase inhibitory drugs.

Considering the pilot nature of the results involving C3HeB/FeJ mice reported by Vilaplana et al, the authors restrained from eluding on the question of the possible target cell for ibuprofen therapy. PMNs need to be considered, bearing in mind that their function is probably defensive early after M. tuberculosis infection but aggravating in advanced disease [16]. Therefore, the timing of ibuprofen therapy would need to aim at the late stage and avoid interfering with the early stage of infection. The protective function has been associated with PMN granule–derived peptide and cationic protein defenses, which can be cidal for both intracellular and extracellular M. tuberculosis [17], or with the activation of macrophages. On the other hand, the pathogenic function of PMNs has recently been attributed to the IFN-inducible programmed death 1 ligand, with the caveat that either its excess or absence could be pathogenic [16]. The perceived need for “balancing” indicates how difficult it may be to identify a beneficial therapeutic regimen. While the influx of PMNs to lesions is due to attraction to interleukin 17, produced by γδT cells or T-helper 17 cells, to interleukin 8, and to the MIG chemokine, the mechanisms resulting in PMN depletion by ibuprofen might involve their apoptotic death and clearance by macrophages. Thus, ibuprofen may act by either reducing the influx of PMNs or by enhancing their clearance.

Inhibition of PGE₂ synthesis by ibuprofen may be favorable for host resistance, considering that PGE₂ is acting against the production of interleukin 1, TNF-α, and reactive oxygen and nitrogen intermediates by macrophages. It also inhibits interleukin 12 expression by dendritic cells and expression of IFN-γ and interleukin 2, while promoting the production of interleukin 10 and interleukin 4 by lymphocytes. On the other hand, COX-mediated inhibition of PGE₂ synthesis in macrophages may be unfavorable for the host in the early phase after M. tuberculosis infection, since PGE₂ protects the mitochondrial membrane against damage from M. tuberculosis, prevents necrosis, and promotes the apoptosis of infected macrophages, which leads to both innate and adaptive immunity [18]. In fact, virulent but not the attenuated M. tuberculosis evades the host response by inducing the production of lipoxin A₄, which inhibits cyclooxygenase 2 production and PGE₂ biosynthesis. However, the picture seems more complex, considering that the ESAT-6 secretory antigen of M. tuberculosis stimulates PGE₂ production, perhaps with the pathogen’s strategy to permit initial but impede later Toll-like receptor–mediated signaling [19]. Finally, the possible action of ibuprofen on alveolar epithelial cells, which also make COX cyclooxygenases, also needs to be considered.

Ibuprofen could also influence the production of leukotriene B₄ (LTB₄), which is anicosanoid whose levels are elevated by M. tuberculosis infection, but with opposite effects than PGE₂ [20]. Blockade of COX-2 by administration of the celecoxib NSAID enhanced metabolism via the 5-LO pathway, indicating that the protective effect against M. tuberculosis may be due to increased leukotriene production by alveolar macrophages and that the immunostimulant effects of LTB₄ dominate over the immunosuppressive actions of PGE₂ [10].

The key open question remains of whether ibuprofen could be beneficial as an adjunctive treatment when combined with tuberculosis chemotherapy. The mouse experimental models offer the best opportunity for further preclinical research. However, suitable conditions will need to be chosen for several aspects, such as the route and dose of infection, the time and schedule of therapy, and the end point criteria, such as lung pathology, bacterial load, weight loss, or survival. It is commendable that mice with human-like lung pathology features, such as the C3HeB/FeJ strain (used by Vilaplana et al) or the I/St strain [21], develop caseating granulomas, which develop into liquefacted lesions, with a massive cellular invasion of alveolar spaces mainly by neutrophils. In common for humans
and mice, tubercle bacilli in such lesions tend to multiply extracellularly and upregulate the expression of hypoxia-associated genes. Significantly, mice with these lesions are prone to postchemotherapy relapse to a greater extent than conventional inbred mice [21]. Use of low-dose aerosol infection that leads to late pulmonary pathology might be most suitable for finding out whether ibuprofen treatment, as an adjunct to chemotherapy, could reduce the relapse rate.

Trials on the use of ibuprofen as an adjunct to tuberculosis chemotherapy in humans are warranted in clinical situations with pronounced inflammatory pathogenesis. This is strongly supported by the already established routine use of corticosteroids with standard tuberculosis drug treatment for tuberculosis meningitis, brain tuberculomas, and severe cases of military tuberculosis, resulting in reduced mortality from tuberculosis meningitis [22]. Aspirin has been proven to be of use in preventing stroke and 3-month mortality in patients with tuberculosis meningitis [23]. A range of pharmacological agents with immunosuppressive and immunomodulatory activity have been used for tuberculosis-related paradoxical immune reconstitution inflammatory syndrome (TB-IRIS) after initiation of antiretroviral therapy in human immunodeficiency virus (HIV)–infected patients with tuberculosis. Adjunct therapy with steroids reduces morbidity associated with moderately severe IRIS [24]. The beneficial effects of prednisone in TB-IRIS appear to be mediated via suppression of predominantly proinflammatory cytokine responses of innate immune origin, rather than via a reduction of the numbers of antigen-specific T cells in peripheral blood. NSAIDs may be as effective as corticosteroids for treatment of non–life-threatening TB-IRIS in HIV-infected patients.

Many patients who need to move on to second-line therapy for drug-resistant tuberculosis do not receive the treatment they need because the tuberculosis drugs are too expensive. Ibuprofen and other NSAIDs are comparatively very cheap. Although ibuprofen does have some potential side effects, these are likely to be acceptable when compared with the toxicity and side effects of tuberculosis drugs. Because ibuprofen has comparatively little risk and good safety profile, the temptation is to immediately evaluate the use of ibuprofen as an adjunct to tuberculosis treatment in humans in phase 3 clinical trials, although other evaluations may be required. Other COX-2 inhibitors with fewer side effects than ibuprofen could be more suitable for adjunctive tuberculosis therapy. Thus, rofecoxib and celecoxib, which preferentially inhibit COX-2, resulting in better tolerability [25], should be evaluated in parallel with ibuprofen. Ibuprofen linsane salt with increased water solubility allows intravenous use with more rapid onset of action and is suitable for topical use. Could ibuprofen-linsane be of interest for aerosol application in tuberculosis? Of the other considerations, the timing of ibuprofen delivery could be critical to improving treatment outcomes: if it is used to target PMN infiltration, than it should be given late, when the inflammatory pathology is excessive, not early, when PMNs might be protective.

Case reports documented reactivation of pulmonary tuberculosis in 2 patients who had used NSAIDs [26]. A case-control study of 38 patients designed to test the hypothesis that such an association exists found a statistically significant relation between the reactivation of latent M. tuberculosis infection and the use of NSAIDs [27]. Whether the association is direct, indirect, or secondary remains unknown, but it may involve mechanisms by which hydrocortisone has been shown to reactivate dormant tuberculosis in Cornell model mice. The studies would need to take into account the influence of human population genetics, the influence of commensal environmental microbiota, and the compound lifetime history of immunological priming due to vaccinations and exposure to infectious diseases. Since all patients with active tuberculosis will be treated by standard chemotherapy, any consideration of clinical trials that evaluate adjunctive treatment with ibuprofen will need to be judged as to whether ibuprofen can shorten the period required to achieve relapse-free cure.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


