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Novel Adjunctive Therapies for the Treatment of Tuberculosis

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Abstract

Despite significant efforts to control tuberculosis (TB), the disease remains a major global threat, with an estimated 8.6 million new cases and 1.3 million deaths in 2012 alone. Significant treatment challenges include HIV co-infection, the dramatic rise of multidrug-resistant TB and the vast reservoir of latently infected individuals, who will develop active disease years after the initial infection. The long duration of chemotherapy also remains a major barrier to effective large scale treatment of TB. Significant advances are being made in the development of shorter and effective TB drug regimens and there is growing evidence that host-directed and “non-antimicrobial” pathogen-directed therapies, could serve as novel approaches to enhance TB treatments. This review highlights the rationale for using these therapies and summarizes some of the progress in this field.

Keywords

Corticosteroids; efflux pump inhibitors; microenvironment; inflammation; TNF- α

INTRODUCTION

There were an estimated 8.6 million new cases of tuberculosis (TB), accounting for 1.3 million deaths in 2012 alone [1]. One third of world’s population is latently infected with *Mycobacterium tuberculosis*, of which 5% to 10% will develop active disease years after the

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CONFLICT OF INTEREST

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initial infection [2]. HIV co-infection dramatically increases the risk of relapse to approximately 10% per year [3]. A recent study has demonstrated that TB is the main cause of death in HIV co-infected patients in Eastern Europe [4]. In 2012, there were an estimated 450,000 new cases of multidrug resistant TB (MDR), defined as disease with *M. tuberculosis* strains resistant to two of the first-line TB drugs (isoniazid and rifampin). Of these, ~10% are estimated to be extensively drug resistant (XDR) TB, defined as disease with MDR strains also resistant to any fluoroquinolone and to at least one of three injectable second-line TB drugs (capreomycin, kanamycin, and amikacin) [1]. It is estimated that a diseased individual can transmit *M. tuberculosis* to 10–15 close contacts over the course of a year. While significant advances are being made in developing shorter and effective TB drug regimens [5], there is growing evidence that host-directed and “non-antimicrobial” pathogen-directed therapies could serve as a novel approaches to shorten TB treatments [6, 7].

HOST MICROENVIRONMENT: FRIEND OR FOE?

After deposition of *M. tuberculosis* in the alveoli *via* an airborne route, the bacteria are phagocytosed by alveolar macrophages and replicate within them. With the emergence of delayed-type hypersensitivity (DTH), infected macrophages in the interior of the granuloma are killed, and the periphery becomes fibrotic. The granuloma enlarges progressively to a macroscopic lesion with central areas of “caseous” necrosis. Occasionally, the necrotic TB granuloma bursts into an airway to form a cavitory lesion. This process releases a large number of bacteria directly into the airway and patients with cavitory TB are highly infectious (Fig. 1).

In the late 1940s, surgical resection of TB lesions became increasingly common. Several reports demonstrated that *M. tuberculosis* could be detected by microscopy in resected TB lesions months after patients on TB treatments had no detectable bacteria in their sputa [8]. Although *M. tuberculosis* could be cultured from some lesions, “closed lesions” lacking patent bronchial communication failed to yield bacilli. Vandiviere *et al*, showed that by extending the incubation period from the standard 8-weeks to 3–10 months, *M. tuberculosis* from “closed lesions” could be cultured [9]. Since isoniazid (a first-line TB drug) was known to readily penetrate lesions in human lungs, lack of drug access was not responsible for the survival of *M. tuberculosis* within the “closed lesions”. Using tissue samples from the lungs of TB patients, Haapanen *et al.*, demonstrated that “closed lesions” are hypoxic and that hypoxia favors survival of dormant *M. tuberculosis* [10]. These classic studies suggest that the bactericidal activity of TB drugs is dependent on the physiological state of the bacteria and the host-microenvironment. Moreover, *M. tuberculosis* adapts to a quiescent physiological state, to successfully evade drugs (“persistence”) and host-immune responses (“dormancy”) for decades [11]. As the immune system falters, *M. tuberculosis* returns to replication mode, leading to relapse. It is therefore accepted that extended TB treatment is required to kill the dormant *M. tuberculosis* [8] (Fig. 2).

Host-directed therapies are well known and widely used to treat a variety of infections. Corticosteroids are recommended in the treatment of some forms of bacterial meningitis and have demonstrated a reduction in both mortality and neurological sequelae in adults [12, 13].

Similarly, adjunctive corticosteroids have been shown to prevent the development of hearing loss in children with *Haemophilus influenzae* type B meningitis [14]. Corticosteroids are used as adjunctive therapy in patients with severe *Pneumocystis* pneumonia, an opportunistic infection known to cause life-threatening pulmonary inflammation in patients with advanced HIV [15]. Macrolides are known to have immunomodulatory properties, and long term azithromycin is recommended for patients with cystic fibrosis. Several studies have also demonstrated the efficacy of azithromycin in reducing the risk of acute exacerbations in patients with chronic obstructive pulmonary disease (COPD) [16]. Adjunctive low-dose corticosteroids are also recommended in the treatment of severe sepsis, as they reduce mortality [17].

CORTICOSTEROIDS

Corticosteroids diffuse across the cell membrane and bind to intracellular receptors to form a complex that translocates into the nucleus. This complex interacts with DNA, resulting in altered transcription of various corticosteroid-responsive genes [18]. Corticosteroid hormones have diverse physiological effects that directly or indirectly regulate several different cell types including T-cells, macrophages, eosinophils, neutrophils, mast-cells, endothelial and epithelial cells (Fig. 3). These actions are accomplished primarily through the modulation of inflammatory cytokines, as well as through induction of apoptosis [19], leading to a dramatic reduction in lymphocytes and accompanied by neutrophilic leukocytosis [20, 21].

Pulmonary TB

In the 1950's corticosteroids were contraindicated as part of TB treatments [22]. However, this concept was rapidly discarded when it was found that corticosteroids in combination with effective chemotherapy proved to be useful in the treatment of TB patients [23]. In addition, adjunct therapy with prednisone (1–2 mg/kg/day) appeared to favorably influence the radiological lesions and hastened clinical improvement in children with severe TB (military TB, TB meningitis and pleural effusion) [24, 25]. Handley *et al.*, demonstrated that the use of high doses of prednisone (15 mg/day for the initial 3 months and 30 mg/day during the final 3 months) in combination with isoniazid was beneficial in patients with advanced bilateral progressive cavitary pulmonary TB [26]. Similarly, the Research Committee of the Tuberculosis Society of Scotland published the first randomized controlled trial in adults comparing TB treatment versus TB treatment plus adjunctive prednisolone (20 mg/day for 3 months) [27]. The clinical improvement in the prednisolone group was hastened, especially in the acutely ill. No permanent side effects were observed in the prednisolone-treated patients. The general radiographic improvement was more rapid throughout the 12-month period in the prednisolone group, although the rate of cavity closure was not increased. Morris *et al.*, studied whether this benefit was maintained in a 2-year follow-up study and demonstrated that the addition of prednisone during the early months of TB treatments not only led to more rapid clinical improvement initially, but also significantly greater radiographic resolution after 12 months [28]. Most of the initial trials utilizing high dose corticosteroids demonstrated an increased risk of side-effects [28–30]. However, subsequent studies using smaller doses of prednisone (1 mg/day) for 2–3 months

also demonstrated remarkable clinical and radiological improvements [31]. More recently, Dooley *et al.*, reviewed data from 11 randomized trials with adjunctive corticosteroids for pulmonary TB that included 1676 patients with different TB regimens (isoniazid, streptomycin, *para*-aminosalicylic acid and pyrazinamide) combined with different steroid regimens (prednisolone, ACTH and methylprednisolone). They concluded that overall, with adequate TB treatments, adjunctive corticosteroids did not affect the rate of culture conversion [32]. However, patients receiving adjunctive corticosteroids had a faster radiological response (except for resolution of cavities). No differences in mortality and chronic restrictive disease were noted amongst patients receiving adjunctive corticosteroids or TB treatments alone. Similarly, Smego *et al.*, analyzed 11 randomized trials of adjunctive corticosteroid therapy in the treatment of pulmonary TB that included 1814 patients treated with different regimens: prednisone and prednisolone (mean dose of 31 mg with a range of 16–60 mg) and/or ACTH (mean daily dose 40 units) [33]. The mean duration of steroid therapy was 85 days (range 30–180 days). They found that adjuvant use of corticosteroids in TB treatments hastened the reduction of fever, improved radiological changes (parenchymal infiltrates and to a lesser extent cavities), enhanced weight gain and reduced the length of hospital stay. It should however be noted that only two of the 11 studies reviewed included regimens that contained rifampin [34, 35]. In one of these studies utilizing rifampin (530 patients in Chennai, India), corticosteroids had no significant effect on bacteriological or radiological response. Therefore, there is a need for new trials evaluating the effect of corticosteroids in modern-era, rifampin-based TB treatments.

Multiple studies have analyzed the role of corticosteroids in TB-HIV co-infection. Mayanja-Kizza *et al.*, conducted a phase 2, randomized, double-blind, placebo-controlled trial in Uganda, to determine the safety and effectiveness of adjuvant prednisolone therapy in TB-HIV co-infected patients with CD4 < 200 [36]. They found that short-term; high-dose prednisolone therapy (2.75 mg/kg/day) enhanced clearance of *M. tuberculosis* from the sputum, decreased levels of TNF- α at 1-month and caused a transient increase in HIV RNA levels which nonetheless receded back after discontinuation of prednisolone. However, the intervention worsened underlying hypertension, caused fluid retention and induced hyperglycemia. Meintjes *et al.*, also reported the use of adjunctive corticosteroids in the setting of HIV-TB associated immune reconstitution inflammatory syndrome (TB-IRIS) [37]. They demonstrated that a 4-week treatment with adjunctive prednisone (1.5 mg/kg/day for 2 weeks followed by 0.75 mg/kg/day for 2 weeks) while receiving TB treatments, improved TB-IRIS symptoms and radiological findings. Adjunctive corticosteroids also led to a reduction in the duration of hospitalization and the number of outpatient therapeutic procedures. Serum concentrations of C-reactive protein, IL-6, IL-10, IL-12 p40, IP-10 and TNF- α were reduced in prednisone-treated patients at 2 and 4-weeks compared to baseline [38]. Another study has demonstrated similar results, with adjunctive corticosteroids favorably modifying the inflammatory profile of patients with TB-IRIS [39].

TB meningitis

Since immunopathology is a major component of central nervous system (CNS) TB, corticosteroids may improve clinical outcomes by reducing inflammation, vasculitis, necrosis and elevated intracranial pressure [40–42]. Several clinical studies have

demonstrated that adjunctive use of corticosteroids decreases both morbidity and mortality in children [41, 43] and adults with CNS TB [44, 45]. A recent study utilizing rifampin and moxifloxacin based regimens with adjunctive corticosteroids to treat TB meningitis, demonstrated significantly lower 6-month mortality in patients receiving a regimen with high-dose versus standard dose rifampin [46]. While the benefits of corticosteroids are clear in HIV-negative patients with CNS TB, there has been some controversy about its use in patients with HIV-coinfection. In the study by Thwaites *et al.*, the treatment effect of adjunctive dexamethasone was homogeneous across HIV subsets, and stratified subgroup analysis showed that though dexamethasone was associated with a reduction in the risk of death, the results were not statistically significant ($P = 0.08$) [44]. However, the 98 HIV-infected patients recruited in this trial were severely immunocompromised (median CD4 = 66), and none were treated with antiretroviral drugs. These patients had a higher case fatality rate than HIV-negative patients in the same trial, and although it was not possible to determine the cause of death, undiagnosed opportunistic infections were postulated to have been a factor. The authors therefore concluded that: a) that the numbers of HIV-infected patients were too small for them to conclusively determine the effect of adjunctive dexamethasone; b) but that adjunctive dexamethasone is safe and may be of benefit in this group of HIV-infected patients and; c) that these results should not be generalized to populations treated with antiretroviral drugs. It should be noted that most studies reported the use of dexamethasone or prednisolone, and there are few data from controlled trials comparing different regimens [47]. However, a small clinical trial in India demonstrated no statistically significant differences between dexamethasone and methylprednisolone [48]. Finally, recent data also suggest that the use of adjunctive corticosteroids based on host genotype may be even more beneficial. A study by Tobin *et al.* demonstrated that host genotype (single nucleotide polymorphism in the LTA4H promoter) was associated with recruitment of inflammatory cell, patient survival and response to adjunctive anti-inflammatory therapies in patients with TB meningitis [49].

In addition to adjunctive use for the treatment of CNS TB, corticosteroids are also useful to treat paradoxical reactions – worsening of disease after initiation of TB treatments – often seen in patients with CNS TB [50, 51].

There have been some concerns about reduced diffusion of antibacterial agents into the subarachnoid space due to corticosteroid therapy. However, it has been demonstrated that equivalent cerebrospinal fluid (CSF) concentrations were achieved with TB drugs (isoniazid, rifampin, pyrazinamide and streptomycin) with and without adjuvant corticosteroid therapy [52]. Based on all of these data, most infectious diseases bodies recommend use of adjunctive corticosteroids for CNS TB [53, 54].

TB pleuritis and pericarditis

Corticosteroids are often used for the treatment of TB pleuritis and pericarditis, but evidence for this remains inconclusive. A prospective, double-blind, randomized study evaluated the role of adjunctive corticosteroids in the treatment of TB pleuritis. All patients received isoniazid, 300 mg/day; rifampin, 450 mg/day; ethambutol, 20 mg/kg/day for more than nine months and were randomly assigned to take either prednisolone 0.75 mg/kg/day orally or

placebo for the initial treatment, which was tapered gradually for the next 2–3 months. Adjunctive use of corticosteroids led to earlier resolution of clinical symptoms (fever, chest pain, dyspnea) and hastened the absorption of the pleural fluid. No serious side effects were noted during the treatment in either group [55]. Other studies also suggest that symptoms resolve faster with the use of adjuvant corticosteroid therapy [32]. A trial in HIV-positive patients with TB pleural effusion demonstrated faster resolution of clinical symptoms and radiological findings with adjunctive corticosteroid treatment. However, it showed no significant difference in survival and a significant risk of Kaposi's sarcoma in the corticosteroid group [56]. A Cochrane review concluded that there are insufficient data to support the use of adjunctive corticosteroids in patients with TB pleuritis [57]. Similarly, Hakim *et al.*, have demonstrated reduced mortality rates and a faster clinical improvement in HIV-positive patients with TB pericarditis receiving prednisolone as adjunctive therapy [58]. While a Cochrane review of four randomized controlled trials demonstrated beneficial effects on mortality with the use of adjunctive corticosteroids in patients with TB pericarditis, these data are inconclusive due to the small size of the studies included in the trials [59]. In summary, overall, the clinical data is supportive of the use of adjunctive corticosteroids for TB pleuritis and pericarditis. However, a careful case-specific assessment must be performed to decide the risk and benefits of corticosteroids in these patients.

TUMOR NECROSIS FACTOR-ALPHA (TNF- α) INHIBITORS

TNF- α is a well studied cytokine and has a central role in the host responses to *M. tuberculosis*, typically manifested by the symptoms of fever, weight loss and sweats. This cytokine is produced predominantly by monocytes and macrophages, but can also be produced by other cells (mast-cells, endothelial cells, neuronal tissue, T and B lymphocytes, and natural killer cells) [60]. TNF- α promotes migration of immune cell to the site of infection, increases the sterilizing ability of *M. tuberculosis*-infected macrophages [61] and is critical in the formation and maintenance of the granuloma complex [62, 63]. Although the granuloma is believed to constitute a host defense mechanism, it may benefit the pathogen by presenting a physical barrier against both the immune response and the antimicrobial therapy [64]. Moreover, central necrosis of the granuloma, leading to caseation, is also driven by TNF- α , and may provide a unique microenvironment that promotes bacterial survival and persistence [65]. A recent review details the molecular mechanisms of TNF- α mediated tissue damage. Using a zebrafish model, this group has demonstrated that excessive levels of TNF- α induce mitochondrial reactive oxygen species (ROS) which induce programmed necrosis in infected macrophages, and that this pathway can be targeted with specific agents [66]. While TNF- α remains critical for controlling bacterial replication, data also demonstrate that *M. tuberculosis* hijack this pathway to facilitate their own survival within the TB granuloma [67]. Tobin *et al.*, have demonstrated that both inadequate or excess TNF- α levels increase host susceptibility to mycobacteria. Moreover, host genotype has also been shown to be a critical determinant of damage due to acute inflammation in patients with TB meningitis [49].

These data suggest that host-directed therapies may also need to be tailored to the host genotype. Thalidomide is known to reduce TNF- α levels, and adjunctive use of thalidomide reduces leukocytosis, brain pathology, and improves survival in a rabbit model of TB

meningitis [68]. Nonetheless, the use of thalidomide as a supplemental therapy for TB is limited by well-known side effects including teratogenicity and peripheral neuropathy. Moreover, a double-blind randomized study in children with TB meningitis did not find adjunctive thalidomide to be beneficial [69]. However, other analogs of thalidomide with greater efficacy and fewer side effects are being synthesized and may prove to be useful adjunctive agents [70, 71].

Newer TNF- α inhibitors such as etanercept, adalimumab, and pentoxifylline have also been investigated for use in TB, and have the potential to shorten treatments [65, 72–77]. This is plausible, as TNF- α levels increase shortly after initiation of TB treatments in humans [78], which leads to tissue destruction and creation of a microenvironment that could favor bacterial survival. In addition to limiting inflammation, adjuvant host-directed therapies may also have other beneficial effects. For example, decreased immunopathology and necrosis due to adjunctive TNF- α inhibition [65], may improve the penetration of TB drugs into the granuloma. It is also possible that by disrupting the microenvironment, host-directed therapies selectively promote the clearance of persistent bacteria [65]. This could be highly beneficial, as some of the best TB drugs, such as isoniazid, are effective only against actively dividing bacilli. A recent study in a mouse model that develops necrotic and hypoxic TB lesions [82, 83], demonstrated that addition of etanercept, a soluble TNF receptor fusion molecule (sTNFR), for the initial 6-weeks to standard TB treatment, accelerated bacterial clearance and reduced the rate of relapse [65]. These animal data are also supported by case reports and small clinical series that demonstrate that adjunctive use of TNF- α inhibitors with TB treatment are beneficial [77, 79–81]. Wallis *et al*, have shown that adjunctive treatment with etanercept reduced time to sputum culture conversion in HIV-positive patients, as well as improved weight gain, performance score, radiographic disease, cavity closure and estimated relapse [70, 76]. However, the major limitation of this study was the small sample size (16 patients) and these data need to be confirmed in a bigger clinical trial. It should also be noted that most of the TNF- α inhibitors reported above are expensive and administered as injectables. However, these data provide proof-of-concept that TNF- α inhibitors could help shorten TB treatments. Moreover, new oral TNF- α inhibitors such as tofacitinib and fostamatinib have been developed to treat chronic inflammatory diseases [84, 85] and may be better suited for resource limited settings.

Phosphodiesterase inhibitors (PDE-I) are another novel group of agents. The concentration of nucleotide 3', 5'-cyclic adenosine monophosphate (cAMP) - a highly conserved second messenger signaling molecule involved in the regulation of many cellular processes [86] - within a cell is determined by the activity of two types of enzymes: adenylate cyclases, which synthesize cAMP, and phosphodiesterases, which break down the cyclic nucleotide [87]. Increases in intracellular cAMP levels can reduce the production of TNF- α but also other innate immune mediators in macrophages. Since PDE-I lead to an increase in cAMP levels, they inhibit inflammation leading to tissue protective effects. Interestingly, it has also been demonstrated that adenylate cyclases of *M. tuberculosis* can directly produce a cAMP burst within macrophages leading to CREB phosphorylation and TNF- α secretion that promote the survival of bacteria [67]. Hence, the host cAMP-mediated signaling pathways represent a promising target against *M. tuberculosis*. Indeed, recent data from several

investigators have shown the benefit of PDE-I as adjunctive therapy during TB treatment in animal models [72–75]. Several PDE-I are orally bioavailable and many are FDA-approved (cilostazol, theophylline, roflumilast, tadalafil and sildenafil).

In summary, TNF- α inhibitors should be evaluated as host-directed adjunct therapies that could shorten TB treatments. However, since TNF- α inhibitors can reactivate latent TB infection [88–90], additional studies need to be performed to evaluate safety.

OTHER HOST-DIRECTED THERAPIES

Matrix metalloproteinases (MMPs) are endopeptidases responsible for degrading components of the extracellular matrix (ECM), such as collagen and proteoglycans. They play an important role in leukocyte migration, granuloma formation, tissue remodeling and in the development of cavitation [91–94]. Like TNF- α inhibitors, MMP inhibitors could reduce necrosis and prevent the creating of host-microenvironments favorable for bacterial survival. In addition, since cavitation is essential for the transmission of *M. tuberculosis*, MMP inhibitors could also be useful to reduce transmission of *M. tuberculosis* for diseased patients. Walker *et al.* have demonstrated that doxycycline inhibits MMP activity *in vitro*, and also decreases mycobacterial burden in guinea pigs, suggesting that adjunctive doxycycline treatments could be beneficial [95].

Decades before the availability of antibiotics, Niels Finsen proposed that sun exposure could be used to treat lupus vulgaris – a cutaneous form of TB. While the mechanism for this therapy was not known, Finsen was awarded the Nobel Prize in 1903 for this discovery [96]. However, recent studies are shedding light on how sunlight may help in fighting infections and stimulation or activation of vitamin D may be an important mechanism in fighting TB. Recently, several clinical studies have associated vitamin D deficiency with increased risk of TB [97–102]. One study has also demonstrated that TB-HIV co-infected patients with severe vitamin D deficiency had high levels of pro-inflammatory cytokines [39]. Moreover, *in vitro* data suggests that 1,25-dihydroxyvitamin D₃ (active form of vitamin D) induces and modulates innate and adaptive antimicrobial responses and suppress proinflammatory cytokine responses [103–106]. Vitamin D₃ acts through the VDR receptor – a transcription factor and part of the superfamily of steroid/thyroid hormone receptors – and up-regulates protective innate host responses [107, 108]. Vitamin D-mediated activity against *M. tuberculosis* is also dependent on the induction of antimicrobial peptides (AMPs) like LL-37 (also known as cathelicidin) [109, 110] which are produced by neutrophils, lung epithelial cells and monocytes [111]. While most clinical studies support the association of vitamin D with TB, adjunctive use of vitamin D with TB treatments is controversial. In one study, HIV-negative TB patients treated with adjunctive vitamin D had a higher rate of sputum conversion and radiological improvement compared with TB treatment alone [112]. Another recent randomized longitudinal study demonstrated that vitamin D supplementation accelerated sputum smear conversion and suppressed proinflammatory cytokines [113]. However, other studies show no overall differences in sputum conversion time [114] or clinical outcomes [115]. It is possible that host genotype may play a role in responses to vitamin D supplementation. Martineau *et al.*, demonstrated that vitamin D supplementation significantly hasten sputum culture conversion in participants with the *tt* genotype of the

TaqI vitamin D receptor [114], supporting this hypothesis. Conversely, a more recent study by the same group demonstrated that vitamin D supplementation also modulated immune responses in patients with the *Tt* and *TT* genotypes [113]. Additional clinical studies need to be performed to determine the role of vitamin D as an adjunctive treatment for TB.

Therapies targeting several important host-pathways could also be potentially useful as adjunctive therapies against TB. Programmed Death-1 (PD-1) is a co-inhibitory receptor that is known to negatively regulate adaptive immune responses and crucial for the development of protective host responses against *M. tuberculosis* [116]. PD-1 deficient mice are highly susceptible to *M. tuberculosis* and mount high levels of proinflammatory cytokines (TNF- α , IL-1, IL-6, IL-17) in response to *M. tuberculosis* infection [117]. It should be noted that as opposed to an anticipated immunostimulatory effect, the mouse studies demonstrated huge detrimental effect in the PD-1 knockout mice. However, the situation here is analogous to TNF- α (where knockout mice also do poorly with *M. tuberculosis* infection), but TNF- α inhibition combined with TB treatments during the early phase is paradoxically beneficial. Therefore, similar to TNF- α inhibition, modulation of the PD-1 during early stages of TB treatments may help in reducing the exaggerated proinflammatory responses and accelerate bacterial clearance. BMS-936558, an injectable antibody that specifically blocks PD-1 is currently under clinical investigation against cancers [118] and could potentially be evaluated for TB treatments. Fibrosis constitutes an important part of TB pathogenesis and may limit the penetration of drugs and immune cells into the granuloma. In addition to increasing penetration into the diseases tissues, anti-fibrotic agents can also reduce inflammation [119, 120] which may further help with TB treatments. Finally, while not host-directed, Gold *et al.* have demonstrated that oxyphenbutazone, a nonsteroidal anti-inflammatory drug, gets hydroxylated under acidic conditions and in the presence of reactive nitrogen intermediates. The hydroxylated compound has activity against both actively dividing and “nonreplicating” *M. tuberculosis* and was also synergistic with several TB drugs [121].

EFFLUX PUMP INHIBITORS

Bacterial efflux pump inhibitors are novel “non-antimicrobial” agents that could shorten TB treatments and also allow effective treatment of drug resistant organisms. Multidrug efflux pumps are broadly recognized as major mediators of drug-resistance to many classes of antimicrobials and anti-cancer agents [122, 123]. Efflux occurs due to the activity of membrane transport proteins known as multidrug efflux systems (MES) [124]. Bacterial efflux pumps are of special interest as they mediate antibiotic tolerance in mycobacteria [7], which can be overcome with efflux pump inhibitors [125, 126]. Since antibiotic tolerance is a major factor in mycobacterial persistence, efflux pump inhibitors have the potential to significantly shorten TB treatments. Moreover, it has also been recently demonstrated that efflux pump induction is a general first step in the evolution of mycobacterial drug resistance [127] and therefore efflux pump inhibitors could also help in prevent in the development of multidrug resistant *M. tuberculosis*. Verapamil is a well known calcium-channel blockers and has been extensively used as an anti-hypertensive in the clinic. Studies in the mouse model of TB demonstrate that verapamil in combination with first-line drugs significantly reduces pulmonary bacterial burden [128].

Phenothiazines are another class of drugs that inhibit bacterial efflux pumps, and have *ex vivo* activity against both drug-susceptible and drug-resistant strains of *M. tuberculosis* [129, 130]. However, phenothiazines may have multiple mechanisms of action against *M. tuberculosis*. Phenothiazine analogs have been shown to directly inhibit NADH:menaquinone oxidoreductase activity of *M. tuberculosis* [131]. Furthermore, they may also enhance intracellular killing of *M. tuberculosis* inside the phagolysosome, by inhibiting host-cell calcium and potassium channels [132]. Indeed, thioridazine has been shown to be effective as salvage therapy in patients with multidrug resistant TB [133, 134]. Other agents include reserpine (ATP-dependent efflux pump inhibitor) that has been shown to enhance the efficacy of ciprofloxacin [135] and linezolid [136] against *M. tuberculosis* strains. Piperine, a component of black pepper, has potential immunomodulatory activity [137] and is also an efflux pump inhibitor of Rv1258c of *M. tuberculosis* [138]. The efficacy of rifampin was increased by 4- to 8-fold in the presence of piperine both in sensitive and rifampin resistant *M. tuberculosis*.

CONCLUSION

In summary, while significant advances have been made in developing shorter TB drug regimens, there is growing evidence that adjunctive use of host-directed and “non-antimicrobial” pathogen-directed therapies could further accelerate TB treatments. While several promising adjunctive therapies are being developed and evaluated in pre-clinical settings, well controlled clinical studies with adequate power are needed to evaluate promising therapeutics with a focus on those that are already approved for clinical use.

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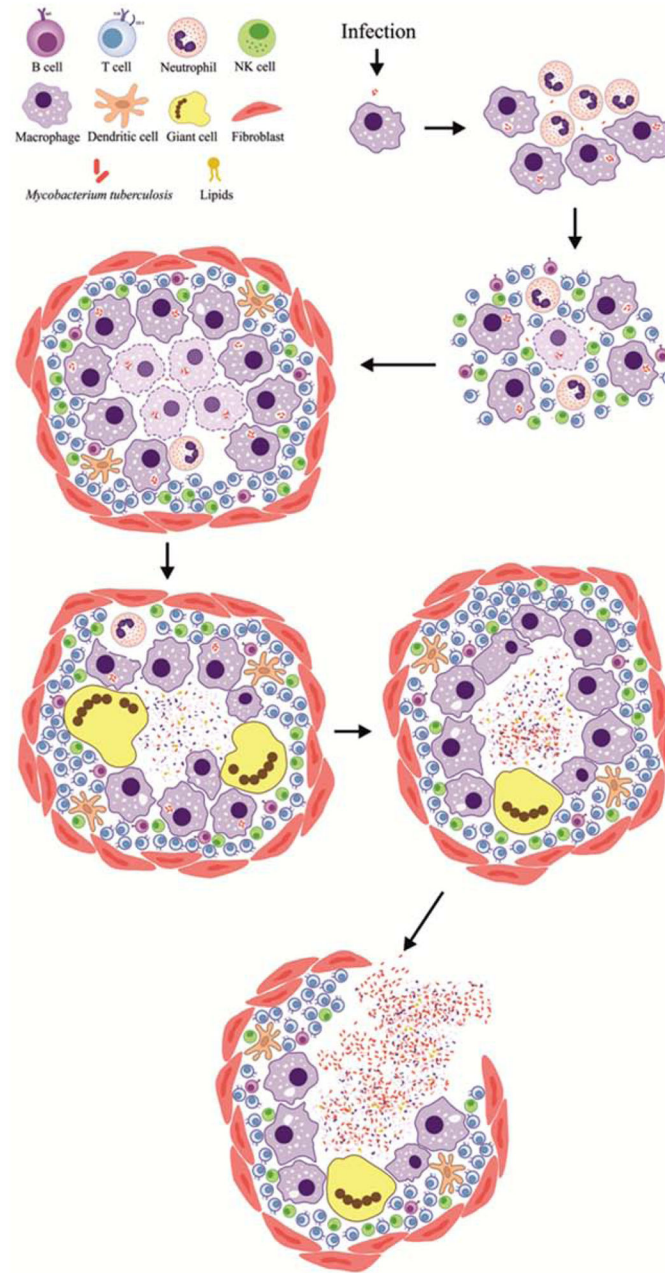


Fig. 1. Formation of cavitary TB lesions

After deposition of *M. tuberculosis* in the alveoli via an airborne route, initial events include phagocytoses by alveolar macrophages, bacterial replication within macrophages, development of delayed-type hypersensitivity (DTH) and the formation of the TB granuloma. These initial microscopic TB granulomas are composed mainly of activated macrophages and lymphocytes and may often have multinucleated giant cells (also called Langhans giant cell) with nuclei arranged like a horseshoe. With the emergence of DTH, infected macrophages in the interior of the granuloma are killed, and the periphery becomes fibrotic due to the production of collagen by fibroblasts. The granuloma enlarges progressively to a macroscopic lesion with central areas of “caseous” necrosis, surrounded

by activated macrophages, lymphocytes, and fibroblasts. Occasionally, the necrotic TB granuloma bursts into an airway to form a cavitory lesion. This process releases a large number of bacteria directly into the airway and patients with cavitory TB are highly infectious.

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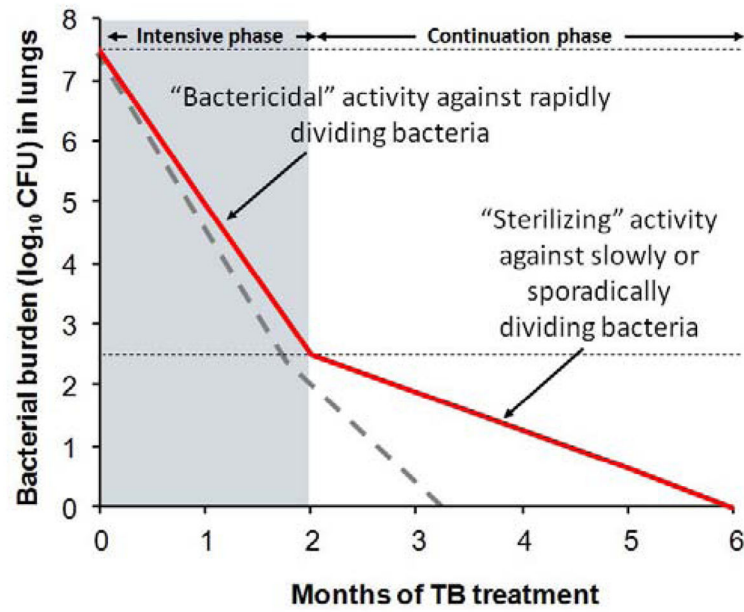


Fig. 2. Current model of TB treatment

Rapid bacterial killing is observed during the initial intensive phase which typically requires 4-drugs. However, the rate of killing is slower during the continuous phase due to “dormant” or “persistent” bacteria which are slowly or sporadically multiplying and therefore not amenable to effective killing by TB drugs. By targeting “dormant” or “persistent” bacteria, adjunctive therapies could hasten bacterial clearance (dotted line) and help in development of shorter and effective TB treatments.

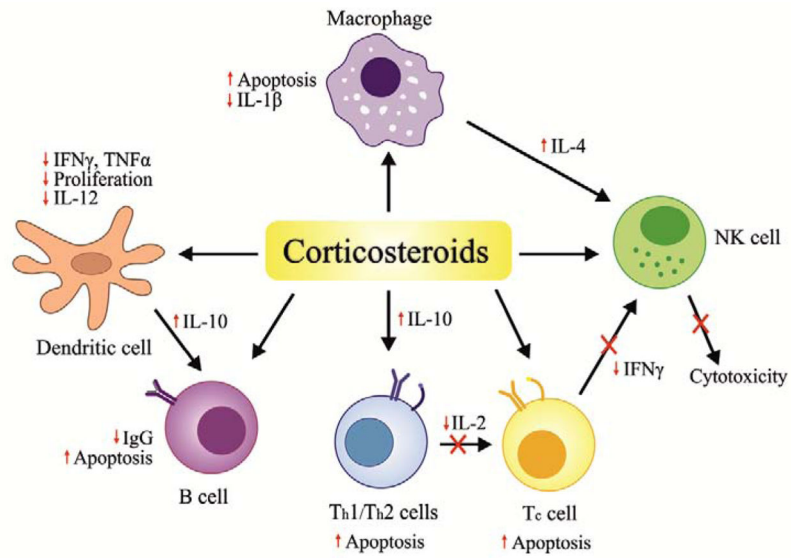


Fig. 3. Mechanism of action of corticosteroids

Corticosteroids diffuse across the cell membrane and bind to intracellular receptors that translocate into the nucleus. This complex interacts with DNA, resulting in altered transcription of various corticosteroid-responsive genes. Corticosteroids have diverse physiological effects and directly or indirectly regulate several different immune cell as shown here. These actions are primarily accomplished by modulating inflammatory cytokines as well as through induction of apoptosis.