Tuberculosis Disease

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Tuberculosis disease is caused by the bacterium Mycobacterium tuberculosis. It is estimated that 10 million people have developed tuberculosis disease globally, leading to 1.4 million deaths in 2019. Treatment of tuberculosis has been especially challenging due to the rise of multidrug-resistant (MDR-TB) and extensive drug-resistant (XDR-TB) tuberculosis. In addition to drug-resistant genotypes, the standard treatment of tuberculosis by first-line agents is also challenging due to toxicity and costs.

tuberculosis adjuvant therapy glutathione everolimus vitamin D steroids aspirin

1. Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (*Mtb*), a bacterium that first appeared roughly 20,000 years ago [1]. TB is transmitted from person to person via air droplets, primarily affecting the pulmonary system as tubercle bacilli infect lung alveoli. Bacilli may cause extrapulmonary TB, as they spread and infect other organ systems including the musculoskeletal system, lymphatic system, central nervous system, and abdominal organs. TB proves to be a significant burden on global public health, as the Global Tuberculosis Report 2020 declared it to be the leading cause of death from an infectious pathogen. The advancement to care and prevent TB has been slow and has not reached the WHO targets [2]. In addition, 10 million people developed TB around the globe, leading to a combined 1.4 million deaths among HIV-negative and -positive people in 2019 [2]. Today's widely accepted treatments for TB include a combination of first-line anti-TB agents: isoniazid (INH), rifampin (RIF), ethambutol (EMB), pyrazinamide (PZA), as well as second-line treatments for TB such as amikacin and capreomycin [3]. Treatment of tuberculosis proves to be a challenge, as the spread of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) continue to rise [4]. Drug resistance is attributed to a variety of factors including disorganized treatment from structural weaknesses in health systems, community transmission, and facility-based transmission, as well as genetic and phenotypic mutations [4][5]. Treating TB, including MDR-TB and XDR-TB, is challenging due to a variety of factors including long duration of therapy, toxicity from first-line anti-TB agents, costs, and substandard outcomes. After four decades, there have been two new anti-TB agents to control MDR/XDR-TB—bedaquiline and delamanid [6]. It is imperative to explore new therapies that are affordable, limit antibiotic resistance, and have a low economic impact while limiting adverse effects.

2. Adjuvants

2.1. Glutathione

Glutathione (GSH) is a tripeptide composed of γ-l-glutamyl-l-cysteinyl-glycine that is present in all mammalian tissues at concentrations of 1–10 mM, in the thiol-reduced (GSH) and disulfide-oxidized (GSSG) forms [7][8] (Meister 1988; Kaplowitz et al., 1985). There are three major reservoirs of GSH in eukaryotic cells. Nearly 85% of the cellular GSH is found in the cytosol, 10–15% is in the mitochondria, and a small amount is in the endoplasmic reticulum [9][10].

Its primary functions are involved in defending cells against oxidative stress and modulating DNA synthesis, apoptosis, immune function, detoxifying electrophiles, scavenging free radicals, and providing a cysteine reservoir [11][12].

The glutamate and cysteine of GSH are linked by a peptide bond between the γ-carboxyl group of glutamate rather than the α-carboxyl group, which makes it subject to hydrolysis only by γ-glutamyltranspeptidase (GGT), only present on the external surfaces of certain cell types. This makes GSH resistant to intracellular degradation because it is only metabolized by GGT extracellularly [11].

GSH is synthesized in the cytosol of all cells involving two ATP-requiring enzymatic steps: formation of γ-glutamylcysteine from glutamate and cysteine and then the formation of GSH from γ-glutamylcysteine and glycine. The first step of GSH synthesis is the rate-limiting step and is catalyzed by glutamate–cysteine ligase (GCL) composed of a heavy/catalytic subunit, GCLC, and a light/modifier subunit, GCLM [13]. The second step of GSH synthesis is catalyzed by GSH synthase, and it is subject to feedback inhibition by GSH [14].

GSH, in the presence of GSH peroxidase, functions to reduce hydrogen peroxide formed from oxidative stress during mitochondrial respiration, where no catalase is present. GSH is oxidized to GSSG, and GSSG reductase reduces it back to GSH, using NADPH, forming a redox cycle [15]. However, in the case of severe oxidative stress, the ability of the cell to reduce GSSG to GSH is diminished and leads to an accumulation of GSSG and depleted levels of GSH [16].

After intracellular infection by Mtb, the immune system attacks the bacteria by either killing them off or engulfing them in a specialized structure composed of immune cells known as granuloma. Granuloma is localized within the lungs and renders the TB inactive, which is referred to as latent TB [17]. The process of granuloma formation is mediated by various cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin-2 (IL-2), IL-6, IL-12, and interferon gamma (IFN-γ) [18]. Several studies have shown IL-2 to have effects on granuloma formation and suppressing the levels of viable Mtb; however, it has also been demonstrated that IL-2 plays an antagonistic role during combined chemotherapy and immunotherapy for Tb infections. TNF-a is an important factor in granuloma formation, as studies have shown that individuals with mutations in TNF-a promoters or patients treated with TNF antagonists show an increased risk of TB infections [19]. In an individual who is immunocompromised, these granulomas may undergo liquefaction, releasing the bacteria and resulting in active TB. GSH levels are significantly compromised in individuals with active pulmonary TB [20]. Previous studies have exhibited that GSH

has antimycobacterial and immune-modulating properties exhibited through their action on NK cells and by restoring TH1 cytokine response [21][22]. GSH, when combined with IL-2 and IL-12, enhances the functional activity of NK cells, making them able to inhibit the growth of Mtb in human cells [23]. IL-12 has also been shown to be effective as adjuvant therapy in TB individually. A case report of a 24-year-old male hospitalized in April 1998 in Germany, diagnosed with pulmonary TB with military spread and TB involvement of cervical lymph nodes, was given IL-12 therapy [24]. The adjuvant therapy was given for 3 months and the patient showed significantly improved clinical results. It was shown that the addition of IL-12 restored the impaired IFN-γ release, which helped further enhance T cell and macrophage activity [24]. As this was a single case, more research into IL-12 treatment should be evaluated, but this case should help encourage the study of IL-12 effects in TB patients.

It has been previously demonstrated that supplementation with liposomal GSH restored redox homeostasis, induced a cytokine balance, and improved immune responses against Mtb infection [22]. It was also shown in a further study, that macrophages treated with suboptimal levels of each of the first-line antibiotics in conjunction with N-acetyl cysteine (NAC) a precursor to GSH, resulted in a significant reduction in the intracellular survival of Mtb, compared to that of antibiotics alone. Combined treatment of NAC with antibiotics resulted in a decrease in the production of TNF-α, an inflammatory cytokine overexpressed in Mtb infection, and IL-10, an immunosuppressive cytokine, by the macrophages [25][26][27]. These findings suggest that GSH can be a potential adjunct treatment with the previously mentioned first-line antibiotics to clear Mtb infection.

2.2. Everolimus

Everolimus is an immunosuppressant drug that has been approved for use in organ transplant recipients and in the treatment of various forms of cancer [28][29]. As an analog to rapamycin, it similarly inhibits the mammalian target of the rapamycin (mTOR) pathway. Rapamycin is not typically used as a host-directed therapy for TB treatment as it has low bioavailability and a high half-life. Everolimus is a more ideal candidate for these purposes, as it is more soluble in water and has a lower half-life [30]. The mTOR pathway is an attractive target for host-directed therapies, as it is a key regulator of cellular growth and proliferation [31]. Previous research has indicated that inhibiting the mTOR pathway can lead to improved cellular survival and antibacterial defense by activating autophagy [32]. Autophagy is an essential response of the innate immune system as it removes intracellular debris introduced by foreign pathogens such as Mtb [33]. Studies have shown that autophagy is successful in eliminating Mtb [34]. As Everolimus inhibits the mTOR pathway, it leads to the induction of autophagy, which then augments cellular defense mechanisms against Mtb.

A 2014 study showed that everolimus modulated immune function in elderly volunteers after they received the 2012 influenza vaccine. Volunteers receiving everolimus displayed a significant decrease in the percentage of programmed cell death receptor-1 CD4 and CD8 T cells, which typically accumulate with age and provide diminished immune responses [35]. Another clinical trial showed that elderly volunteers receiving a combination of everolimus and dactolisib, both mTOR inhibitors, resulted in a decreased rate of infections and increased humoral responses to influenza vaccination [36]. Latent TB infections may lead to inflammatory cytokine responses resulting in the formation of lung granulomas. Everolimus treatment alone, as well as in conjunction with isoniazid was

shown to significantly decrease levels of the pro-inflammatory cytokine TNF-a in a human granuloma model [37]. More recently, researchers assessed rifampin-susceptible pulmonary TB patients and their lung function by measuring FEV1 and found that patients treated with everolimus displayed enhanced FEV1 recovery at 180 days of treatment, compared to the control group [38]. These studies demonstrate how everolimus can be beneficial as a host-directed adjuvant in the treatment of pulmonary TB.

While everolimus is efficient in stimulating the immune system, its use as an adjuvant in TB treatment may be counterproductive, as it has powerful immunosuppressive properties as well. The administration of everolimus has been associated with the activation of pulmonary TB. A case report from 2011 found that a kidney transplant recipient developed tuberculosis after 3 months of everolimus administration. The authors proposed that everolimus may have been given at too high of a dose, resulting in over suppression of the immune system and reactivation of latent TB [39]. In addition, researchers performing a matched case–control study, found that organ transplant recipients who received everolimus and hemodialysis were more likely to develop TB [40]. Everolimus must be carefully dosed and administered due to its immunosuppressive qualities. A study delivering rapamycin as an inhalable particle showed that it was more effective in the removal of intracellular Mtb when compared to rapamycin in solution [41]. Delivering everolimus as an inhalable particle to treat TB is worth exploring further, as it may prevent the unwanted consequences of over-immunosuppression. More studies should be conducted in order to better understand the effects of different Everolimus doses and delivery mechanisms with respect to the mTOR pathway and immunosuppression in the treatment of TB.

2.3. Vitamin D

As part of the adaptive immune response, different types of T cells exist to provide protection for the human body. T helper (Th) cells are one of the major types of T cells that release specific cytokines to mediate immune responses. Specifically, Th1 cells are critical for regulating intracellular infections from Mtb [42]. Vitamin D and 1,25 $(OH)_2D$ inhibit the proliferation of Th1 and Th17 cells and their pro-inflammatory cytokines such as IL-2, IFN-γ, IL-17 secretion, as well as induce T regulatory responses [42]. While the inhibition of Th1 and Th17 CD4 T cell responses would allow the pathogen to replicate and cause active disease, Vitamin D has a role in the innate immune response, which reduces the viability of Mtb (**Figure 1**). A 2006 paper showed that when human macrophages were activated by Toll-like receptors (TLR) there was an overexpression of vitamin D receptor (VDR) and the vitamin D-1-hydroxylase genes. This overexpression led to the destruction of Mtb via induction of the antimicrobial peptide cathelicidin [43]. This study showed that when human macrophages that had been infected with Mtb were treated with 1,25 $(OH)_2D_3$, there was a reduction in the number of viable bacilli [43]. While the innate immune system is responsible for the first-line defense, the adaptive immune response has a larger role in pathogen neutralization. Vitamin D is a primary target for antigen-presenting cells (APCs), a critical component of the adaptive immune system [44]. In addition, 1,25 $(OH)_2D_3$ regulates the cytokines and chemokines released by dendritic cells (DC) by inhibiting IL-12 and IL-23 cytokines from Th1 while upregulating IL-10 cytokine, which shows anti-inflammatory properties [44]. Due to Vitamin D's involvement in the inflammatory process, it is worth evaluating its efficacy in combating TB disease. In a vast majority of patients with TB, 25(OH)D levels fall below 20 ng/mL [45]. In 2018, a meta-analysis was conducted to investigate the association between vitamin D levels and children with

TB showed that children with latent TB had significantly lower Vitamin D levels than controls [46]. A 2019 study performed to determine the impact of vitamin D levels and risk of TB disease showed vitamin D predicts TB disease in a dose-dependent manner [47]. Before antibiotic use, vitamin D was already used to treat TB as seen in an 1848 study that evaluated the role of sun exposure and administration of cod liver oil, both rich in Vitamin D [45]. In the study, 18% of patients who were treated with cod liver oil were stabilized, compared to 6% of the control group [48]. In 1998, a study showed that in children who took vitamin D supplementation along with first-line anti-TB drugs, clinical improvement occurred at a quicker rate [45]. Salahuddin et al. demonstrated that vitamin D supplemented in high doses leads to improvements in radiographs and weight gain in patients with TB. The study was limited in the fact that it did not show a difference in sputum conversion rates, a clinical tool used to assess the efficacy of treatments [49]. However, there have also been studies that did not support clinical improvements. **Table 1** summarizes the findings of key studies. A meta-analysis conducted in 2019 to analyze the effectiveness of vitamin D supplementation on pulmonary TB, indicated that vitamin D did not have any beneficial effect on anti-TB treatment. However, in participants with a tt genotype, sputum culture conversion times were shortened [50]. Based on the analyzed studies, vitamin D was most effective in shortening sputum conversion times but given the conflicting results, more randomized control trials are needed to establish its clinical efficacy. Therefore, the use of vitamin D supplementation is not unambiguously correlated to an enhanced anti-TB response.

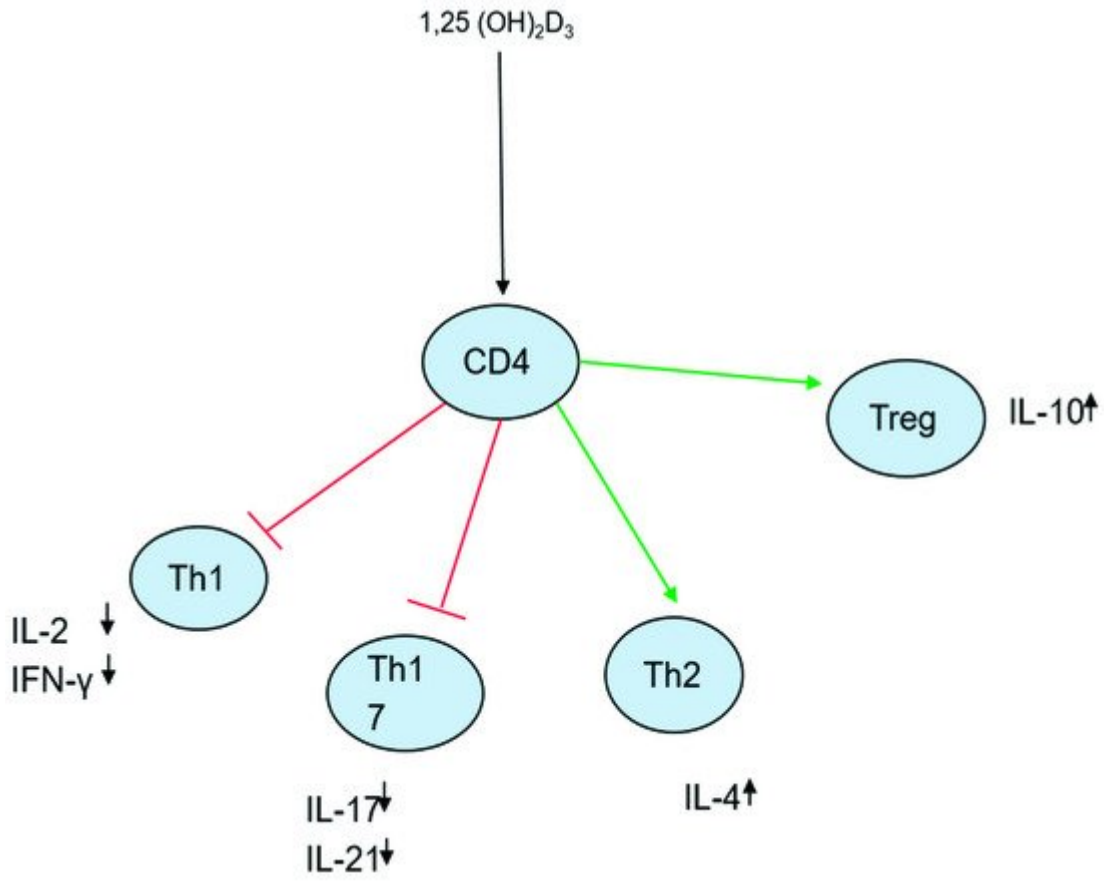

Figure 1. Immunomodulatory effects of 1,25 $(OH)_2D$.

Table 1. Overview of major clinical studies.

Author	Population	Vitamin D Dose	Duration	Findings
Martineau et al. (Mathyssen, Carolien et al., 2017)	146 adults	2.5 mg at start, and at days 14, 28, and 42	56 days	No effect on sputum culture conversion on the overall population.
Wejse et al. (Mathyssen, Carolien et al., 2017)	365 adults	100,000 IU at start, 3 months, 5 months, and 8 months	1 year	No effect on clinical outcome/mortality
Tukvadze et al. (Mathyssen, Carolien et al., 2017)	199 adults	50,000 IU 3×/week for 8 weeks, followed by every other week for another 8 weeks	16 weeks	No improvement in sputum TB clearance
Ganmaa et al. (Ganmaa, Davaasambuu et al., 2020) [51]	8851 children	14,000 IU vitamin D_3 or placebo	3 years	Not lower risk of TB infection
Sudfeld et al. (Sudfeld, Christopher R et al., 2020) [52]	6250 HIV+ adults	50,000 IU Vitamin D_3 for first month of ART followed by 2000 IU Vitamin D_3 daily	3 years	No overall effect of supplementation on mortality risk. No difference in incidence of pulmonary TB between Vitamin D_3 vs. placebo
Morcos et al. [41] (Mathyssen, Carolien et al., 2017)	24 children (<13 y/o)	1000 IU daily. No placebo implemented	8 weeks	Clinical improvement in radiography (X-ray and Ultrasound). Weight gain in patients
Nursyam et al. [41] (Mathyssen, Carolien et al., 2017)	67 patients (15–59 y/o)	0.25 mg daily × 6 weeks	12 weeks	Increased rate of sputum conversion. Improved radiologic findings
Salahuddin et al. [41] (Mathyssen, Carolien et al., 2017)	259 patients (>16 y/o)	2 IM injections of 600,000 IU given at 1 month apart	12 weeks	Faster clinical and radiographic improvement. Enhanced host immune activation
Hassanein et al. [41] (Mathyssen, Carolien et al., 2017)	60 adults	1 IM injection of 200,000 IU	8 weeks	Enhanced TB score and more rapid sputum conversion rates

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