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Clofazimine Mechanisms of Action in Mycobacteria, HIV, and Cancer

Reply to Singh et al.—Singh et al. reported that clofazimine blockade of Kv1.3 K^+ channels enhances BCG vaccine efficacy by expanding central memory T lymphocytes [1]. This discovery, along with the recent discovery of clofazimine increasing the anti-inflammatory interleukin-1 receptor antagonist (IL1RA) [2], help explain the long-known, empirically proven efficacy of clofazimine for leprosy, both as an antimycobacterial antibiotic and as an anti-inflammatory treatment for leprosy reactions, including late neuropathies.

The use of clofazimine for leprosy was empirically developed over years treating various types of leprosy. The current U.S. guidelines according to National Hansen's Disease Program (www.hrsa.gov/hansensdisease) recommend 1 year for paucibacillary (tuberculoid and borderline tuberculoid) clinically and 2 years for multibacillary diseases (mid–borderline, borderline lepromatous, and lepromatous) by the Ridley–Jopling classification [3]. Many patients develop reactions, both type I and type II, beyond the recommended 2 years, including serious late neuropathies. These cases respond nicely to clofazimine monotherapy and only rarely require corticosteroids.

The Singh et al. discovery may also explain how clofazimine shortens the duration of experimental chemotherapy in tuberculosis [4]. Human immunodeficiency virus (HIV) protein trans-activator of transcription (Tat) [5] increases the Kv1.3K^+ channel, suggesting that clofazimine could play a role in improving HIV outcomes and may be involved in what Ustanowski et al. have called the HIV paradox, as leprosy patients appear to handle HIV infection better than tuberculosis patients [6].

Trinchieri has suggested that the study of intracellular infections such as tuberculosis and leprosy can also help us understand modern cancer immunotherapy [7, 8]. In this regard, clofazimine is effective in both murine B16 melanoma and pancreatic cancer [9]. IL1 and IL1RA [10] play a role in cancer progression and amelioration. Thus, further study of clofazimine mechanisms have the potential for improving our understanding of mycobacterial and HIV pathogenesis, as well as cancer immunotherapy.

Notes

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Reply to Levis and Rendini

Reply to Levis and Rendini—We appreciate the comments by Levis et al. on our work documenting the potential utility of clofazimine for the treatment of tuberculosis. We support their view on the efficacy of clofazimine in leprosy, both as an antibacterial and an anti-inflammatory agent. In addition to mycobacterial infections, the vast majority of infectious diseases and cancers involve pathology induced by inflammation. Although inflammatory responses play a central role in inducing protective immune responses, profound inflammation can exacerbate pathology. Thus, the addition of anti-inflammatory agents to the treatment regimens for certain infections and cancers might be beneficial. Consistent with this notion, corticosteroids enhance the efficacy of tuberculosis treatment regimens [1]. However, corticosteroids also suppress host immunity, which might have deleterious effects on the host, such as the risk for disease relapse and reinfection. Clofazimine, an inhibitor of the voltage-gated K^+ channel Kv1.3, has antimicrobial and anti-inflammatory activities and is beneficial for the treatment of infectious diseases such as leprosy [2] and tuberculosis [3]. Interestingly, effector memory T (T_{EM}) cells abundantly express Kv1.3. We have recently shown that inhibition of Kv1.3

by clofazimine promotes the induction of long-lived, antigen-specific central memory T (T_{CM}) cells, which are crucially important for the efficacy of vaccines [4]. Therefore, clofazimine may be effective as an adjunct to a variety of therapies and vaccines:

Tuberculosis therapy: Tuberculosis is associated with potent inflammatory responses; consequently, corticosteroids can curb such responses [1]. Clofazimine exhibits immunosuppressive effects and inhibits T_{EM} cells, which are associated with inflammation and pathology [3]. The addition of clofazimine to antibiotic regimens yields improved treatment efficacy and simultaneously enhances *Mycobacterium tuberculosis*–specific T_{CM} responses that protect the host against future reinfection, a property we have termed "self-propelled vaccination" [4].

Tuberculosis vaccine: The only approved vaccine for tuberculosis, bacillus Calmette Guérin (BCG), is efficacious for meningitic and disseminated tuberculosis in children but lacks efficacy in adult pulmonary tuberculosis [4]. Although the exact cause of BCG failure is unclear, optimal vaccine efficacy against tuberculosis requires both T helper 1 (Th1) and T helper 17 (Th17) immune responses [5]. Therefore, the addition of clofazimine to BCG may provide improved vaccine efficacy, as was recently confirmed in our studies with a mouse model of *M. tuberculosis* infection [4].

Cancer: Cancer is associated with inflammation and dysfunction of tumor-infiltrating antigen-specific T cells. It is well known that tumor-infiltrating T cells become dysfunctional in the tumor microenvironment where they adopt a regulatory phenotype [6]. Therefore, overcoming the tolerance of these cells may enhance antitumor immunity. BCG has been employed in bladder cancer, where it promotes T-cell functions, likely because of its capacity to induce interleukin 6 (IL-6) [7]. BCG-induced IL-6 together with transforming growth factor-β, which is readily available in the tumor microenvironment, induce Th17 cell responses with potent antitumor activities. Thus, clofazimine might be able to promote tumor antigen–specific, Th17-type T_{CM} cells, acting as a "self-propelled vaccine." Numerous studies have shown direct killing of cancer cells by modulating the extracellular/intracellular and mitochondrial K^+ ion balance [8]. Furthermore, by inhibiting T_{EM} cells, clofazimine might be effective in curbing inflammation and preventing T cell immune suppression (via tolerance, exhaustion, or anergy) during tumor progression. Additionally, the enhancement of T_{CM}-cell differentiation by clofazimine should be effective in preventing tumor metastasis. Such T_{CM} responses are expected to impart long-term protection against tumor relapses, while avoiding the development of autoimmunity, a common side effect of cancer immunotherapy.

Human immunodeficiency virus/AIDS: Levis et al. also suggested the potential utility of clofazimine in human immunodeficiency virus (HIV)/AIDS, owing to the well-documented neurotoxicity of HIV proteins (eg, trans-activator of transcription [Tat], envelope glycoprotein 120 [gp120]) against microglia [9]. This neurotoxicity was abrogated by pharmacological or genetic inhibition of Kv1.3 [9]. Clofazimine should also provide benefits by enhancing T-cell–mediated immunity against HIV. Additionally, clofazimine might influence immune reconstitution following antiretroviral therapy (ART). ART treatment of patients with advanced immunosuppression may cause immune reconstitution inflammatory syndrome (IRIS), with delayed restoration of host immunity [10]. Clofazimine might be able to prevent IRIS, while preserving the integrity of HIV-specific effector T-cell responses.

In summary, clofazimine shows promise for prophylactic and therapeutic intervention in a variety of diseases and their comorbidities, including infections, autoimmunity, and cancer.

Notes

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