Review Article

A narrative review of the controversy on the risk of mycobacterial infections with immune checkpoint inhibitor use: does Goldilocks have the answer?

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Background and Objective: Immune checkpoint inhibitors (ICIs) have revolutionized oncologic treatment. Whether ICIs increase susceptibility to or provide protection against mycobacterial infections remains controversial. The objective of this narrative review is to summarize the literature on the link between ICI use and mycobacterial infections—tuberculosis and non-tuberculous mycobacterial (NTM) infections—and to critically discuss evidence linking ICIs with mycobacterial infections, the possible confounders, and, if indeed the ICIs predispose to such infections, the potential mechanisms of how this may occur.

Methods: We conducted a literature search on PubMed for relevant articles published from 2011 to current time [2024] utilizing specific keywords of "immune checkpoint inhibitors", "programmed cell death protein-1", "PD-1", "programmed death-ligand 1", "PD-L1", "cytotoxic T-lymphocyte-associated protein-4", or "CTLA-4" with that of "non-tuberculous mycobacterial lung disease", "tuberculosis", or "mycobacteria". The bibliographies of identified papers were perused for additional relevant articles.

Key Content and Findings: *Ex vivo* studies using human cells indicate that ICIs would be salubrious for the host against mycobacteria. Yet, many case reports associate ICI use with mycobacterial infections, mostly tuberculosis. Potential confounders include immunosuppression from the cancer, concomitant use of immunosuppressive drugs, lung injury and distortion from chemotherapeutics or radiation, and reporting bias. Mice with genetic disruption of the programmed cell death protein-1 (*PD-1*) gene are paradoxically more susceptible to *Mycobacterium tuberculosis* (*M. tuberculosis*). In contrast, mice administered neutralizing antibody to T cell immunoglobulin and mucin domain-containing protein 3 (TIM3) or knocked out for *TIM3* gene have greater capacity to control an *M. tuberculosis* infection. We posit that hosts with greater baseline immunodeficiency are more likely to derive benefit from ICIs against mycobacterial infections than those with more intact immunity, where ICIs are more likely to be detrimental.

Conclusions: Studies are needed to test the hypothesis that ICIs may either protect or predispose to mycobacterial infections, depending on the baseline host immune status. Prospective studies are required of patients on ICIs that control for potential confounders as anecdotal case reports are insufficient to provide a causal link. Murine studies with ICIs are also required to corroborate or refute studies of mice with genetic disruption of an immune checkpoint.

Keywords: Mycobacteria; tuberculosis (TB); non-tuberculosis mycobacteria; immune checkpoint inhibitors (ICIs)

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Introduction

The interaction between T cells and antigen-presenting cells (APC), the latter cells represented by dendritic cells and macrophages, is a fundamental process that links the innate and adaptive branches of the immune system. In addition to the presentation of antigenic peptides bound to class I or II major histocompatibility complex molecules—the former present on all cell types and the latter on APC—to the T cell receptor (TCR), other accessory molecules also mediate the interaction between APC and T cells. For instance, the engagements between cell surface CD80 and CD86 (formerly known as B7-1 and B7-2) molecules on APC and CD28 molecule on T cells augment T effector cell activation (*Figure 1A*). In contrast, the interactions between CD80/CD86 on APC with cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) on T cells deactivate T effector cells (1-3). Similarly, the engagement of the programmed-death ligand 1 (PD-L1) on APC and programmed cell death protein-1 (PD-1) receptor on T cells also deactivates T effector cells and induces their apoptosis (*Figure 1A*) (3). Hence, both CTLA-4 and PD-1 as well as T cell immunoglobulin and mucin-domain containing-3 (TIM-3) (4) are known as "immune checkpoints" because they put a "check" on excessive immune responses by the APC-T cell interaction. There are other immune checkpoints that may also deactivate T effector cells (*Figure 1B*). Whereas CD80/CD86-CTLA-4 or PD-L1/2-PD-1 engagement inhibits activation of FOXP3-negative T effector cells and induces their "exhaustion" (defined broadly as reduced T effector function) (5), these interactions enhance the suppressive activity of $FOXP3^+$ regulatory T cells (Tregs); i.e., a form of Treg "rejuvenation" (6).

Many cancers have increased expression of PD-L1 on their cell surface. Teleologically, the heightened PD-L1 expression serves as a survival mechanism for cancer cells by thwarting the ability of cytotoxic T cells to kill them. Hence, by upregulating PD-L1 expression, cancer cells evade host immune surveillance by deactivating and inducing apoptosis of $PD\text{-}1^+$ T effector cells (*Figure 1A*) (7).

As predicted, monoclonal antibodies that neutralize PD-1, PD-L1, and CTLA-4—collectively known as immune-checkpoint inhibitors (ICIs)—avert T cell deactivation as well as enhance T effector cell activation (*Figure 1C*) by preventing the binding of PD-L1 to PD-1 or CD80/CD86 to CTLA-4. Hence, ICIs restore type 1 immune responses, including the production of interferon-gamma (IFNγ) and T cell-mediated cytotoxicity against cancer cells (1,8).

Presently, several ICIs are approved or are in clinical trials to treat several types of cancers (9,10) (*Table 1*). The impact of ICIs on the prognosis and survival times of subjects with various cancer types indicated has been transformative. For instance, the ICI combination of nivolumab (an anti-PD-1 neutralizing antibody) and ipilimumab (an anti-CTLA-4 neutralizing antibody) for metastatic melanoma is associated with a 5-year survival rate of 52%, a substantial improvement from the <25% survival rate before the availability of ICIs (12). Similarly, in advanced melanoma cases, the utilization of combined nivolumab and ipilimumab has nearly doubled the median survival time (72 months) as compared to nivolumab alone (37 months) (13).

Not surprisingly, based on their mechanism of action, ICIs are known to cause autoimmune and inflammatory disorders that may affect virtually any organ (*Table 2*) (14-16). It is increasingly recognized that many microbial pathogens including *Mycobacterium tuberculosis* (*M. tuberculosis*)—the causative agent of tuberculosis (TB)—are able to induce host immune checkpoint molecules and exploit them to evade host immunity, inducing a state of $CD4^+$ and $CD8^+$ T cell exhaustion as well as natural killer cell deactivation (5,17-20). Indeed, *M. tuberculosis* induction of IFNγ upregulates PD-1, which, in turn, inhibits IFNγ-producing T effector (T_H1) cells, a form of negative feedback mechanism to prevent excessive IFNγ production (21). Given that ICIs prevent T effector cell exhaustion, it is reasonable to predict that the ICIs would be protective against infections (20,22). Indeed, promising beneficial results have been observed with ICIs used against infections due to simian immunodeficiency virus, human immunodeficiency virus (HIV), malaria, hepatitis B virus, hepatitis C virus, influenza virus, *Toxoplasma*, and

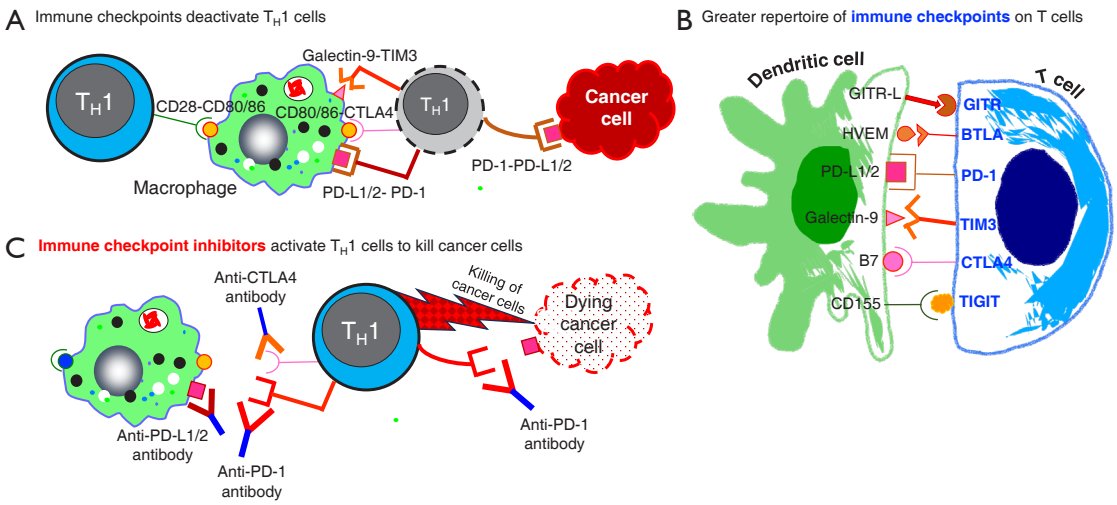

Figure 1 Diagram of the relationship between T effector cells and antigen-presenting cell resulting in activation or deactivation of the T cells. (A) CD28-CD80/CD86 interaction activates T effector cells, as exemplified by the "larger" (blue colored) T_H1 cell. In contrast, CTLA-4-CD80/CD86, PD-1-PD-L1, or TIM3-galectin-9 interaction causes exhaustion (and apoptosis) of T effector cells, as shown by the "smaller" (gray colored and dashed outline) T_H1 cell. Cancer cells (red globular shaped cell) that express PD-L1 are also able to deactivate T effector cells following binding to PD-1, thwarting the ability of T_H1 effector cells to kill them. (B) A larger repertoire of immune checkpoints on T cells and their respective receptors on antigen-presenting cells, the latter represented by a green colored dendritic cell (modified from Wykes MN and Lewin SR. *Nat Rev Immunol* 2018;18:91-104 with permission obtained from Springer Nature Publisher). (C) Several specific antibodies have been developed to the immune checkpoints (or their ligands), activating T effector cells to kill cancer cells (depicted by the red lightning bolt). How these antibodies may predispose to mycobacterial infections or conversely, to help treat them, remains controversial. TIM3, T cell immunoglobulin and mucin domain-containing protein 3; CTLA-4, cytotoxic T-lymphocyte-associated protein-4; PD-L1/2, programmed-death ligand 1/2; PD-1, programmed cell death protein-1.

Leishmania (20,22). While one would intuitively expect that ICIs will also fortify host immunity against mycobacterial infections such as TB and non-tuberculous mycobacterial (NTM) diseases, case reports and experimental findings in animals suggest that ICIs may paradoxically increase host vulnerability. Another unanswered question, which should be predicated on the unresolved issue of whether ICIs predispose to TB, is whether to test for latent TB infection and to treat if present in those who will be undertaking ICI treatment (23,24). The goal of this narrative review is to address this controversy on the risk (or non-risk) of mycobacterial infections (TB and diseases caused by NTM) with the use of ICIs. We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1395/rc).

Methods

We conducted a literature search of PubMed for relevant articles utilizing search terms and strategies noted in *Table 3*. Citations from 2011 to 2023 were reviewed given that the first ICI ipilimumab was approved by the Food and Drug Administration (FDA) in 2011. The bibliographies of identified articles were further perused for additional relevant articles. Subsequently, each relevant article was reviewed by one or more of the authors and a narrative review was composed.

Experimental and clinical evidence implicating that ICIs may predispose to mycobacterial infections

Experimental animals and ex vivo cell models

In mice with genetic disruption of the *PD-1* gene, resulting in the lack of interaction between PD-1 and PD-L1, one could reasonably predict that they would have increased ability to control *M. tuberculosis* infections due to heightened activation of T effector cells. Yet, three

Table 1 Cancer types targeted by ICIs

ICI	Cancer types undergoing therapeutic intervention (list not exhaustive, varying levels of evidence, and many in combination with other immunotherapy or chemotherapeutic agents) (11)
Anti-PD-1	
Nivolumab	Melanoma, NSCLC, malignant pleural mesothelioma, RCC, Hodgkin's lymphoma, HN-SCC, urothelial carcinoma, colorectal cancer, HCC, esophageal cancer, gastric cancer, gastroesophageal junction cancer, esophageal adenocarcinoma
Pembrolizumab	Melanoma, NSCLC, small cell lung cancer, HN-SCC, Hodgkin's lymphoma, primary mediastinal large B-cell lymphoma, urothelial carcinoma, microsatellite instability-high or mismatch repair deficient (colorectal) cancer, gastric cancer, esophageal cancer, cervical cancer, HCC, Merkel cell carcinoma, RCC, endometrial carcinoma, tumor-mutational burden-high cancer, cutaneous squamous cell carcinoma, triple-negative breast cancer
Cemiplimab	Cutaneous squamous cell carcinoma, basal cell carcinoma, NSCLC
Dostarlimab	Mismatch repair-deficient recurrent or advanced endometrial cancer
Sintilimab	Hodgkin's lymphoma and investigational for NSCLC
Camrelizumab	Investigational for HCC and Hodgkin's lymphoma
Anti-PD-L1	
Atezolizumab	Urothelial carcinoma, NSCLC, small cell lung cancer, HCC, melanoma
Avelumab	Urothelial carcinoma, RCC, Merkel cell carcinoma
Durvalumab	NSCLC, extensive stage-small cell lung cancer, biliary tract cancer, HCC
Sugemalimab	NSCLC, advanced esophageal squamous cell carcinoma
Anti-CTLA-4	
Ipilimumab	Colorectal cancer, HCC, melanoma, mesothelioma, NSCLC, RCC

ICIs, immune checkpoint inhibitors; PD-1, programmed cell death protein-1; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; HN-SCC, head and neck squamous cell carcinoma; HCC, hepatocellular carcinoma; PD-L1, programmed-death ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein-4.

Table 2 Autoimmune inflammatory disorders associated with ICIs

Organ or organ system	Associated autoinflammatory disorder
Skin	Rash/erythema and vitiligo
Endocrine system	Thyroiditis (hypothyroidism, hyperthyroidism), hypophysitis, diabetes mellitus, Addison's disease (adrenal insufficiency)
Gastrointestinal system	Diarrhea, colitis, pancreatitis, and hepatitis
Pulmonary system	Pneumonitis and sarcoidosis
Eyes and neurological system	Episcleritis, uveitis, conjunctivitis, keratitis, orbital inflammation, myelitis, and aseptic meningitis
Hematological system	Red cell aplasia and autoimmune pancytopenia
Renal system	Interstitial nephritis, granulomatous nephritis, and glomerular lupus-like nephropathy
Musculoskeletal system	Polyarthritis and arthralgia

ICIs, immune checkpoint inhibitors.

Table 3 The search strategy summary

Items	Specification
Date of search	Periodically from August 31, 2022 to August 30, 2023
Databases and other sources searched	PubMed and bibliographies of relevant articles
Search terms used	"Immune checkpoint inhibitors", "programmed cell death protein-1", "PD-1", "programmed death-ligand 1", "PD-L1", "cytotoxic T-lymphocyte-associated protein-4", or "CTLA-4" with that of "non-tuberculous mycobacterial lung disease", "tuberculosis", or "mycobacteria"
Timeframe	January 1, 2011 to August 30, 2023
Inclusion criteria	English language only
Selection process	E.D.C. did the initial literature search with subsequent help from all authors

PD-1, programmed cell death protein-1; PD-L1, programmed-death ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein-4.

studies demonstrated that mice with genetic disruption of PD-1 are more vulnerable to TB with increased bacterial burden, increased inflammatory cytokines [e.g., IFNγ, interleukin (IL)-17, and/or tumor necrosis factor (TNF)], and neutrophilic tissue necrosis, with the lattermost finding possibly related to reduced autophagy in the macrophages of the *PD-1* gene knockout mice (25-27). One of these studies implicated increased Treg number as being responsible for the reduced proliferation of *M. tuberculosis* antigen-specific T cells in the PD-1 knockout mice (27). However, since immune checkpoints are known to enhance Treg activation, ICIs would be expected to reduce Treg activation (6). Thus, a common explanation for the seemingly paradoxical finding that absence of PD-1 induces T effector cell hyperactivation and yet predisposes to TB is that the resulting "altered immune homeostasis"—characterized by excess inflammation, increased tissue necrosis, and reduced ability to control *M. tuberculosis*—is responsible, a theme elaborated below. Interestingly, PD-L1 knockout mice also had increased susceptibility to *M. tuberculosis* but were less severely affected, indicating that T cells are regulated by multiple ligands to the PD-1 receptor with *M. tuberculosis* infection (26).

Similar findings were found in non-human primates. Rhesus macaques administered anti-PD-1 antibody 2 weeks after infection, despite increased number and function of *M. tuberculosis*-specific $CD8^+$ T cells and pro-inflammatory cytokines in the granulomas (but no difference in *M. tuberculosis*-specific $CD4^+$ T cells), developed higher *M. tuberculosis* burden and worse TB disease than isotype control-treated monkeys (28). Furthermore, PD-1 blockade led to an upregulation of CTLA-4 and TNF in TB-specific $CD4^+$ T cells isolated from the granulomas, while TNF^+ TB-specific $CD8^+$ T cells had increased production of IFNγ, IL-2, and granzyme B compared to isotype control-treated animals (28).

Using a 3-dimensional (3D) cell model—comprised of aggregates of peripheral blood mononuclear cells (PBMC) surrounding *M. tuberculosis*—it was shown that PD-1 and PD-L1 were expressed in the cells that comprised this 3D microsphere model and that inhibition of PD-1 (with either a small molecule inhibitor or an anti-PD-1 antibody) increased cell-associated *M. tuberculosis* burden (29). This process was mediated by an increase in TNF; i.e., compared to control antibody, 3D microsphere model + *M. tuberculosis* + anti-PD-1 antibody → increased TNF → increased *M. tuberculosis* burden (29). In simplistic terms, this 3D model showed that PD-1 is host-protective whereas ICI and TNF are not although the investigators acknowledge that some (but not excess) TNF is still required for host-defense against TB. This *ex vivo* finding was supported by the presence of $CD4^+PD\text{-}1^+$ and $CD8^+PD\text{-}1^+$ T cells in non-caseating granulomas present in the lung tissues of TB patients (29). In contrast, caseating TB granulomas were essentially void of $PD\text{-}1^+$ T cells, the presence of abundant TNF^+ cells, and presumably greater *M. tuberculosis* burden, supporting their *ex vivo* 3D cell model findings. Interesting, the number of $CD4^+PD\text{-}1^+$ T cells in the peripheral blood inversely correlated with the level of TNF in the sputa, supporting their experimental findings (29).

Summarization of these murine, non-human primate, *ex vivo* cell model, and human lung tissue studies indicates that at least a certain amount of immune checkpoint activation is necessary for optimal control of mycobacterial infection.

Human studies

In a retrospective review using the U.S. FDA Adverse

Reporting System for TB and NTM infections, of the ~74,000 adverse events reported with anti-PD-1 and anti-PD-L1 antibodies, 72 cases of TB and 13 cases of NTM infections were found (30). Unfortunately, this study lacked sufficient details to definitively ascertain a causal link since no data were provided on concomitant administration of other chemotherapeutic agents/glucocorticoids in the mycobacteria-infected patients; moreover, a comparison group of control cancer patients not treated with ICIs was not included in the analysis (30). Fujita *et al.* (31) noted a 1.6% incidence of active TB in 178 patients being treated with ICIs although a control group was not included for comparison. Studies associating ICIs with mycobacterial infections in humans are comprised mostly of case reports and case series (*Table 4*). While these case reports do not prove that ICIs predispose to mycobacterial infections, they do at least suggest that possibility. Alternatively, ICIs may have "unmasked" pre-existing, subclinical active

Table 4 Case reports associating ICIs and mycobacterial infection (TB and NTM)

Reference	Age; gender; race; country/region (TB incidence)[†]	Cancer type; ICI used	Other immunosuppressives or confounders	Site of mycobacterial infection and TB treatment
Tuberculosis				
Lee *et al.* (32)	87; M; Asian; Singapore (49 per 10^5) (33)	Hodgkin's lymphoma; pembrolizumab	ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine); chlorambucil + GC; gemcitabine + oxaliplatin; brentuximab (anti-CD30)	Pulmonary TB[‡] after 5th ICI cycle
Fujita *et al.* (34)	72; M; Asian; Japan (16 per 10^5) (33)	Stage IV lung cancer; nivolumab	Carboplatin + docetaxel; carboplatin + gemcitabine	Pulmonary TB[‡] after 8th ICI cycle
Chu *et al.* (35)	59; M; Asian; Taiwan (41.4 per 10^5) (36)	Metastatic NSCLC; nivolumab	Gefitinib, GC	Pericardial TB[‡] after 3rd ICI cycle
Elkington *et al.* (37)	62; F; NS; United Kingdom (8.1 per 10^5) (33)	MetMelanoma; ipilimumab, pembrolizumab	None	Pulmonary and hepatic TB[‡] 2 years after completion of ICI
He *et al.* (38)	65; F; Asian; China (61 per 10^5) (33)	MetMelanoma; pembrolizumab	None; IL-2	Pulmonary TB[‡] after 10th ICI cycle
Jensen *et al.* (39)	56; M; Caucasian; Denmark (5.4 per 10^5) (33)	NSCLC; nivolumab	Pemetrexed, XRT	Pulmonary TB[‡] after 12th ICI cycle
Picchi *et al.* (40)	50; M; Caucasian France (9 per 10^5) (33)	MetMelanoma; pembrolizumab	None	Pulmonary TB[‡] after 4th ICI cycle
	64; M; Caucasian; France (9 per 10^5) (33)	Metastatic NSCLC; nivolumab	None	Spinal bone TB after 2nd ICI cycle. Death from spinal cord compression
Tetikkurt *et al.* (41)	53; M; NS; Turkey (16 per 10^5) (33)	Squamous cell carcinoma of oral cavity; pembrolizumab	Cisplatin, XRT	Pulmonary and adrenal TB[‡] after 6th ICI cycle
Kim & Kim (42)	60; M; NS; South Korea (64 per 10^5) (33)	Lung cancer; nivolumab	None	Pulmonary TB[‡] after 15 months of ICI
Inthasot *et al.* (43)	69; M; NS; Belgium (7.7 per 10^5) (33)	NSCLC; nivolumab	Cisplatin + pemetrexed	Pulmonary TB[‡] after 18th ICI cycle
van Eeden *et al.* (44)	56; F; Caucasian; South Africa (615 per 10^5) (33)	NSCLC; nivolumab	Gemcitabine + carboplatin; pemetrexed + XRT	Pulmonary TB[‡] after unspecified cycles of ICI. Died from cancer

Table 4 *(continued)*

Table 4 *(continued)*

Reference	Age; gender; race; country/region (TB incidence)[†]	Cancer type; ICI used	Other immunosuppressives or confounders	Site of mycobacterial infection and TB treatment
Tsai *et al.* (45)	49; M; NS; Taiwan (37 per 10^5) (36)	Metastatic HNSCC; nivolumab	Cisplatin + XRT; cetuximab, paclitaxel, carboplatin	Pulmonary TB[‡] after 3 months of ICI. Died 5 months after TB diagnosis from bacterial pneumonia
Takata *et al.* (46)	75; M; Asian; Japan (13 per 10^5) (33)	Metastatic NSCLC; nivolumab	Carboplatin + pemetrexed; carboplatin + paclitaxel; S-1 (tegafur, gimeracil, oteracil potassium) + gemcitabine + XRT	Pulmonary TB[‡] after 15th ICI cycle
Barber *et al.* (47)	59; M; Asian; USA. Emigrated from Vietnam (176 per 10^5) (33)	Metastatic HNSCC; nivolumab	XRT, gemcitabine	Pulmonary TB after 3rd ICI cycle. TB treatment unsuccessful and patient died
	83; M; Caucasian; USA. Prior history of travel to Europe, China, South America, and the Caribbean (2.9 per 10^5) (33)	Metastatic Merkel cell carcinoma; pembrolizumab	None	Pulmonary TB[‡] after 11th ICI cycle
Anastasopoulou *et al.* (7)	76; F; Caucasian; Greece (4.7 per 10^5) (33)	Advanced melanoma; nivolumab ipilimumab	Methylprednisolone, infliximab	Pulmonary TB[‡] after 8th ICI cycle. Died 2 days after starting anti-TB treatment
	85; M; Caucasian; Greece (4.7 per 10^5) (33)	MetMelanoma; atezolizumab + cobimetinib (MEK inhibitor)	None	Pulmonary TB[‡] after 5 months of combined immune-therapy
Im *et al.* (48)	63; M; NS; South Korea (48 per 10^5) (33)	Lung adenocarcinoma; nivolumab	Prior chemotherapy (agents not specified)	Pulmonary TB[‡] after 41th ICI cycle
	79; M; NS; South Korea (48 per 10^5) (33)	Lung squamous cell carcinoma; pembrolizumab	Prior chemotherapy (agents not specified) Prednisone 30 mg 1 month before TB diagnosis	Pulmonary TB[‡] after 14th ICI cycle. Died from peritonitis
	59; F; NS; South Korea (48 per 10^5) (33)	Lung adenocarcinoma; nivolumab	Dexamethasone 128 mg total before TB diagnosis	Pulmonary TB[‡] after 3rd ICI cycle. Died from cancer
Chan *et al.* (49)	67; M; NS; Singapore (46 per 10^5) (33)	Lung adenocarcinoma; durvalumab	NS	Pulmonary TB[‡] 1.5 years after ICI initiation
	86; M; NS; Singapore (46 per 10^5) (33)	Lung adenocarcinoma; pembrolizumab	NS	Pulmonary TB[‡] 77 days after ICI initiation
	62; M; NS; Singapore (46 per 10^5) (33)	Lung squamous cell carcinoma; durvalumab	NS	Pulmonary TB 50 days after ICI initiation. Died 4 days after starting anti-TB treatment
	41; M; NS; Singapore (46 per 10^5) (33)	Lung adenocarcinoma; pembrolizumab	NS	Pulmonary TB[‡] 8 days after ICI initiation
Kato *et al.* (50)	75; F; NS; Japan (12 per 10^5) (33)	Lung squamous cell cancer; durvalumab	Carboplatin, paclitaxel, XRT	Reactivation pulmonary TB[‡] after 5th ICI cycle

Table 4 *(continued)*

Table 4 *(continued)*

Reference	Age; gender; race; country/region (TB incidence)[†]	Cancer type; ICI used	Other immunosuppressives or confounders	Site of mycobacterial infection and TB treatment
Lau *et al.* (51)	29; F; NS; Hong Kong, China (57 per 10^5) (33)	Nasopharyngeal carcinoma; pembrolizumab	Gemcitabine + cisplatin; cisplatin + 5-fluorouracil; docetaxel + cisplatin; gemcitabine + carboplatin; capecitabine; metronomic cyclophosphamide	Ileal TB[‡] after unspecified cycles of ICI
Suliman *et al.* (52)	58; F; NS; Qatar (42 per 10^5) (33)	Metastatic NSCLC; pembrolizumab	Carboplatin + pemetrexed after TB diagnosis	Pulmonary TB[‡] after unspecified cycles of ICI
Lin *et al.* (53)	68; M; NS; China (52 per 10^5)[§] (33)	Squamous cell lung cancer; camrelizumab	Cisplatin + docetaxel	Pulmonary TB[‡] 1 month after initiating ICI
Non-tuberculous mycobacterial infections				
Fujita *et al.* (54)	66; F; NS; Japan	Recurrent NSCLC; nivolumab	Carboplatin, pemetrexed, XRT	*M. intracellulare* lung disease
	80; M; NS; Japan	Metastatic NSCLC; atezolizumab	Carboplatin, paclitaxel, XRT	MAC lung disease
	66; M; NS; Japan	Stage 4a NSCLC; atezolizumab	Carboplatin and nabPTX, docetaxel, and XRT	*M. intracellulare* lung disease
Baba *et al.* (55)	80; M; NS; Japan	NSCLC; durvalumab	Carboplatin	*M. avium* lung disease
Okamoto *et al.* (56)	69; M; NS; Japan	NSCLC; pembrolizumab	Carboplatin, paclitaxel	*M. abscessus* lung disease
Koyama *et al.* (57)	44; F; Asian; Japan	Breast cancer; nivolumab	Doxorubicin + tamoxifen; leuprorelin acetate; bevacizumab + paclitaxel	*M. mageritense* SSTI & CRBSI
Chi *et al.* (58)	58; M; NS; Taiwan	Renal cell carcinoma; pembrolizumab	Axitinib (inhibits tyrosine kinase receptors including vascular endothelial growth factor receptor)	MAC lung disease
Omori *et al.* (59)	74; M; NS; Japan	Lung cancer; pembrolizumab	Unknown	*M. abscessus* subsp. *abscessus* vertebral osteomyelitis & epidural abscess
Yamaba *et al.* (60)	82; M; NS; Japan	Advanced stage gastric cancer; nivolumab	Tegafur + gimeracil + oteracil; XRT	MAC lung disease
Pang *et al.* (61)[¶]	53; M; Asian; China	Hepatocellular carcinoma; camrelizumab	Exacerbated severe psoriasis; chronic indwelling central venous catheter; topical glucocorticoids	*M. neoaurum* bacteremia (multiple blood cultures)

[†], TB incidence for the publication year of the cited publication; [‡], TB treated successfully; [§], TB incidence data for 2022; [¶], see text as this patient has at least two major risk factors for NTM bacteremia without necessarily invoking the ICI as a risk factor. ICIs, immune checkpoint inhibitors; TB, tuberculosis; NTM, non-tuberculous mycobacteria; M, male; GC, glucocorticoids; NSCLC, non-small cell lung cancer; F, female; NS, not specified; MetMelanoma, metastatic melanoma; XRT, radiotherapy; NSCLC, non-small cell lung cancer; HNSCC, head and neck squamous cell carcinoma; MAC, *Mycobacterium avium* complex; nabPTX, nab-paclitaxel; SSTI, skin and soft tissue infection; CRBSI, catheter-related blood stream infection.

mycobacterial infections, invoking overt inflammation without necessarily increasing vulnerability to the mycobacteria (62). As we posit later, it appears that either possibility (ICIs predisposing to mycobacterial infections or unmasking a pre-existing infection) as well as ICIs providing protection against mycobacterial infections may occur, depending on the baseline immune status of the host. In a patient with advanced hepatocellular carcinoma treated with anti-PD-1 antibody who developed multiple positive blood cultures for *Mycobacterium neoaurum*, the paramount risk factor was the presence of a chronic indwelling port catheter combined with the severe psoriasis that was exacerbated by the ICI (61). In other words, the prominent skin disease combined with a transcutaneous foreign object provided a likely portal of entry for the NTM invasion; i.e., there were significant pre-existing risk factors without necessarily incriminating the ICI.

Ogishi and colleagues (63) reported a child with inherited PD-1 deficiency who developed abdominal TB (and successfully treated) but subsequently died from excessive and systemic autoimmune inflammation. Interestingly, the child's lymphocytes produced only small amounts of IFNγ with mycobacterial stimulation due to combined depletion of various lymphocyte populations that included a specific subset of gamma-delta T cells, mucosal-associated invariant T (MAIT) cells, and $CD56^+$ natural killer lymphocytes (63). The excessive autoimmune inflammation was due to increased activation of STAT3 by IL-6 and IL-23 with subsequent increased expression of RORγ (RAR-related orphan receptor gamma) (63), another transcription factor mainly expressed by T_H17 cells. Since IL-17 is a neutrophil chemoattractant, it is interesting to speculate whether the inherited PD-1 deficiency ultimately included an ineffective hyperinflammatory (neutrophilic) response to both the TB and the autoimmune inflammation.

Chen and colleagues (64) recently reported a retrospective analysis of the incidence of TB in lung cancer patients who were treated with ICIs versus tyrosine kinase inhibitors (TKIs). They found that those treated with ICIs had significantly higher incidence of TB (2,298 per 10^5 person-years) than those who received TKIs (412 per 10^5 person-years) even after matching the two cohorts. One caveat is that the number of actual TB cases were quite small in both groups with 7 TB cases in 442 patients treated with ICI (1.58%) and 11 TB cases in 1,607 patients treated with TKI (0.68%) and thus the much higher incidence rate in the ICI group was calculated from a shorter period of cumulative time than the TKI group. A potential remaining confounder to their findings is that the ICI group still had significantly greater use of systemic glucocorticoids than the TKI group even after the matching process. While these investigators also showed in a prospective component of their study that those on ICIs were more likely to have conversion of their interferon-gamma release assay (IGRA) for latent TB infection, an inherent confounder is that ICIs normally function by increasing activation of IFNγ-producing T_H1 cells and thus may be more likely to result in a more positive IGRA (64).

Experimental and clinical evidence indicating that ICIs do not increase vulnerability or are host-protective against mycobacterial infections

Experimental animals

Antibodies to the immune checkpoint TIM3 have also been developed to augment host T effector function against cancer (65). In both *ex vivo* mouse lung T cells and *in vivo* murine models, TIM3 was found to cause T cell exhaustion (66). In contrast to the findings with the *PD-1* gene knockout mice (25-27), administration of blocking antibodies to TIM3 in *M. tuberculosis*-infected C57BL/6J mice significantly reduced the bacilli burden in the lungs compared to mice treated with isotype control antibody (66). Furthermore, *TIM3* gene knockout mice also had reduced *M. tuberculosis* burden in the lungs and spleens as well as significantly longer survival than wildtype BALB/c mice (66). Similarly, administration of an anti-CTLA-4 antibody enhanced mycobacterium-specific T cell proliferation and IFNγ production in the mediastinal lymph nodes of mice as well as a decrease in *Mycobacterium bovis* (*M. bovis*) Bacillus Calmette Guerin (BCG) burden by one-half log at 6 weeks post-infection (although this did not reach statistical significance) (67). Hu *et al.* (68) also showed that a PD-L1 "blocker" in mice infected with *M. tuberculosis* (paradoxically) reduced expression of pro-inflammatory cytokines/IFNγ and of apoptosis compared to infected mice alone; unfortunately, the burden of *M. tuberculosis* in the alveolar macrophages or mouse lungs were not reported.

Human studies

Two separate single-center studies from Kyoto, Japan and Seoul, Korea showed that the incidences of TB reactivation in those on ICI was similar to the general population of Kyoto, Japan but significantly greater than the general

population of Seoul, Korea, respectively (48,69). However, because the TB incidence in the Korean patients on ICI was similar to that in (all) cancer patients in Korea, it suggests that development of TB and use of ICIs may be coincidental in both Asian populations and not necessarily a cause-and-effect (48).

In South Korea (a TB-endemic country), only three cases of TB were reported out of 1,144 solid cancer patients treated with ICIs (pembrolizumab, nivolumab, or atezolizumab) with a median follow-up period of 187 days (48). Furthermore, a retrospective study in Korea of 6,335 lung cancer patients—of whom 899 were treated with ICIs—did not find an association between the use of ICIs and active TB (70). In 51 patients with skin cancer who were undergoing immunotherapy, 9 (18%) were found to have latent TB infection but none developed TB; however, it was unclear if patients received treatment for their latent TB infection or other forms of cancer chemotherapy, and the length of follow-up after initiating skin cancer treatment was not stated (24).

There are also reported cases in which ICIs may have a salubrious effect against mycobacterial infections. A 73-year-old man with stage IV lung adenocarcinoma was treated with paclitaxel, carboplatin, and bevacizumab (anti-vascular endothelial growth factor antibody). During the course of treatment, he developed a cavitary lung nodule with peri-cavitary consolidation with sputum positive for *M. abscessus* subsp. *massiliense* (71). Due to a recurrence of lung cancer, his treatment strategy shifted to nivolumab and he also received 2 weeks of imipenem and amikacin to treat the *M. massiliense*. Despite only a brief period of suboptimal antimicrobial intervention, the cavitary nodule and infiltrate resolved with sputum culture conversion, leading the authors to speculate that nivolumab helped in treating the NTM lung disease; at the very least, the ICI did not exacerbate the *M. massiliense* infection (71). In a clinically remarkable case, Liu *et al.* (72) reported a 25-year-old man with acquired immunodeficiency syndrome (AIDS) and disseminated *Mycobacterium avium* complex (MAC) infection. Because he was recalcitrant to both anti-retroviral and anti-MAC therapies and there was high expression of PD-1 on his peripheral T cells, he was begun on sintilimab (an anti-PD-1 antibody), resulting in resolution of the disseminated MAC (72) (near the end of this paper, we will use this AIDS case, *PD-1* knockout mice studies, and others to illustrate that ICIs may be either salubrious or detrimental depending on baseline immune status). A 61-year-old man was diagnosed concomitantly with poorly-differentiated lung adenocarcinoma and *Mycobacterium fortuitum* (*M. fortuitum*) lung infection (73). Following treatment with pembrolizumab and anti-mycobacterial antibiotics (isoniazid, clarithromycin, and moxifloxacin), all cultures were negative but a new lung mass developed which on biopsy revealed a large number of "carbon particles" with histiocytes and multinucleated giant cells (73). Given that essentially all *M. fortuitum* strains are resistant to isoniazid and most strains have a functional *erm39* gene (conferring inducible macrolide resistance) (74), it gives credence to the authors position that pembrolizumab may have helped clear the NTM infection (73). Nevertheless, we opine that the *M. fortuitum* isolated may not have been significant in this patient for several reasons: (I) *M. fortuitum* is historically more likely to be a colonizer than a true pathogen; (II) on chest computed tomography imaging, no features typical of NTM lung disease was cited; i.e., centrilobular nodules, bronchiectasis, and cavities were not described; (III) the histopathologic findings of the new nodule could also be consistent with a pneumoconiosis nodule. But at least the pembrolizumab did not exacerbate the *M. fortuitum* infection.

Ex vivo human cellular studies support the paradigm that partially blocking immune checkpoints improves host immunity against mycobacteria. In TB patients, blocking PD-1, PD-L1, or PD-L2 *ex vivo* in blood lymphocytes: (I) rescued the host protective IFNγ-producing T cells and MAIT cells from exhaustion following *M. tuberculosis* antigen and *M. bovis* BCG stimulation, respectively; (II) enhanced specific degranulation of $CD8^+$ T cells; and/or (III) abrogated Treg-mediated immune suppression (21,75,76). Pan and co-workers (77) found higher PD-1 and PD-L1 expression in $CD4^+$ T cells and $CD14^+$ monocytes, respectively, from active TB patients compared to monocytes from non-TB subjects as well as a correlation between lack of sputum smear/culture conversion and higher PD-L1 expression on monocytes. Compared to healthy controls, active TB patients were found to have increased number of $PD\text{-}1^+$ and $PD\text{-}L1^+$ $CD4^+$ T cells (including both T effector cells and Tregs), increased PD-1 expression on natural killer cells, and greater expression of PD-1, PD-L1, and PD-L2 on $CD14^+$ monocytes (17-19). With effective treatment of TB, PD-1 expression on $CD4^+$ T cells decreased (19). Similar findings were seen in another cohort of active TB patients—increased gene expression of PD-L1 in peripheral blood cells—but with successful TB treatment, there was a decline in the expression of PD-1, PD-L1, and PD-L2 and a decrease

in PD-1 protein expression on $CD4^+$, $CD8^+$, and natural killer cells, leading the investigators to conclude that targeting PD-1 may be beneficial host-directed therapy (78). Peripheral blood $CD4^+$ T cells from TB patients stimulated *ex vivo* with killed *M. tuberculosis* produced less IL-17, IL-23 receptor, and phosphorylated STAT3 and expressed more PD-1 (that decreased with anti-TB treatment) than cells from healthy controls; addition of anti-PD-1 antibody led to increased production of IL-17, IL-23 receptor, and phosphorylated STAT3 (79). *Ex vivo* blockade of both PD-1 and PD-L1/PD-L2 in co-cultures of $CD4^+$ T cells and monocyte-derived macrophages augmented both phagocytosis and intracellular killing of *M. bovis* BCG (18). *M. tuberculosis* whole cell lysate/EsxA (aka ESAT-6) stimulation of THP-1 cells and murine bone marrow-derived macrophages increased cell surface expression of PD-L1 (77). Additionally, pulmonary TB patients who were acid-fast bacteria positive or who failed to culture convert at 2 months into TB treatment had significantly greater proportion of blood monocytes that were PD-$L1^+$ compared to those who were smear negative or culture converted at 2 months, respectively (77).

The PBMC from 50 subjects with MAC lung disease demonstrated lower levels of TNF and IFNγ compared to the PBMC of 30 healthy controls following *ex vivo* stimulation with MAC (80). Furthermore, the white blood cells of patients with MAC lung disease exhibited higher PD-1 and PD-L1 expression and greater apoptosis in the lymphocytes compared to control lymphocytes. Following a partial blockade of PD-1, PD-L1, and PD-L2 using antagonizing antibodies, there was a notable increase in MAC-stimulated IFNγ production and a reduction in lymphocyte apoptosis (80). These findings suggest that the T cells in patients with MAC lung disease are in a state of exhaustion due to chronic antigen exposure. Thus, one could posit that such patients may benefit from adjunctive anti-PD-1 or anti-PD-L1 antibody therapy.

Discussion

The controversy

Based on the ability of ICIs to augment the activity of T_H1 cells against cancer cells that express PD-L1, it seems plausible that ICIs can also enhance control of mycobacterial infections. However, as noted above, mice harboring genetic disruption of PD-1 demonstrated greater bacterial burden and worse survival following *M. tuberculosis* infection, raising the possibility that excessive inflammation was detrimental to the animals, an ineffective hyperinflammatory response was present, or both (25-27). In contrast, mice with genetic disruption of PD-1 or wildtype mice administered anti-PD-1 neutralizing antibody and then infected with *Histoplasma capsulatum* had reduced fungal burden and improved survival (81). Additionally, in a cecal-ligation-and-puncture model of sepsis, administration of anti-PD-1 antibody improved survival (82). Mice administered the ICI anti-TIM3 antibody or have genetic disruption for *TIM3* gene, in contrast to the findings with the *PD-1* gene knockout mice, were more protected against *M. tuberculosis*. One important consideration is the genetic background of these knockout mice wherein the *TIM3* gene knockout mice are in a BALB/c background, a strain that is considered to be more susceptible to TB (perhaps due to a greater induction of a T_H2 response) than the C57BL/6 background of the *PD-1* gene knockout mice (83,84). These murine studies indicate that whether complete or partial inhibition of immune checkpoint-cognate ligand interaction is salubrious or detrimental is likely to be pathogen-specific, immune checkpoint-specific, and/or dependent on the baseline immunity of the host.

As a preview to our hypothesis discussed later, these opposing findings in mice of the protective and deleterious response to genetic disruption of immune checkpoints suggest that hosts that are more or frankly immunocompromised may be more likely to benefit from ICIs whereas those with pre-existing intact or even heightened immune status may be more likely to deteriorate with ICIs.

Confounders that could undermine the link between ICIs and vulnerability to mycobacterial infections in human case reports

We next discuss potential confounders by which ICIs may be associated with increased mycobacterial infections and yet do not actually raise the risk of such infections. Some of these confounders include: (I) immune suppression from the cancer itself and/or the presence of other co-morbid conditions such as diabetes, smoking, and end-stage renal disease that predispose to mycobacterial infections; (II) concomitant or sequential use of other cancer chemotherapeutic(s) or adjunctive glucocorticoids that are able to suppress host-protective immune cell function (85); and/or (III) lung injury from radiation or chemotherapeutic agents resulting in architecturally distorted lungs and

predisposing such patients to secondary mycobacterial lung infections. Reporting bias is also likely to be present with human case reports that associate ICIs with mycobacterial infections; i.e., if no mycobacterial infections occurred during ICI treatments, such cases are unlikely to be reported. Case reports and case series also lack robust evidence of a causal relationship along with several potential confounders that are inherently present and unable to be accounted. We will not discuss the use of anti-TNF biologic agents and/or glucocorticoids to treat ICI-induced autoimmune/inflammatory complications as a confounder since it is obvious that these treatment strategies are independent risk factors for mycobacterial diseases.

Immune suppression from cancer itself and co-morbid conditions

Cancer has been recognized as an independent risk factor for developing active *M. tuberculosis* infection since the 1950s; however, this association is likely to vary depending on the cancer types (e.g., those that compromise the immune cells directly such as the leukemias), the country reporting the association (i.e., TB endemic *vs.* non-endemic countries), and concomitant use of immunosuppressive agents (discussed below) (7,85-87). Lymphopenia, a well-known entity associated with cancer (88)—whether due to the cancer itself, treatment (discussed below), or both—would likely increase the risk for TB and NTM infections.

Use of immunosuppressive drugs in the setting of cancer treatment

Glucocorticoids suppress the adaptive arm of the immune system, resulting in predisposition to TB or NTM infection, particularly when administered at supraphysiologic doses and for an "extended period" of time (89,90). Since glucocorticoids are commonly used in cancer treatment—whether as part of the regimen to treat lymphoid cancers or as symptomatic treatment for nausea that commonly accompanies cancer chemotherapy—it is quite plausible that glucocorticoids contribute to increased risk of TB reactivation during cancer treatment. As noted in *Table 4*, most of the patients in whom ICI administration was linked to mycobacterial infections were on other chemotherapeutic agents that can suppress immune function (91). Several chemotherapeutic drugs are known to cause lymphopenia including cyclophosphamide, cisplatin, methotrexate, and taxanes (88). Fludarabine, used to treat hematological cancers, can strongly diminish the numbers of cytotoxic T cells (92). It is also plausible that glucocorticoids were prescribed to treat chemotherapy-induced nausea but their use may not have been mentioned in the case reports as "relevant" medications.

Distortion of lung architecture

Due likely to greater virulence of *M. tuberculosis* compared to NTM, pulmonary TB may occur in previously normal lungs whereas NTM lung disease typically requires some pre-existing structural lung disease—most commonly bronchiectasis and emphysema (93). Parenchymal lung injury that occurs with certain chemotherapeutic agents and radiation treatment and any sequela of lung architectural distortion (e.g., lung fibrosis and traction bronchiectasis) is a plausible mechanism by which such abnormal areas are more vulnerable to mycobacterial infections. Furthermore, the influx of "wound-healing immune cells" to the site of the lung injury may also predispose those areas to mycobacterial infections as such recruited, reparative immune cells are "immunosuppressive" in the context of infections, a concept known as locus minoris resistentiae ("site of least resistance"); i.e., a site of previous injury is more susceptible to infections (94). Radiation therapy may cause mucosal injury, increasing susceptibility to infections. Additionally, radiotherapy, especially when applied to larger tumors, is known to induce lymphopenia (95). Thus, because radiation therapy and concomitant administration of immunosuppressive chemotherapy are commonly employed in cancer treatment, the occurrence of mycobacterial infections with ICIs may only be associative and not necessarily causative (54,60).

Potential mechanisms directly linking ICIs with susceptibility to mycobacterial infections

While there is a paucity of data directly linking ICIs and increased susceptibility to mycobacterial infections in humans, the evidence showing increased susceptibility to *M. tuberculosis* in PD-1 knockout mice, PD-L1 knockout mice, and administration of anti-PD-1 antibody in non-human primates cannot be ignored (25-28). We discuss below the potential mechanisms by which ICIs may directly predispose to mycobacterial infections, namely: (I) lymphopenia that rarely may be associated with the ICIs and (II) dysregulated hyperimmune responses caused by the ICIs that then predisposes to mycobacterial infections. It is also important to emphasize that these potential risk factors to mycobacterial infections posed by the ICIs are not mutually exclusive from the potential confounders

discussed above, possibly working in synergy to increase such susceptibility.

ICI-related lymphopenia and mycobacterial infections

One hypothesis proposed of ICI-associated mycobacterial infection is ICI-related lymphopenia (23,35). However, this phenomenon is a rare event with a reported incidence of grade 3 to 4 leukopenia of 1% (96,97) as well as grade 1 to 2 lymphopenia of 1.2% and 0.6% with pembrolizumab at doses of 2 and 10 mg/kg, respectively (98). The absence of a dose-response of pembrolizumab with lymphopenia raises doubts about the ICIs causing lymphopenia; indeed, one could contrarily argue that the higher dose of pembrolizumab reduced the frequency of lymphopenia. Whether ICIs can cause lymphopenia is not definitive and even if they can, the peripheral blood lymphopenia may be due to increased migration of T cells to the site of the tumor.

Induction of detrimental hyperinflammatory response to mycobacteria

"Dysregulated immunity" is an often-cited but unproven mechanism through which ICIs, despite enhancing host-protective immunity, might paradoxically predispose individuals to *M. tuberculosis* and NTM. While it is logical to infer that ICIs may contribute to increased lung inflammation and subsequent injury, the specific mechanism(s) by which ICIs compromise the ability to control mycobacterial infection—resulting in increased mycobacterial burden—remains unintuitive and difficult to rationalize. The goal of this section is to clarify how a robust but excessive host immune response could predispose to mycobacterial infections. We posit three plausible and not necessarily mutually exclusive mechanisms by which enhancing T effector function may be associative or predispose to mycobacterial infections: (I) unmasking of a pre-existing subclinical mycobacteria infection without being causative; (II) excessive inflammation by ineffective immune cell types that dilutes a salubrious immune response; (III) excessive inflammation by normally effective immune cell types and cytokines that paradoxically impairs host-protective immune response.

Unmasking of a pre-existing subclinical mycobacteria infection without being causative

As previously mentioned, case reports and case series describing mycobacterial infections in the context of ICI use can only be associative with several potential confounders. Their co-occurrence may be merely coincidental. However, it is possible that ICIs, by inducing increased inflammation, can uncover a covert, pre-existing active mycobacterial disease that then becomes overt, coming to clinical attention. A well-described and possibly related syndrome is the immune reconstitution inflammatory syndrome (IRIS) seen in AIDS patients with mycobacterial (or other types of) infections who are prescribed highly active antiretroviral therapy (HAART) (99). In these patients, pre-existing *M. tuberculosis* infection that may be subclinical or is being treated, is exacerbated as the patient regains the capacity to mount an inflammatory response from the HAART (100). In fact, many of these patients exhibited elevated number of activated $CD4^+$ T cells, consistent with T cell activation in patients treated with ICIs (101). Similar paradoxical inflammatory syndromes with re-emergence of active infection have been observed in HIV-uninfected patients on treatment for TB or leprosy (102). One illustrative case is that of a patient with severe combined immune deficiency (SCID) who developed disseminated *M. bovis* BCG infection as new immune cells engrafted following allogeneic hematopoietic stem cell transplant (103). It is possible that patients on ICIs who have subclinical active TB or who were treated for TB but still harbored live *M. tuberculosis* prior to ICI therapy, might experience an exacerbation of *M. tuberculosis* infection when ICIs create a hyperimmune response, manifesting an illness that led clinicians to diagnose a previously active but subclinical mycobacterial disease.

It has been posited that lowering the mycobacterial burden with anti-mycobacterial drugs before starting ICIs may not only prevent a hyperinflammatory state but also prevent a dysregulated and ineffective immune state akin to IRIS. One anecdotal supporting evidence for this is that in the aforementioned patient with AIDS and recalcitrant, disseminated MAC infection, addition of an ICI after the patient was given antibiotics for MAC (that presumably lowered the mycobacterial burden) affected a salubrious host-protective response (72,104). We also posit that his baseline compromised immune function likely affected a favorable response to the ICI.

Excessive inflammation by ineffective immune cell types that dilutes a salubrious immune response

One study that examined neutrophilic influx in *PD-1* gene knockout mice infected with *M. tuberculosis* found large numbers of degenerating and fragmented neutrophils accompanied by tissue necrosis compared to infected control mice (25). The allusion is that tissue injury and perhaps the influx of large numbers of ineffective neutrophil phenotypes

prevented—by steric interference—more effective immune cells from reaching the site of the infection and exerting their host-protective functions.

Excessive inflammation by normally effective immune cell types and cytokines that paradoxically impairs host-protective immune response

Overall, there are conflicting data between *ex vivo/in vitro* human cell studies *vs. in vivo* murine studies (with the *PD-1* gene knockout mice) on whether ICIs are protective or predisposing to infection with *M. tuberculosis*. As discussed above, *ex vivo* studies applying ICIs in human T cells and monocytes/macrophages showed that these agents prevented their exhaustion, activated their function, and/or enhanced their ability to clear mycobacteria (17-19,21,75-79). Whereas *PD-1* gene knockout mice are paradoxically more susceptible to *M. tuberculosis* (25-27,105), mice in which TIM3 was antagonized with a specific ICI (anti-TIM3 antibody) or the *TIM3* gene was knocked out are more protected against *M. tuberculosis* (66). Plausible mechanistic explanations for these differences include intrinsic differences among the different immune checkpoints (PD-1 *vs.* TIM3), the difference between partial inhibition of immune checkpoints with an antibody *vs.* genetic disruption of an immune checkpoint, and different background strains of mice used (C57BL/6 *vs.* BALB/c) wherein mice that are intrinsically and relatively more immunosuppressed (e.g., the BALB/c background in the *TIM3* gene knockout mice) may be more likely to benefit from ICIs. Further confounding the relationship between PD-1, IFNγ and *M. tuberculosis* infection is that IFNγ upregulates both PD-1 and PD-L1 expression (21,106,107); this form of negative feedback indicates that the host-protective immune response to *M. tuberculosis* is a delicate combination of proinflammatory and immune-dampening responses (108).

If there is a direct causative link of ICIs and mycobacterial infections, the most obvious paradox is that IFNγ plays a key role in host defense against mycobacterial disease *via* macrophage activation. Indeed, severely decreased or absence of IFNγ function due to T cell deficiency/exhaustion impairs the ability to form mature granulomas and increased vulnerability to severe disseminated mycobacterial infections (93,109-112). This phenomenon is obviously not occurring with ICI-associated mycobacterial infections because ICIs will induce more IFNγ and essentially all reported cases of ICI-associated human TB or NTM infections are localized disease (*Table 4*) and not the disseminated disease seen in those with profound defect in the IFNγ-IL-12 axis. However, one supporting clue that excess IFNγ (and its downstream effects) may contribute to a detrimental immune response to the host is based on a study showing that IFNγ production by T_H1 cells is far more important for TB control in the spleen than in the lungs and that increasing the IFNγ-producing capacity by the T_H1 cells actually exacerbated the lung infection and led to more rapid mortality (113). Furthermore, the inflammatory response to *M. tuberculosis* is not limited to IFNγ and includes pro-inflammatory cytokines such as TNF, IL-6, and IL-12/23 (114). These cytokines and chemokines, if excessive, could lead to hyperinflammation and dysregulated immune responses.

The scenario of how either hypoinflammation or hyperinflammation is detrimental to the host, respectively, may be illustrated by the following paradigm (108,115,116): (I) with "too little" inflammation (a more "logical" or easier concept to envision), insufficient T effector (T_H1) activation results in overwhelming mycobacterial infection, necrotic macrophage death, and further spread of live mycobacteria released from the dying phagocytes (*Figure 2A*, left-hand side); (II) with "too much" inflammation, as seen with the absence or severe inhibition of immune checkpoints, there is excess amounts of IFNγ production that induces TNF and other downstream inflammatory mediators (117), causing activation of receptor-interacting serine-threonine kinases 1 and 3 (RIP1 and RIP3), necrotic macrophage death (necroptosis), and release and proliferation of mycobacteria (115) (*Figure 2A*, right-hand side); (III) between these two extremes (as represented by the Goldilocks tale of "too cold" and "too hot" porridges), there is "just the right amounts" of IFNγ and TNF ("porridge temperature just right") resulting in an optimal host protection against mycobacteria (*Figure 2A*, middle). Another analogy to this paradigm can be made wherein a civil demonstration by protestors (i.e., mycobacteria) and a fair and professional response by police officers (i.e., immune cells and cytokines) results in a peaceful resolution of the demonstration (i.e., resolution of TB or NTM disease) (*Figure 2B*, left-hand side). In contrast, if there is an inciting event (i.e., strong and prolonged immune checkpoint inhibition) by either side, chaos (i.e., excess inflammation) may ensue resulting in a violent demonstration (i.e., inability to resolve TB or NTM disease) (*Figure 2B*, right-hand side).

This paradigm of insufficient and excess inflammation (the latter due to ICIs) associated with worse outcome in TB is analogous to studies showing differential TB outcome based on the activity of leukotriene A_4 hydrolase (LTA_4H)—

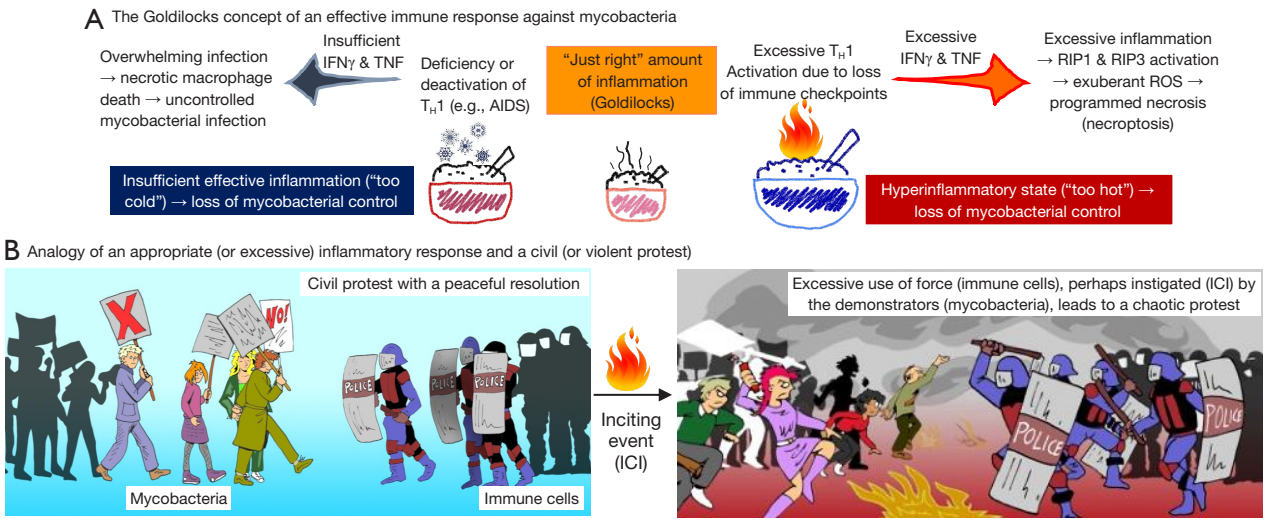

Figure 2 Hypothesized mechanism of how excessive inflammation due to ICI may increase vulnerability to mycobacterial infections. (A) The Goldilocks concept of how too little or too much inflammation produces specific phenotypic milieu that leads to ineffective control of mycobacterial infections (this figure was drawn *de novo* based on text from Roca FJ and Ramakrishnan L. *Cell* 2013;153:521-34; Tezera LB *et al*. *Elife* 2020;9:e52668; Morelli T *et al*. *Thorax* 2022;77:304-11). Insufficient T effector (T_H1) activation results in overwhelming infection, necrotic macrophage death, and spread of uncontrolled mycobacterial infection (left-hand side, represented by the "too cold" porridge). If there is excessive inflammation due to complete loss of immune checkpoints, the increased IFNγ and induced TNF activates RIP1 and RIP3, leading to necrotic macrophage death (necroptosis), also impairing control of mycobacteria (right-hand side, represented by the "too hot porridge"). With an "appropriate" amount of effective inflammation (middle, represented by the "just right" temperature porridge), control and resolution of the mycobacterial infection are achieved. (B) An analogy of using police officers and demonstrators to show how an excessive cellular immune response induced by ICIs may increase vulnerability to mycobacterial infections. With civil and professional behaviors by the protestors and officers, respectively, the demonstration is peacefully conducted and ended (left-hand side); in this less than perfect analogy, elimination of the mycobacteria is analogous to peaceful resolution of the demonstration. However, if there is an external inciting event (ICI), the demonstrators (mycobacteria) and police officers (immune cells) further alienate each other, resulting in a violent demonstration (the disease is exacerbated and poorly controlled) (right-hand side). IFNγ, interferon-gamma; TNF, tumor necrosis factor; AIDS, acquired immunodeficiency syndrome; RIP, receptor-interacting serine-threonine protein kinase; ROS, reactive oxygen species; ICI, immune checkpoint inhibitor.

an enzyme that normally metabolizes LTA_4 to the pro-inflammatory molecule LTB_4 as well as increases the metabolism of the anti-inflammatory molecule lipoxin A_4 (LXA_4), creating a net pro-inflammatory state (*Figure 3A*). The CC genotype of the *LTA4H* promoter [single nucleotide polymorphism (SNP) rs17525495] is associated with decreased LTA_4H activity, resulting in less pro-inflammatory LTB_4 and more anti-inflammatory LXA_4 (118) (*Figure 3B*). An immunodeficient state would be analogous to this CC genotype (*Figure 3B*). In contrast, the TT genotype is associated with greater LTA_4H activity, resulting in increased conversion of LTA_4 to LTB_4, decreased levels of LXA_4, resulting in a hyperinflammatory phenotype (*Figure 3C*). Use of an ICI that results in worse outcome would be analogous to this TT genotype (*Figure 3C*). A study showed that both the hypoinflammatory (CC) and hyperinflammatory (TT) genotypes of LTA_4H ("the two extremes") were associated with poorer outcomes compared to the heterozygous (CT) genotype (119). A subsequent Cochrane review of nine randomized controlled studies (1,337 participants with TB meningitis) reported that compared anti-TB treatment alone, addition of glucocorticoids reduced death by about 25% (120); as could be rationally predicted, those with the hyperinflammatory (TT) genotype benefited most from glucocorticoids (119). In contrast, a subsequent study from Vietnam showed that those with the hyperinflammatory (TT) genotype had better survival than those with the hypoinflammatory

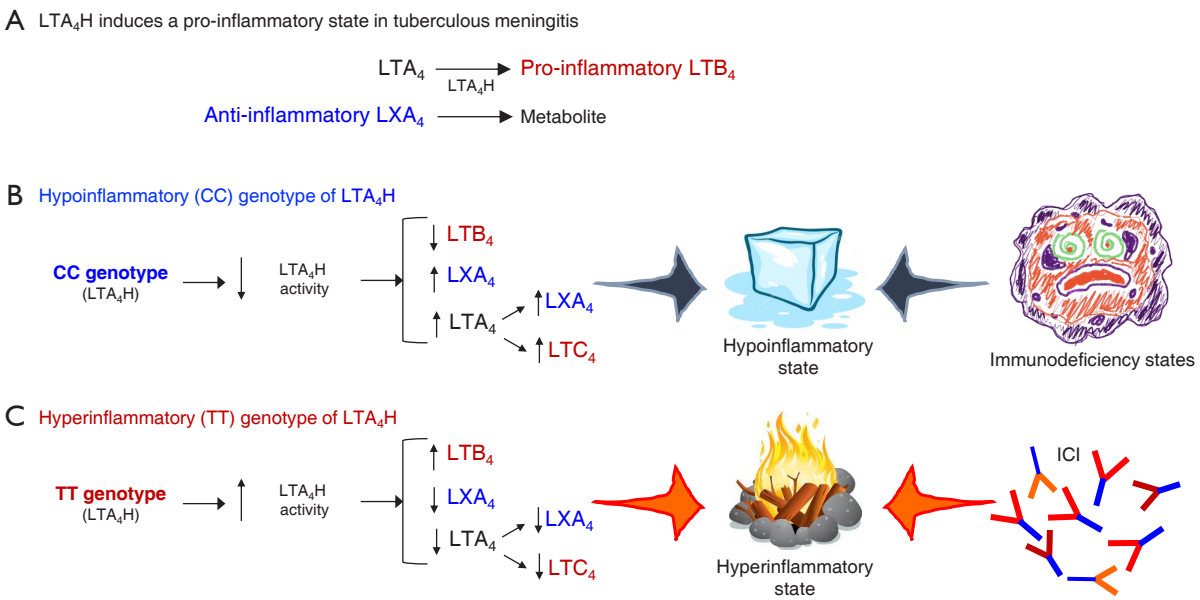

Figure 3 The genotype of LTA_4H influences the inflammatory response to tuberculous meningitis and analogy with the ICIs. (A) LTA_4H metabolizes the substrate LTA_4 to the pro-inflammatory LTB_4 as well as metabolizes the anti-inflammatory LXA_4. Thus, increased LTA_4H activity is pro-inflammatory. (B) With the CC genotype of LTA_4H, there is decreased LTA_4H activity, resulting in decreased LTB_4 and increased LXA_4 and LTA_4; the LTA_4 may be metabolized to LXA_4 (anti-inflammatory) and LTC_4 (pro-inflammatory) with a net effect of a hypoinflammatory state. Those with various forms of immunodeficiencies are analogous to those with the hypoinflammatory state (CC genotype of LTA_4H). (C) With the TT genotype of LTA_4H, there is increased LTA_4H activity, resulting in increased LTB_4, decreased LXA_4, and decreased LTA_4 as well as reduced amount of LTC_4 with still a net effect of a hyperinflammatory state. While unproven, ICI-induced hyperinflammatory state may be associated with a dysregulated and ineffective immune response to mycobacteria. Blue color font is used to denote anti-inflammatory status whereas red color font denotes pro-inflammatory effect. LTA_4H, leukotriene A_4 hydrolase; LTA_4, leukotriene A_4; LXA_4, lipoxin A_4; ICIs, immune checkpoint inhibitors.

(CC) genotype with the CT genotype in between the two homozygous genotypes (121). Another study from Indonesia of patients with TB meningitis showed that the *LTA4H* genotype did not show significant association to mortality although there was a non-significant trend toward better survival in the hyperinflammatory (TT) phenotype (122). These conflicting findings in the *LTA4H* genotype on mortality may be due to a number of factors that potentially or actually differ between the two populations studied including differences in linkage disequilibrium (particularly relevant with SNP analysis in different ethnic groups) and patient characteristics (e.g., higher proportion of patients with greater severity and mortality in the Indonesian groups, older age in the Vietnam group, etc.) (121-123). Overall, these *LTA4H* genotype studies support the paradigm that either excessive/prolonged inflammation or insufficient inflammation may compromise the ability of the host to control TB.

The phenotypic heterogeneity of human TB (latent TB infection, primary TB, reactivation TB, and intervening TB phenotypes) may be reflected mechanistically ("endotypically") by heterogeneity at the TB granuloma level (124). Cardena and co-worker's (124) discourse on heterogeneity at both the host and granuloma levels supports the paradigm that either excessive or insufficient immune response against *M. tuberculosis* is detrimental to the infected host. While severe immunodeficiency (e.g., untreated AIDS) can result in overwhelming mycobacterial infection (TB or NTM), they noted that an excessive pro-inflammatory response can lead to liquefaction of the granuloma core, breach of the granuloma boundary, and spread of the tubercle bacilli and the accompanying inflammatory cellular and cytokine response to the previously unaffected lung parenchyma, signs that denote active TB (124). Thus, a balanced cytokine response—comprised of both pro-inflammatory and anti-inflammatory

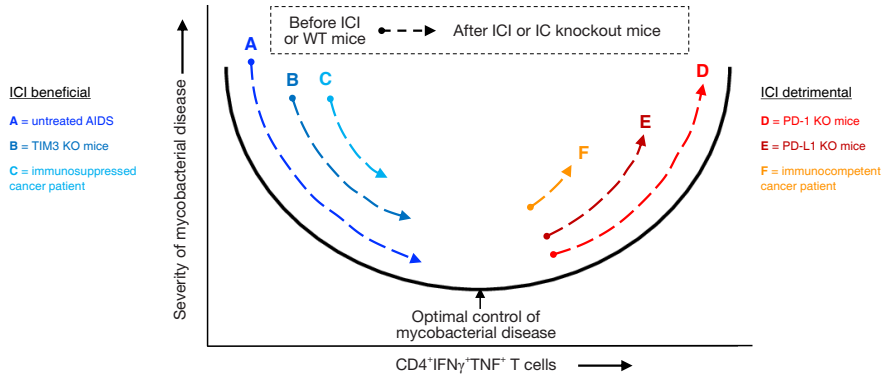

Figure 4 Examples of published or hypothetical conditions where inhibition of immune checkpoints would be beneficial or detrimental. We posit that in conditions where the host is either severely immunocompromised, immune checkpoint inhibition would be beneficial against mycobacterial infection, as exemplified by: (A) advanced AIDS patient with severe mycobacterial infection that improved with an ICI; (B) TIM3 antagonism or *TIM3* gene knockout mice are protected against mycobacteria; (C) hypothetical cancer patient 1 with severe immunocompromised status in which ICI affords protection against mycobacteria. Why the *TIM3* gene knockout mice are more resistant to *M. tuberculosis* and the *PD-1* gene/*PD-L1* gene knockout mice are more susceptible is unknown although we posit it may be due to differences in baseline immunity of their respective background mouse strains—BALB/c and C57BL/6 (see text). Conversely, in hosts with preserved immune function, immune checkpoint inhibition results in a hyperinflammatory state, worsening control of mycobacterial infections, as exemplified by: (D) *PD-1* gene knockout mice; (E) *PD-L1* gene knockout mice; and (F) hypothetical cancer patient 2 with relatively intact immune function. Patients in categories C and F may have either overt or subclinical mycobacterial infections whereas example patients or mice in the other categories (A,B,D,E) have overt and likely high mycobacterial burden due to natural or experimental infections. The arrow of "F" is relatively short because we do not see an overwhelming number of mycobacterial infections in cancer patients on ICI. Because "F" subjects are relatively more immunocompetent, they may be more likely to manifest prior subclinical mycobacterial infection ("more severe disease") upon administration of ICI; i.e., ICIs do not necessarily cause the mycobacterial infection but "unmask" a pre-existing subclinical infection. ICI, immune checkpoint inhibitor; AIDS, acquired immunodeficiency syndrome; TIM3, T cell immunoglobulin and mucin domain-containing protein 3; KO, knockout; WT, wild type; IC, immune checkpoint; PD-1, programmed cell death protein-1; PD-L1, programmed-death ligand 1; IFNγ, interferon-gamma; TNF, tumor necrosis factor.

cells and soluble mediators in an orchestrated temporal fashion—is best associated with granuloma integrity and sterility (124).

How can we shed more light on these conflicting data on whether the ICIs are detrimental or beneficial with mycobacterial infections? An insightful diagram published by Tezera and co-workers (108) helps to illustrate that these conflicting reports are perhaps not contradictory when analyzed in the context of the baseline immune status of the host (*Figure 4*) as well as the immune checkpoint types involved (e.g., PD-1 *vs.* PD-L1 *vs.* TIM3) and the degree of immune checkpoint inhibition (e.g., neutralizing antibody *vs.* genetic disruption). Tezera *et al.* (108) proposed a "U" shape paradigm in which too little or too much host-protective immune response (which we have arbitrarily represented by $CD4^+IFN\gamma^+TNF^+$ T cells on the x-axis of *Figure 4*) may result in disseminated or severe localized disease (severity of disease on the y-axis) as alluded to above. We have superimposed on this "U" diagram two published reports where the use of ICIs were shown to protect the host against mycobacterial infections along with a hypothetical case: (I) advanced AIDS patient with severe NTM infection that resolved with ICI (72); (II) mice with TIM3 antagonism or *TIM3* gene knockout are protected against mycobacteria (66); (III) Hypothetical Cancer Patient 1 who is severely immunocompromised and ICI affords protection against mycobacteria (*Figure 4*, left-hand side). Because (I) and (III) have in common severe baseline immunodeficiencies, it seems plausible that they would derive benefit from inhibiting an immune checkpoint. Although it is not known why antagonizing TIM3 would benefit the host against the mycobacterial infection but antagonizing PD-1 is detrimental, it is interesting to speculate that perhaps it is related to the fact that the BALB/c genetic background of the *TIM3* gene knockout mice is known to be more susceptible to TB than

the C57Bl/6 background of the *PD-1* gene knock mice; i.e., the genetic background of the *TIM3* gene knockout mice is relatively more immunocompromised than that for the *PD-1* gene knockout mice and thus knocking out *TIM3* was more beneficial to the host against *M. tuberculosis* than knocking out *PD-1*. Another possibility is that different immune checkpoints have different degrees of T effector cell exhaustion and thus different ICIs may also have varying degrees of rescue of the exhausted T cells.

We have also superimposed published reports where antagonizing immune checkpoints were shown to increase host vulnerability to mycobacterial infections along with a hypothetical case: (IV) *PD-1* gene knockout mice are more predisposed to *M. tuberculosis* (25-27); (V) *PD-L1* gene knockout mice are also more vulnerable but less so than the *PD-1* gene knockout mice (26); and (VI) hypothetical cancer patient 2 with immunocompetence in whom administration of ICI predisposes to more severe mycobacterial infection (*Figure 4*, right-hand side). We posit that because in each of these three examples the baseline immune function is intact or relatively more so, inhibiting immune checkpoint worsened mycobacterial disease. Perhaps the *PD-L1* knockout mice developed less severe mycobacterial disease than the *PD-1* knockout mice is because the *PD-L1* knockout mice still has PD-L2 present to bind the PD-1 receptor (26).

How can we incorporate the civil or uncivil demonstration analogy (*Figure 2B*) with that of baseline immune function impacting whether ICIs become beneficial or detrimental to the host with a mycobacterial infection (*Figure 4*)? In individuals with a pre-existing or inducible heightened immune cellular and cytokine response (analogous to a police force with a heightened or anxious emotional state), addition of ICI (inciting event) creates an excessive immune response that results in poor control of infection and increase in mycobacterial burden (analogous to a disproportionate law enforcement response that brings in more demonstrators, resulting in a civil demonstration that becomes violent and out of control). Conversely, in the presence of a subdued immune response (analogous to a calm police force with a measured and professional response to the demonstration), ICI (inciting behavior by a one or few demonstrators) is likely to improve the immune response to the infection and efficient killing of the mycobacteria (analogous to disruptive behavior by one or few demonstrators that is skillfully quelled, leading to the mutual respect between the demonstrators and the police force and a peaceful resolution of the demonstration).

One inherent limitation to the anecdotal human data linking ICI use to mycobacterial infections is that there are no prospective studies with adequate controls on whether ICIs truly increase the risk for mycobacterial infections; i.e., the case reports listed in *Table 4* simply cannot implicate ICIs as predisposing factors for the mycobacterial infections. Particularly lacking from these retrospective analyses is the inability to control for potential confounding factors and the possibility of reporting biases and in the case of TB, from countries with high endemicity for TB. Thus, based on all these factors, presence of active TB and ICI use may be merely coincidental.

There are several strengths to this paper. We organized the existing experimental data and clinical case reports that either link or refute ICIs with mycobacterial infections. We discussed the potential confounders that could undermine the seeming causative link between use of ICIs and mycobacterial infections. Given the possibility that ICIs may paradoxically increase vulnerability to mycobacterial infections, we discussed several potential mechanisms by which this may occur. Based on insightful published studies, we generated a (testable) hypothesis wherein ICIs may be either salubrious or detrimental to the host with mycobacterial infections in the context of baseline host immune status.

Conclusions

Whether ICIs predispose to mycobacterial infections remain controversial. While the preponderance of human cell studies supports the notion that ICIs are protective against mycobacterial infections, most of the experimental murine studies implicate ICIs as being predisposing agents with important exceptions in both models. To determine more definitively whether the ICIs predispose to mycobacterial infections, further prospective human case-control studies are needed, controlling for potential confounders. Murine studies that simultaneously compare specific ICIs that target different immune checkpoints (and given at various times in relationship to the mycobacterial infections) are needed to determine whether they corroborate or refute studies using mice with a genetic disruption for an immune checkpoint. The potential role of an ICI-induced hyperinflammatory response leading to dysregulated pathogen-specific responses that predispose to mycobacterial infections is an intriguing possibility and needs further study in both humans and animal models. Such studies will begin to help test the hypothesis that ICIs may induce either protection

or predisposition against mycobacterial infections, depending on the baseline immune status of the host.

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