Open Forum Infectious Diseases
CORRESPONDENCE

Comments on "PD-1 Inhibitor for Disseminated *Mycobacterium avium* Infection in a Person Living With HIV"

To the Editor—We have read with great interest the manuscript by Liu et al [1] titled "PD-1 Inhibitor for Disseminated *Mycobacterium avium* infection in a Person Living with HIV". In their work, the authors described a case of disseminated *Mycobacterium avium* complex (MAC) infection in a patient with acquired immune deficiency syndrome who was not responding to the combined administration of antiretroviral therapy (ART) and anti-MAC therapy. After having assessed a high expression of programmed cell death protein 1 (PD-1) on the patient's peripheral T cells, they decided to administer the immune checkpoint inhibitor (ICI) sintilimab, alongside ART and extended anti-MAC therapy, achieving control of the disease, thus suggesting a role for ICI in the management of this chronic infectious disease.

This case report supports a statement previously done by our group. Indeed, the authors started the ICI treatment after having administered 24 weeks of anti-MAC therapy, which, despite the severe immunocompromise, had probably reduced the overall bacterial load in the organism. We have previously speculated regarding the need of reducing the antigenic burden before administering any ICI in patients with chronic mycobacterial infections, to avoid immune reconstitution inflammatory syndrome, which may be detrimental to the host [2]. Supporting that, several real-life data are accumulating, showing how ICI treatment for neoplastic conditions may be associated with a reactivation and/or recrudescence of nontuberculous mycobacterial (NTM) infection [3], in the absence of any predisposing immunosuppressive therapy, a condition defined as immunotherapy infections due to dysregulated immunity, according to the classification proposed by Morelli et al [4].

The brilliant responses observed in this case, both in clinical terms and in the decrease of PD-1 expression on peripheral T cells, must take into account that the patient simultaneously displayed two chronic diseases associated with persistent host exposure to pathogen antigens and thus to the development of immune exhaustion (IE) (eg, HIV and NTM infection). The administration of ICI probably had positive effects on HIV-specific T cells also, thus obtaining a synergistic effect in the patient, and the use of ICI has also been previously suggested in this population [5, 6].

Regarding the high expression of the immune checkpoint PD-1 observed on peripheral T cells and its role as a tool to guide the administration of ICI, we suggest a note of caution. The authors examined the expression of PD-1 on the total amount of peripheral T cells, in the setting of uncontrolled HIV infection, with relevant systemic inflammation and severe depletion of T $CD4^+$ cells, all elements implicated in the mechanisms leading to IE. Moreover, in individuals with a normal immune system with ongoing MAC lung disease, the number of T cells expressing PD-1 in the peripheral blood is quite limited, at approximately 1%–2% (AL, 2022, unpublished data). Therefore, the high expression of PD-1 reported by Liu et al [1] should probably be linked more to uncontrolled HIV infection than to MAC infection. Consequently, we believe that the high increase in MAC spot count after the first administration of ICI has to be correlated to the action of the drug on all T lymphocytes, with a global recovery of their function and thus also the ability to mount an effective response also against MAC, probably due to both the efficacy of ART added to the effect of immunomodulatory therapy. Moreover, it is unclear whether the observed high PD-1 expression is found only in conventional T cells or also in regulatory T cells, which may lead to an opposite immunological effect [7]. Finally, an accurate IE assessment should also investigate immunological markers of T-cell activation (CD69), maturation, and concomitant expression of different exhaustion (eg, TIGIT, CD39) or senescence markers (KLRG-1, CD57).

Overall, we thank Liu et al [1] for sharing this experience, but we believe that further studies are needed to strengthen the theoretical knowledge regarding IE among patients with NTM and/or HIV infection. Moreover, ICI administration among patients with NTM disease should be assessed in well designed, randomized, controlled trials, to provide solid evidence in the treatment of an illness, which is still based on long regimens composed of old drugs.

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Potential conflicts of interest. AL reports personal fees from Gilead Sciences Inc. and Isnmed Italy. AGr reports personal fees from Grifols, Chiesi, GSK, Vertex, and Insmed Italy. FB reports grants and personal fees from AstraZeneca, grants and personal fees from Chiesi, personal fees from Grifols, grants and personal fees from GSK, personal fees from Guidotti, personal fees from Insmed, grants and personal fees from Menarini, personal fees from Novartis, personal fee from OM Pharma, personal fees from Pfizer personal fees, personal fees from Janssen, personal fees from Vertex, personal fees from Viatris, and personal fees from Zambon, in the last 3 years outside the submitted work. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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