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Commentary

Thalidomide as a Potential HIV Latency Reversal Agent: Is It the Right Time to Forget the Ancestral Sins?

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Despite its notoriety in history, for having been established as a teratogen, thalidomide arguably has become a subject of renewed interest as a therapeutic agent in recent years against several dermatologic, infectious, autoimmune and malignant disorders (Chen et al., 2010; Millrine and Kishimoto, 2017). The discovery of anti-tumor necrosis factor-α (TNF-α) effects of thalidomide has led to increased interests in the evaluation of its potential pharmacological roles (Rosenbach and Werth, 2007; Wu et al., 2005). The immunomodulatory, anti-inflammatory and anti-angiogenic properties of thalidomide are largely attributed to the modulation of various cytokines, including interleukin-6 (IL-6), IL-10, IL-12, IL-1β and TNF-α and the likely down-regulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) that mediates TNF-α protein transcription (Franks et al., 2004; Zhou et al., 2013).

Notwithstanding that thalidomide is contraindicated in HIV infection, it continues to be used in the management of aphthous ulcers, gastrointestinal lesions, Kaposi sarcoma and other HIV-associated manifestations. Notably, thalidomide, owing to its immunomodulatory activity, has also been used in the treatment of tuberculosis (TB) and cryptococcosis-associated immune reconstitution inflammatory syndrome (IRIS) in HIV-infected individuals (Fourcade et al., 2014; Franks et al., 2004).

Immune activation and inflammation have long been known to play a significant role in the pathogenesis of HIV, and are implicated in the enhanced loss of CD4+ T cells, destruction of lymphoid tissues and other complications of HIV disease. This emphasizes the necessity for designing effective anti-inflammatory treatment strategies for the prompt management of HIV-associated complications.

In a study published in this issue of *EBioMedicine*, Vergara et al. hypothesized that use of thalidomide would decrease the levels of surrogate markers of HIV-associated inflammation (Vergara et al., 2017). This is based on the rationale that the anti-inflammatory potentials of thalidomide mediated *via* inhibition of TNF-α, could decrease the rates of HIV replication and the consequent onset of inflammation. In an open-label, randomized, controlled, pilot proof-of-concept clinical trial, the authors had a randomized study population that received thalidomide or not, for 3 weeks and followed-up for 48 weeks. The HIV plasma viral loads, CD4/CD8+ T cell counts, markers of inflammation, immune activation markers and plasma lipopolysaccharide (LPS) levels were measured.

Interestingly, the study found that short-term use of thalidomide was associated with an intense transient surge in T-cell activation and inflammation. Further, there was a decrease in CD4+ T cell counts observed, and a non-statistically significant spike in the levels of LPS across the thalidomide-treated group, with reduction in LPS levels at subsequent follow-ups. While earlier studies using thalidomide on HIV-infected individuals have reported increase in HIV viral load, this study has shown a non-statistically significant increase across the thalidomide-treated group during the therapeutic phase with declining levels at subsequent visits. The conflicting results of the present study against the hitherto proposed hypothesis and results of earlier studies, are intriguing. In order to substantiate the possibility of ART naïve study population, the authors also discuss the results of a viremic elite controller (EC) subject, a part of the study group (at recruitment). In this patient, during thalidomide administration there indeed was an increase in immune activation markers and ultra-sensitive C-reactive protein (US CRP) levels, followed eventually by a blip in HIV viremia.

Based on the altered laboratory values observed in the thalidomide-treated group that returned to baseline values upon drug withdrawal, the authors speculated if these could probably be due to the purging activity of thalidomide. The novelty of the study includes this speculation confirmed by the results of *in vitro* studies demonstrating the interruption of HIV latency and thus a potential application for thalidomide as a HIV latency reversal agent (LRA).

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HIV proviral latency continues to be a major barricade to the global efforts of research towards HIV cure strategies. A fundamental approach to resolve this problem would be to necessitate targeted strategies for reversing latency so that the latently-infected cells would necessitate immune clearance mechanisms (Margolis et al., 2016). Thus, the findings of the present study have important clinical implications that, apart from its role in the management of HIV-associated manifestations, it could possibly serve as a HIV LRA for effective 'shock-and-kill' cure strategy. While notable drug classes of LRAs including PKC agonists and HDAC inhibitors have shown to be effective in inducing HIV-1 transcription in cell lines, they were unable to induce substantive amount of HIV-1 transcription in experiments with primary resting CD4 + T cells from patients on ART. Also, some LRAs have been known to cause immune suppression due to the adverse effects on CD8 + T cells (Walker-Sperling et al., 2016). In such scenario, the current findings suggest that the administration of thalidomide is safe for use in addition to its likely use as a potential LRA in HIV-infected individuals.

As affirmed by the authors themselves, the pilot proof-of-concept open-label nature of the study and the small sample size of study patients are part of limitations. Future prospective studies addressing these limitations and with extended methodologies to further elucidate the basic immunologic mechanisms would add more interesting data. The possibility of using thalidomide as an immunomodulatory as well as HIV latency reversal agent shows promise as a treatment strategy in our concerted crusade against HIV. A better understanding of its pharmacology and the underlying mechanistics of LRA action is further required to harness the complete potential of thalidomide against HIV infection. Also, considering the dark history of thalidomide misuse, there should be appropriate caution and standard precautions in place to ensure patient safety and judicious use of the drug.

Conflict of Interest

The authors declare no conflict of interest.

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