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Using Host-Directed Treatments To Combat TB-IRIS: An Untested Area In The Management of Tuberculosis

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Abstract

HIV-positive individuals receiving antiretroviral therapy (ART) are made more difficult by tuberculosis immune reconstitution inflammatory syndrome (TB-IRIS), which causes significant immunological responses and inflammation. Significant management issues are associated with this illness, which is generally treated with anti-tuberculosis drugs to target the underlying infection and corticosteroids to control inflammation. Instead of going after the infection head-on, the development of host-directed treatments (HDTs) presents a fresh strategy by adjusting the patient's immune system. TB-IRIS patients are treated with HDTs, which include medications such as metformin, statins, IL-1 blockers, and TNF-α inhibitors, with the goal of reducing excessive inflammation and immune activation. By offering a customised approach to immune dysregulation management, these medicines may lessen the requirement for corticosteroids while also enhancing patient outcomes. More clinical research is required to confirm the safety, efficacy, and suitable application of HDTs in the context of TB-IRIS treatment despite their promising nature. By using HDTs, treatment regimens could be changed to provide TB-IRIS patients with more individualised care.

Keywords: Tuberculosis-Immune Reconstitution Inflammatory Syndrome (TB-IRIS), Host-Directed Treatments (HDTs), Antiretroviral therapy (ART).

Introduction

Tuberculosis (TB) is a major global health problem, especially in areas where HIV is also common. Thanks to antiretroviral therapy (ART), people with HIV are living longer, but a complication called Immune Reconstitution Inflammatory Syndrome (IRIS) can occur when people with both HIV and TB start ART **[2]**. IRIS happens because the immune system, weakened by HIV, becomes too active after starting ART, reacting strongly to TB bacteria and causing TB-IRIS **[3]**.

Treating TB usually involves antibiotics, but managing TB-IRIS is more complex because it’s not just about fighting the bacteria, but also controlling the overactive immune response. This is where Host-Directed Therapies (HDTs) come in. HDTs aim to adjust the immune system to reduce harmful inflammation without weakening the body’s ability to fight TB **[1]**. This article looks at how HDTs work, potential treatments, and the evidence supporting their use in managing TB-IRIS.

TB-IRIS: How It Happens and Why It's a Problem

- **Paradoxical TB-IRIS:** Symptoms get worse even though the patient is already being treated for TB.
- **Unmasking TB-IRIS:** Hidden or undiagnosed TB becomes obvious after starting ART.

The problem with TB-IRIS is that the immune system overreacts, leading to a sudden increase in immune activity after starting ART. A strong inflammatory response to TB bacteria. High levels of inflammatory substances (like TNF-α and IL-6) in the body **[4]**. Balancing the need to control inflammation with the use of antibiotics for TB is tricky. Corticosteroids are often used to reduce inflammation but can have serious side effects, including a higher risk of other infections. HDTs offer a different approach by fine-tuning the immune response rather than just suppressing it **[6]**.

HDTs are treatments that focus on boosting the body’s defense system against infections by targeting the host's (the person’s) immune system, rather than the infection itself. HDTs have gained attention for treating diseases, especially those caused by drug-resistant bacteria **[1]**.

HDTs aim to control the overactive immune response while still allowing the body to fight TB, Target specific inflammation pathways, like those involving TNF-α and IL-6 **[4]**. Encourage a balanced immune response to prevent tissue damage **[5]**.

Several types of HDTs are being explored for TB-IRIS, including immune-modulating drugs, metabolic modulators, and repurposed drugs **[7]**.

Possible HDTs for Treating TB-IRIS

- TNF-α Inhibitors: These drugs, such as etanercept and infliximab, reduce TNF-α, a key factor in inflammation. However, TNF-α is also important for controlling TB, so these drugs must be used carefully **[4]**.
- IL-1 Blockers: Inflammation in TB-IRIS is partly driven by IL-1. Drugs like anakinra block this pathway and are being studied for their potential to reduce TB-IRIS symptoms without making TB worse **[5]**.
- Alternatives to Corticosteroids: Corticosteroids have side effects, so alternatives like aspirin, which reduces inflammation and blood clotting, are being considered for treating TB-IRIS **[6]**.
- Statins: Besides lowering cholesterol, statins have anti-inflammatory effects. Early studies suggest they may help control TB-IRIS without weakening the body's ability to fight TB **[7]**.
- Autophagy-Inducing Agents: Autophagy is a process that helps the body clear out harmful bacteria. Drugs like metformin and rapamycin can boost this process, helping to fight TB and reduce inflammation **[3]**.

Although research on HDTs in TB-IRIS is still in the early stages, some studies show promising results. For example, one study showed that corticosteroids reduced the severity and length of TB-IRIS symptoms **[6]**. However, due to the side effects of corticosteroids, researchers are looking at HDTs as safer alternatives. Ongoing studies are testing various HDTs to see if they can offer better, more targeted treatments **[1]**.

Challenges and Future Directions

- Safety vs. Effectiveness: Many HDTs target immune pathways that are also important for fighting TB. It's crucial to balance reducing inflammation without worsening the infection **[5]**.
- Personalized Treatment: Each person's immune response to TB-IRIS is different, so individualized treatment plans are needed **[3]**.
- Limited Data: Most of the research on HDTs for TB-IRIS is from small trials, and larger studies are needed to confirm their safety and effectiveness **[1]**.

Conclusion

Host-directed therapies are a promising new approach for treating TB-IRIS. They offer a way to manage the immune system without compromising the body's ability to fight TB. TNF-α inhibitors, IL-1 blockers, statins, and autophagy inducers are among the therapies being explored as alternatives to corticosteroids. Ongoing research and clinical trials will provide more insight into their potential to improve treatment for TB-IRIS **[1,7]**.

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