A Paradoxical Treatment of Mycobacterial Immune Reconstitution Inflammatory Syndrome

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Introduction

Immune reconstitution inflammatory syndrome (IRIS):

- A collection of inflammatory disorders in HIV-infected patients with severe lymphopenia after the initiation of antiretroviral therapy (ART).
- IRIS can cause significant morbidity and mortality.
- Corticosteroids are the mainstay of therapy in managing severe IRIS.

Tumor Necrosis Factor (TNF):

- Critical in the defense against mycobacterial infections.
- Inhibition of TNF has been shown to lead to the increased incidence of active TB.

Infliximab:

- A chimeric anti-TNF monoclonal antibody.

Here we report the use of infliximab in HIV-infected patients with mycobacterial IRIS unresponsive to prednisone or corticosteroid treatment.

Methods

- The three patients were participants of a completed observational study evaluating predictors of IRIS
  - ❖ NCT00286767: study of HIV-infected, ART-naïve patients with CD4⁺ T cells <100 cells/μL; patients were followed for up to 96 weeks after ART-initiation
- CD4 T cell count and HIV-RNA were measured at week(s) 0, 2, 4, 8, 12, 24, 36 and 48.
- Cryopreserved peripheral blood mononuclear cells from each patients were thawed, rested for 2hrs, and stimulated for 6hrs with heat-killed MAC or PPD in the presence of anti-CD49d and anti-CD28, brefeldin and monensin at 37°C and 5% CO_2.
- After stimulation, cells were stained with fluorescent conjugated antibodies to intracellular cytokines and detected using an LSR II flow cytometer.
- Plasma inflammatory markers including CRP, IL-6, IFNγ, and TNF were measured using a multi-array electrochemiluminescence assay.
- Data were analyzed using FlowJo version 9.7.6.

Case Reports

Patient 1

- 31 years old African American male diagnosed with Pneumocystis jiroveci pneumonia (PCP).
- Treated with trimethoprim/sulfamethoxazole and prednisone with good clinical response.

ART

- Emtricitabine 200mg daily.
- Tenofovir 300mg daily.
- Atazanavir 300mg/ ritonavir 100mg daily.

Unmasking MAC-IRIS

- Presented with R cervical lymphadenopathy 4 weeks after the initiation of ART.
- LN bx confirmed *M. avium*.
- Managed with anti-MAC therapy, ultrasound guided drainage and prednisone 60mg daily.

Infliximab

- Tapering of prednisone was unsuccessful with worsening of lymphadenopathy.
- Infliximab 5mg/kg was given every 2 weeks for a total of 3 infusions.
- Prednisone was completely tapered off and cervical lymphadenopathy was reduced.

Patient 2

- 41 years old male from Honduras presented with R knee pain and swelling.
- Miliary pattern on CXR. Positive sputum culture for MTB.
- Treated with standard quadruple TB therapy with good clinical response.

ART

- Emtricitabine 200mg daily.
- Tenofovir 300mg daily.
- Efavirenz 600mg daily.

Paradoxical TB-IRIS

- Worsening R knee pain and swelling, high fevers, and lymphadenopathy 2 weeks after the initiation of ART.
- Treated with prednisone 80mg daily, intra-articular corticosteroid, and moxifloxacin with some improvement.

Infliximab

- On tapering of prednisone developed chylothorax likely due to obstruction of thoracic duct by lymphadenopathy.
- Single dose of infliximab 4mg/kg was given.
- Patient improved clinically and prednisone was completely tapered off after 2 weeks.

Patient 3

- 42 years old male from Cameroon presented with cervical and axillary lymphadenopathy.
- Positive culture for MTB.
- Treated with standard quadruple TB therapy with good clinical response.

ART

- Emtricitabine 200mg daily.
- Tenofovir 300mg daily.
- Efavirenz 600mg daily.

Paradoxical TB-IRIS

- Presented with painful cervical and axillary lymphadenopathy and fevers a week after the initiation of ART.
- Treated with prednisone 50mg.

Infliximab

- No clinical improvement with prednisone.
- Lymph node discharged spontaneously.
- Infliximab 5mg/kg was given every 2 weeks for a total of 3 infusions.
- Lymphadenopathy reduced gradually and prednisone tapering was successful.



Figure 1: CT scan of the neck showing lymphadenopathy occluding the right internal jugular vein in patient 1 (a) before and (b) after infliximab infusion. Chest X-ray showing right pleural effusion in patient 2 (c) and over 2L of fluid drained from chylothorax (d).

Results

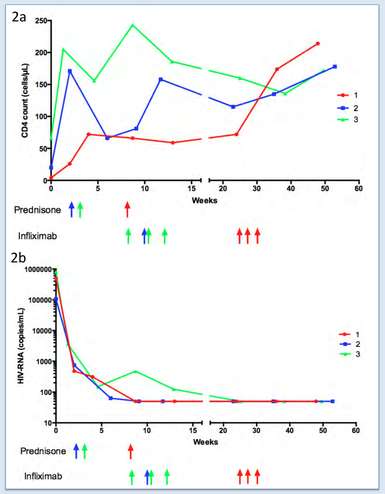


Figure 2: CD4 count (a) and HIV-RNA (b) during the first year on ART.

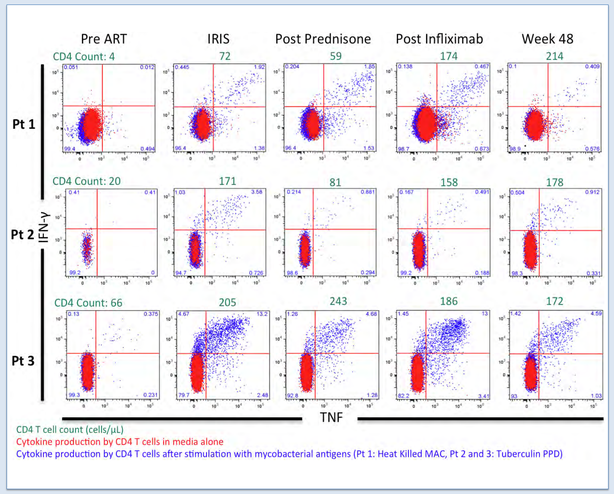


Figure 3: CD4 T-cell IFNγ and TNF responses after stimulation with mycobacterial antigens.

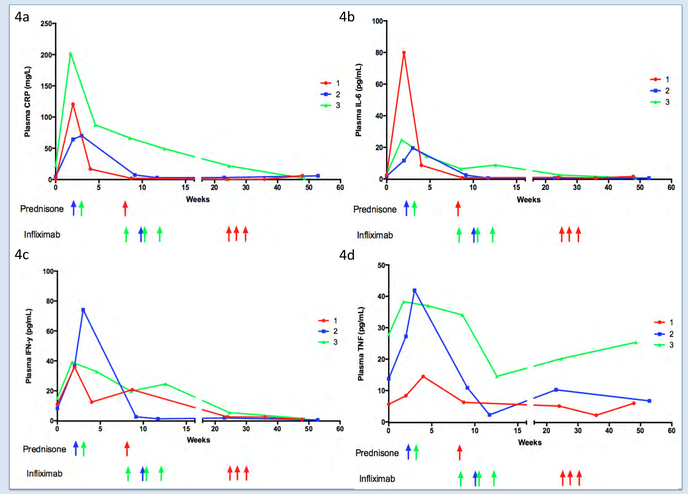


Figure 4: Plasma inflammatory marker CRP (a) and cytokine levels IL-6 (b), IFNγ (c), and TNF (d) in the first year of ART.

Conclusions

- Infliximab use was associated with clinical improvement in three steroid-unresponsive mycobacterial IRIS patients.
- No obvious adverse impact on immune recovery and virologic control was observed in these patients.
- The use of TNF inhibitor in treating severe mycobacterial IRIS could merit further assessment in clinical trials.

Acknowledgement

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