CASE REPORT

Use of tumor necrosis factor alpha (TNF α) antagonists in a patient with psoriasis and Chagas disease

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INTRODUCTION

Long-term safety data on the use of TNF-α antagonists in psoriasis, as well as their interaction with concurrent comorbidities are still to be properly evaluated. TNF-α agents have been associated with increased risk of serious infections and reactivation of tuberculosis. Increased incidence of opportunistic infections such as cerebral toxoplasmosis and toxoplasmic chorioretinitis have also been reported secondary to the use of Infliximab. Interactions with chronic infectious illnesses such as Chagas disease (CD) have not been previously assessed.

CASE REPORT

A 52-year-old man from a rural-zone in northern Chile sought our clinic in December 2007 with a diagnosis of psoriasis established when he was 14-years-old. He had over 80% of cutaneous involvement (PASI 20.6, Figure 1). He had been treated with methotrexate, PUVA and acitretin with limited response. Chest radiography and PPD test were both within normal limits and we decided to start Etanercept 25 mg twice a week, subsequently titrated to 50 mg achieving only partial response. After five months, the patient was switched to adalimumab with significant improvement.

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Abstract: There are several studies on the benefits of using TNFα antagonists in the treatment of psoriasis, but few studies addressing the interaction of these drugs with chronic infections. We report the case of a 52-year-old patient diagnosed with psoriasis refractory to traditional systemic agents, who was treated with biologic therapies. After one year of treatment with biologic agents, the patient was diagnosed with Chagas Disease.

Keywords: Biological agents; Chagas disease; Psoriasis; Tumor necrosis factor-alpha
Additionally, he referred a 5-year history of progressive constipation with poor response to laxatives. In August 2009 he underwent surgery due to megacolon (Figure 2). Histology was consistent with chagasic megacolon. The patient had not been previously diagnosed with Chagas disease (CD), but he most likely had it since childhood. Biologic therapy was subsequently discontinued while the extent of CD was assessed.

Indirect immunofluorescence (IIF) IgG, qualitative polymerase chain reaction (qPCR), and real-time polymerase chain reaction (rtPCR, Chart 1) were performed in order to investigate Trypanosoma cruzi. Esophageal involvement was evaluated with barium swallow and cardiac involvement was explored with electrocardiogram and echocardiogram, all of which were normal. Specific therapy for CD was initiated with 5-nitrofurazan 5 mg/kg/day and increased to 7 mg/kg/day for a 60-day regimen on two occasions (August 2009 and May 2010) due to an alteration in the parasitemia dynamics.

Meanwhile, the patient’s psoriatic lesions recurred, dramatically affecting his quality of life. The patient requested to have biologic therapy restarted. Potential adverse effects were carefully explained and discussed with him.

The patient was prescribed adalimumab 40 mg twice a month with excellent response (PASI 2.1, Figure 1) without evidence of CD reactivation as indicated by a non-reactive rtPCR after one-year follow-up.

DISCUSSION

Trypanosoma cruzi infection is a vectorial parasitic zoonosis caused by a hemoflagellate organism.3 The infection, known to be highly burdensome, is classified as a Neglected Tropical Disease that affects people in extreme poverty and helps to perpetuate their impoverishment.4

Twenty-percent of Latin American inhabitants (109 million individuals) are at risk of acquiring the infection, with 7.7 million individuals infected in 2005.3,5,6 In Chile, there isn’t enough information on the

![Figure 2: Abdominal X-ray examination with Barium enema. Note the dilatation of the sigmoid colon](image)

![Figure 1: A: Patient before treatment with adalimumab. B: after treatment with adalimumab](image)

**Chart 1: Parasitological study and follow-up of the patient**

| DATE     | Antibody studies | Parasitemia studies |
|----------|------------------|---------------------|
|          | IIF T. cruzi     | Qualitative PCR T. cruzi (PUC) | Quantitative PCR T. cruzi (ISP) |
| 08/2009  | Positive 1/20    | Negative            | —                      |
| 04/2010  | Positive 1/20    | Negative            | —                      |
| 05/2010  | Positive 1/20    | Positive            | Positive               |
|          |                  |                     | Real-time PCR: Quantification: 3000 DNA copies/ul. |
| 12/2010  | Positive 1/20    | Negative            | Negative               |
| 05/2011  | Positive 1/20    | Negative            | Negative               |

Captions: IIF: indirect immunofluorescence; PCR: polymerase chain reaction; PUC: Pontificia Universidad Católica de Chile; ISP: Instituto de Salud Pública de Chile.
disease, however 0.4 – 0.7% of blood donors test positive for T. cruzi.7

With the advent of traveling and migration, the disease is not only restricted to endemic areas but it is spread worldwide, making the knowledge on CD mandatory to all physicians and not only those living in the Americas.3

The effects of immunomodulatory drugs on T. cruzi parasitemia dynamics and CD course in humans are not known, with only experimental evidence available from animal models with contradictory results.8-10 Some studies demonstrated myocardial tissue alteration in Chagasic hamsters, with decrease in left ventricular systolic function, increase in IL-10-mRNA expression and an increase in the subendocardium inflammatory foci.4 Other reports have shown even a decrease in the myocardial inflammatory foci and myocarditis in animals treated with TNFα antagonists and a down regulation of CD4+ and CD8+ T cells in cardiac tissue, keeping the expression of normal cardiac proteins like connexin-43, which is reduced and disorganized in untreated infected mice.8-10 The most likely explanation is that TNFα in CD may act as a pro-inflammatory cytokine, inducing target-organ damage secondary to the recruitment and chemotaxis of neutrophils, lymphocytes and macrophages, thereby maintaining tissue inflammation.8-10

Conversely, TNFα may aid in containing T. cruzi infection and thus help maintaining low serologic levels of the hemoflagellate organism, leading to a complex interaction between the host and the agent. T. cruzi parasitemia did not change subsequent to anti-TNF administration in any of these studies.8-10 Similarly, strict follow-up with rtPCR studies did not show any evidence of reactivation of CD with the use of etanercept or adalimumab in our patient. The detection of 1000 copies of T. cruzi DNA in the rtPCR performed in May 2010 represents a very low level and could be explained by the natural fluctuation of T. cruzi parasitemia (or parasitemia dynamics) since this change occurred while the patient was off biologic therapies. This alteration in parasitemia responded well to an additional course of 5-nitrofurural, and the rtPCRs performed in December 2010 and May 2011 were negative for T. cruzi DNA despite the patient being on anti-TNF since May 2010.

The possibility that Chagas megacolon was triggered in our patient by our initial TNF-α-antagonist therapy seems very unlikely, as the mean time of development of this chronic complication is namely 20 – 30 years.

Anti-TNF drugs’ safety profiles and their use in patients with chronic infections such as CD are still undergoing long-term evaluation. This issue is of particular concern given the increasing prevalence of biologic therapy for multiple inflammatory disorders worldwide and the potential for their use in patients with unknown concurrent chronic infections such as CD.3

Screening recommendations for certain chronic infections prior to biologic therapy initiation have already been published and they include testing for hepatitis and tuberculosis at baseline.1 Screening for additional infectious diseases are not included in these guidelines.

Lassoued et al postulated performing Toxoplasma serology as an initial workup, prior to the starting

### CHART 2: Suggested work-up for patients in endemic areas (or who are traveling/ have traveled to them) planning to start biologic therapies. Treatment could be performed with Nifurtimox or Benznidazole but not with both. Captions: IIF: indirect immunofluorescence

**Step 1: Serologic screening**
- IIF IgG T. cruzi (qualitative serology)
  - Seropositive patients go to Step 2.

**Step 2: Enter Chagas disease protocol - Therapy**
- Evaluation of organ involvement (heart, esophagus, colon)
  - Symptomatic therapy according to clinical data.
  - Go to Step 3.

**Step 3: Quantitative polymerase chain reaction (PCR) to T cruzi (not qualitative)**
- Specific anti-parasitic therapy.

**Step 4: Clinical-serological control**
- IIF IgG T. cruzi and quantitative PCR T. cruzi
  - Lifetime follow-up.
of anti-TNFα therapy. Screening for hepatitis B virus is also part of the initial workup due to known cases of HBV reactivation and even death secondary to anti-TNF therapy. Furthermore, we suggest adding CD serology to initial screening studies before starting biologic therapies in CD endemic areas. This would allow a full treatment course with 5-nitrofuran prior to anti-TNF therapy, similar to concurrent HBV infection or TB infection. It would reduce and prevent an unknown but potential risk of CD reactivation, as occurs in 20% of HIV patients with severe meningoencephalitis, myocarditis, high parasitemia levels and even death (workup is listed in chart 2). Recently, T. cruzi serology was added as a screening tool in all patients who are candidates to solid organ transplants (unpublished data, observation of MT).

A consensus on guidelines for biologic therapy in the presence of CD has yet to be established and it would aid physicians in the initial workup of patients, in order to offer the highest safety and risk-benefit profiles to patients.

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