In his article in *Seminars in Arthritis and Rheumatism*, Furst (1) provides an accurate analysis of the infections that are related to the use of biologic therapies for rheumatoid arthritis. We would like to add *Leishmania* spp to the list of the infectious agents that can cause disease during the course of biologic therapies.

Eight cases of leishmaniasis have been diagnosed during biologic therapies for rheumatoid arthritis or other rheumatologic diseases (Table 1) (2-9). We found the above cases through a MEDLINE search of the international literature combining the terms (leishmaniasis OR leishmania) AND (antitumor necrosis factor OR infliximab OR adalimumab OR rituximab OR alemtuzumab OR etanercept OR efalizumab OR IL-1RA agonist).

Leishmaniasis is a group of parasitic diseases encompassing cutaneous, mucocutaneous, and visceral manifestations caused by obligate intracellular protozoa of the genus *Leishmania* (10). In endemic countries, the number of asymptomatic visceral leishmaniasis (VL) infections is greater than the number of clinically apparent VL disease cases, and among immunocompetent people it is estimated that only 1 in every 5 or 10 develops clinically overt VL (11).

### Table 1 Clinical characteristics, therapy,* and outcome of rheumatologic patients receiving biologic drugs and suffering from Leishmaniasis

<table>
<thead>
<tr>
<th>Author, yr, country (ref)</th>
<th>Age/sex</th>
<th>Disease</th>
<th>Biological drug (dose) and duration</th>
<th>Immunosuppressive agents associated with biological drug</th>
<th>Previous immunosuppressive agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romaní-Costa et al. 2004 Spain (2)</td>
<td>55/M</td>
<td>Psoriatic arthritis</td>
<td>Infliximab (3 mg/kg) 9 mo</td>
<td>NR</td>
<td>NR for 300 mo</td>
</tr>
<tr>
<td>Fabre et al. 2005 France (3)</td>
<td>53/F</td>
<td>Rheumatoid arthritis</td>
<td>Infliximab (3 mg/kg) 9 mo</td>
<td>Steroids, azathioprine (100 mg/d)</td>
<td>NR</td>
</tr>
<tr>
<td>Bassetti et al. 2006 Italy (5)</td>
<td>69/F</td>
<td>Rheumatoid arthritis</td>
<td>Adalimumab (40 mg every other week) 25 mo</td>
<td>MTX (7.5 mg weekly) and prednisone (5 mg/d) 360 mo</td>
<td>NR</td>
</tr>
<tr>
<td>Bagalas et al. 2006 Greece (4)</td>
<td>60/F</td>
<td>Rheumatoid arthritis</td>
<td>Etanercept for 18 mo-24 mo before VL; Anakinra, for 2 to 3 weeks 6 mo before VL</td>
<td>NR</td>
<td>Steroids and cyclosporine for 7 yr</td>
</tr>
<tr>
<td>Koné-Paut et al. 2007 France (6)</td>
<td>9/F</td>
<td>Systemic juvenile arthritis</td>
<td>Etanercept (to cure an episode of MAS), then anakinra (1 mg/kg/d) 6 mo</td>
<td>NR</td>
<td>Steroids, MTX, cyclosporine.</td>
</tr>
<tr>
<td>Tektonidou and Skopouli 2008 Greece (7)</td>
<td>45/M</td>
<td>Psoriatic arthritis</td>
<td>Infliximab (3 and then 5 mg/kg) 3 yr</td>
<td>MTX, prednisolone for 3 yr</td>
<td>NR</td>
</tr>
<tr>
<td>Balato et al. 2008 Italy (9)</td>
<td>42/M</td>
<td>Psoriasis</td>
<td>Efalizumab (1 mg/kg/wk) 3 mo</td>
<td>NR</td>
<td>Cyclosporine for 1 mo</td>
</tr>
<tr>
<td>Garcia-Vidal et al. 2009 Spain (8)</td>
<td>55/M</td>
<td>Rheumatoid arthritis</td>
<td>Infliximab (Tot 40 mg/kg) 11 mo</td>
<td>MTX, steroids</td>
<td>MTX, steroids, azathioprine, cyclosporine for 10 yr</td>
</tr>
</tbody>
</table>

F, female; IFAT, immunofluorescent antibody test; L-amB, liposomal amphotericin B; M, male; MAS, macrophage activation syndrome; MTX, methotrexate; Neg, negative; ND, not done; NR, not reported; PCR, polymerase chain reaction; Pos, positive; VL, visceral leishmaniasis.

*Dosage of the drugs and duration of therapy are reported in those cases in which this information was noted in the original paper.*

There was no financial support for this research.

The authors have no conflicts of interest to disclose.

Address reprint requests to: Antonio Cascio, MD, PhD, UO Medicina Tropicale e Parasitologia, Policlinico “G. Martino”, Via Consolare Valeria n. 1, 98125 Messina, Italia. E-mail: acascio@unime.it.
Malnutrition and immunosuppression may reactivate latent *Leishmania* infection and, among human immunodeficiency virus/acquired immunodeficiency syndrome infected patients, the risk of clinical VL is increased 100 to 1000 times (12). Transplant patients living or traveling to areas where the disease is endemic are also at risk (13). Leishmaniasis is a granulomatosis disease and granulomas represent the tissue expression of the successful T-cell-dependent immune response (14). Analysis of the retrieved cases showed that the median duration of biologic drug treatment was 11 months (range, 3-36 months).

All 8 patients suffered from VL, and in 6 of them VL presented with the classical symptoms: fever, splenomegaly, and pancytopenia. In 1 case splenomegaly was not present (5); in another case leukocytosis instead of leukopenia was reported (6). Serology was positive in 4 of 5 in which this information was available. The search of *leishmania* amastigotes in bone marrow smears was positive in 7 cases. Culture of bone marrow was positive in 2 cases. Polymerase chain reaction on peripheral blood samples and/or bone marrow blood sample was positive in all 4 patients in which the test was performed. Of note, in the cases in which both serology and bone marrow microscopy were negative, laboratory diagnosis was made by polymerase chain reaction (7) or by a positive culture (6).

In all patients biologic drugs were stopped when VL was diagnosed, and only in 1 case was it reintroduced after VL was cured (3). VL was treated with a single cycle of liposomal amphotericin B in 4 cases, of meglumine antimoniate in 2 cases, and of amphotericin B deoxycholate in 1 case. In 1 case antileishmania therapy was not administered; nevertheless the patient was cured (9). All but 1 patient recovered from VL; that patient died from pneumonia and other opportunistic infection (4).

Considering the concomitant long-term use of other immunosuppressants, it is not possible to determine the

<table>
<thead>
<tr>
<th>LV symptoms</th>
<th>Amastigotes in bone marrow smears</th>
<th>IFAT</th>
<th>PCR</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever, asthenia, hepatosplenomegaly, pancytopenia</td>
<td>Pos</td>
<td>ND</td>
<td>ND</td>
<td>Meglumine antimoniate (840 mg/d for 28 d)</td>
<td>Cure</td>
</tr>
<tr>
<td>Fever, splenomegaly, and pancytopenia. Inflammatory markers increased</td>
<td>Neg; Pos a 2nd bone marrow aspirate</td>
<td>1:5120</td>
<td>Pos</td>
<td>Amphotericin B (0.7 mg/kg/d for 15 days, then 0.7 mg/kg every 15 d)</td>
<td>Cure—The patient was then treated for 1 yr with etanercept</td>
</tr>
<tr>
<td>Fluctuant fever with several peaks at 39°C, pancytopenia</td>
<td>Pos</td>
<td>1/160</td>
<td>Pos</td>
<td>L-amB (3 mg/kg/d for 5 d, and 3 mg/kg on d 10).</td>
<td>Cure—MTX was started again after 30 d Death due to severe pulmonary infection</td>
</tr>
<tr>
<td>Temperature up to 39.5°C every 3 to 4 days, pancytopenia, splenomegaly</td>
<td>Pos</td>
<td>Pos</td>
<td>ND</td>
<td>L-amB (4 mg kg/d, then, due to acute renal failure, 1 mg kg/d, which was gradually increased)</td>
<td>Cure</td>
</tr>
<tr>
<td>Fever, scarlet fever-like pruritic rash and hepatosplenomegaly, anemia, thrombocytopenia</td>
<td>Neg</td>
<td>NR</td>
<td>ND</td>
<td>L-amB steroids to cover the risk of MAS</td>
<td>Cure</td>
</tr>
<tr>
<td>High-grade fever, splenomegaly, acute reactive proteins, pancytopenia</td>
<td>Neg</td>
<td>Neg</td>
<td>Pos</td>
<td>L-amB (3 mg/kg/d for 5 d, and 3 mg/kg on d 20)</td>
<td>Cure</td>
</tr>
<tr>
<td>Intermittent fever, hepatosplenomegaly, pancytopenia</td>
<td>Pos</td>
<td>1:640</td>
<td>Pos</td>
<td>No anti-leishmania drugs were given</td>
<td>Cure</td>
</tr>
<tr>
<td>NR</td>
<td>Pos</td>
<td>NR</td>
<td>ND</td>
<td>Meglumine antimoniate</td>
<td>Cure</td>
</tr>
</tbody>
</table>
role played by biologic drugs in the development of leishmaniasis. Indeed, there are at least 7 cases of leishmaniasis that occurred in patients with rheumatoid arthritis or other rheumatologic diseases who were treated with classical immunosuppressive drugs (15-21).

Although pancytopenia or thrombocytopenia may be due to lupus or rheumatoid arthritis, dysplasia and lymphoma, or side effects of methotrexate or other drugs, the association of fever, asthenia, splenomegaly, and pancytopenia should prompt the search for VL in patients living in endemic leishmaniasis areas and treated with biologic therapies (3).

In immunocompromised patients, atypical forms of VL (for example, without splenomegaly or fever or with negative serology or with leukocytosis) may occur or mucocutaneous disease may develop in geographic regions where the typical mucocutaneous leishmaniasis is not endemic.

Antonio Cascio, MD, PhD
Tropical and Parasitological Diseases Unit
Department of Human Pathology
University of Messina
Messina, Italy

Maurizio Iaria, MD
Division of General Surgery
Department of Human Pathology
University of Messina
Messina, Italy

Chiara Iaria, MD
Department of Infectious and Tropical Diseases
“La Sapienza” University
Rome, Italy

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