Case Series

Efficacy and Safety of Secukinumab in Patients with Plaque Psoriasis and Latent Tuberculosis

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Keywords
Psoriasis · Secukinumab · Latent tuberculosis infection

Abstract
Upon the association of biologic treatments with reactivation of latent tuberculosis infection (LTBI), screening for *Mycobacterium tuberculosis* infection and anti-tuberculosis chemoprophylaxis in positive patients are required prior to biologic drug administration. Nevertheless, the risk of infection relapses associated with biologic drugs seems to be different. No cases of reactivation of LTBI have been observed in secukinumab-treated subjects, in contrast with clinical reports on the risk associated with anti-tumor necrosis factor α-based therapy. Twelve patients with moderate to severe plaque psoriasis eligible for systemic treatment and found to have LTBI received secukinumab without previous chemoprophylaxis initiation because of clinical contraindication for 10 cases and refusal by 2 patients. None of them had tuberculosis reactivation.

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Risk of Latent Tuberculosis Infection Reactivation

By blocking critical mediators of innate and adaptive immunity, biotherapeutics may carry a risk of increased opportunistic infections [1–5]. Upon the association of biologic treatments with reactivation of latent tuberculosis infection (LTBI), screening for Mycobacterium tuberculosis infection and anti-tuberculosis chemoprophylaxis in positive patients are required prior to biologic drug administration. Nevertheless, the risk associated with biologic drugs seems to be specifically related to the therapy. A complex interplay between the host and the intracellular pathogen M. tuberculosis occurs, and interference with some pathways may affect the safety of biologic treatments. Tumor necrosis factor (TNF) α has an established role in the host defense against intracellular infection by M. tuberculosis, documented clinically by the association of anti-TNFα therapies with reactivation of LTBI in psoriasis and rheumatoid treated patients [3–7]. TNFα contributes to balancing cell survival, apoptosis, and programmed necrosis in M. tuberculosis infections [5, 8]. TNFα-mediated apoptosis has a direct antimicrobial effect on intracellular bacilli. In addition, M. tuberculosis and antigens are packaged in apoptotic bodies, thereby eliminating the niche for mycobacterial growth [5, 8]. As a result, treatment with anti-TNFα antibodies may prevent apoptosis of M. tuberculosis-infected macrophages and enhance bacterial growth [5]. Elevated M. tuberculosis infection rates have been reported, in association with anti-TNFα therapies, in subjects with psoriasis and rheumatoid conditions [3, 4, 6, 7].

The role of IL-17A in host resistance to M. tuberculosis is more equivocal [9–13]. IL-17A-producing γδT cells and CD4+ T cells have been reported to exert either protective or pathologic roles during different phases of M. tuberculosis infection [9–15]. M. tuberculosis infections have been associated with increased IL-17A levels in in vitro human peripheral blood mononuclear cell cultures, in in vivo mouse models, and even in patients with acute tuberculosis [16–19]. Although early granuloma formation may be dependent on IL-17A, IL-17A-induced neutrophil recruitment may also increase pathological lesions and bacterial burden in chronic pulmonary infections [17, 20].

In contrast with clinical reports on the risk of infection associated with anti-TNFα treatment, no cases of reactivation of LTBI were observed in the pooled safety analysis of 10 phase II or III clinical trials in patients with moderate to severe plaque psoriasis treated with secukinumab, a fully humanized, monoclonal anti-IL-17A antibody [21]. The studies included in this analysis had a duration of 52 weeks, compared etanercept, a TNFα inhibitor, and secukinumab treatments, were placebo controlled, and included 3,993 subjects in total. Safety data of 5 secukinumab randomized, double-blind, placebo-controlled phase III clinical trials in 2,044 subjects with moderate to severe plaque psoriasis were pooled to identify subjects with LTBI or previously treated TB and examine rates of reactivation. In 132 subjects treated with secukinumab (median duration 364 days) with a history of treated pulmonary TB, no reactivation of LTBI was observed in 25 individuals who tested negative by interferon-γ release assay (and receiving no anti-TB medication) and in 107 subjects who tested positive for LTBI and hence received anti-TB medication [22]. In addition, secukinumab was well tolerated in combination with anti-TB therapy in subjects who began chemoprophylaxis for LTBI before randomization and no subjects discontinued secukinumab treatment while receiving chemoprophylaxis. Specifically, the incidence of elevated liver enzymes in isoniazid-treated patients was not increased during secukinumab treatment [23, 24].
Adalimumab, a TNFα inhibitor, and secukinumab effects were compared side by side in an *M. tuberculosis* three-dimensional human microgranuloma model. No reactivation of dormant *M. tuberculosis* was detected after anti-IL-17A treatment, in contrast to anti-TNFα treatment [22].

**Screening and Chemoprophylaxis**

Given the limited role exerted by the cytokines different from TNF, data from controlled trials, national registries of biologics, and post-marketing surveillance show that the risk of TB reactivation in patients receiving non-anti-TNF-targeted biologics is negligible [25]. Nevertheless, established guidelines in Europe recommend screening before starting any biologic therapy for psoriasis [26, 27]. Screening for LTBI is based on a diagnostic algorithm that incorporates medical history, chest radiography, and tests that evaluate immunologic response to *M. tuberculosis*. Several tests are available, with some limitations, such as purified protein derivative skin test using the Mantoux method and in vitro interferon-γ release assays [27]. When LTBI is demonstrated or suspected, starting with chemoprophylaxis, prior to biologic treatment for psoriasis, is recommended [26, 27]. The main contraindications remain hypersensitivity to isoniazid and/or rifampicin; pregnancy; concomitant therapy with hepatotoxic drugs; thrombocytopenia (if rifampicin is to be used); alcoholism (increased risk of fulminant hepatitis and peripheral neuropathy with isoniazid); severe alterations of hepatic function; concomitant use of drugs that interact with isoniazid such as benzodiazepines, anticonvulsants, oral anticoagulants, vitamin D, and valproate; malnutrition (increased risk of peripheral neuropathy with isoniazid); diabetes; chronic renal insufficiency (increased risk of peripheral neuropathy with isoniazid) [27]. Although screening for LTBI and chemoprophylaxis for positive patients are recommended prior to biologic therapy, and no distinction among classes or different drugs has been established, the question whether the screening procedures for LTBI would be necessary still needs an answer. Available evidence suggests that it is safe to use IL-17 inhibitors in patients with LTBI [28].

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Out of the twelve patients, 7 had moderate to severe plaque psoriasis and 5 palmoplantar psoriasis not controlled by topical treatment, with failure of systemic drugs (11 out of 12 subjects), and were found to have LTBI and received secukinumab without previous chemoprophylaxis because of clinical contraindication for 10 cases and refusal by 2 patients. Mean age was 55.9 years (range 29–77), 9 were males, and PASI at baseline ranged between 13 and 27. 60% of the patients had a scalp involvement of the psoriasis. Screening for LTBI was performed with purified protein derivative skin test. Failed treatments and contraindications to chemoprophylaxis are shown in Table 1. Secukinumab 300 mg subcutaneous was administered at weeks 0, 1, 2, 3, 4, and subsequently every 4 weeks. Patients were followed-up for 52 weeks, and checked every 8 weeks by clinical observation, chest X-ray, and inflammation marker evaluation (CRP, VES, and blood count). All patients attained either PASI90 or PASI 100 during the follow-up period, between week 5 and week 24, and improvement was maintained.
during the whole 52-week period of follow-up. No signs of tuberculosis reactivation were observed.

Conclusion

Although guidelines are lacking on this issue, pharmacological evidence and clinical data suggest that secukinumab is not associated with a risk for reactivation of LTBI, and that it could be safely used in patients with psoriasis, demonstrated to have LTBI, eligible for systemic treatment, and who cannot receive tuberculosis chemoprophylaxis.

Key Message

Clinical and preclinical investigations with secukinumab found no evidence of increased risk of *M. tuberculosis* infections.

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Statement of Ethics

The authors declare that the research was conducted in accordance with the World Medical Association Declaration of Helsinki. The patients have given their written informed consent to publish their case, including publication of images.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All the authors contributed to study design, data collection, and study execution as well as to manuscript preparation.
References


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Table 1. Failed treatments and contraindications to chemoprophylaxis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age</th>
<th>Previous failed treatment</th>
<th>Reason not to perform prophylactic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>37</td>
<td>Cyclosporine, methotrexate 15 mg/week</td>
<td>Hepatotoxicity was reported during treatment with methotrexate</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>77</td>
<td>Cyclosporine 3 mg/kg</td>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>68</td>
<td></td>
<td>Increased liver enzymes due to treatment with carbamazepine (400 mg ×3/die)</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>73</td>
<td>Acitretin</td>
<td>Autoimmune hepatitis in treatment with azathioprine 100 mg ×2/die and prednisone 10 mg/die</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>53</td>
<td>Cyclosporine</td>
<td>Antiviral therapy with high level of liver enzymes for treatment of HCV infection</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>63</td>
<td>Methotrexate</td>
<td>Pulmonary fibrosis and hepatotoxicity, methotrexate related</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>50</td>
<td>Acitretin, methotrexate</td>
<td>Refused the prophylactic therapy</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>64</td>
<td>Cyclosporine, methotrexate</td>
<td>Methotrexate hepatotoxicity</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>38</td>
<td>Cyclosporine</td>
<td>Alcoholism</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>29</td>
<td>Cyclosporine, methotrexate</td>
<td>Refused the prophylactic therapy</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>73</td>
<td>Acitretin 25 mg and methotrexate</td>
<td>Elevation of liver enzymes due to the statin therapy</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>46</td>
<td>Cyclosporine</td>
<td>Poor tolerability to prophylactic therapy</td>
</tr>
</tbody>
</table>