Sirs,

Low-dose interleukin-2 (ld-IL2) expands and activates Tregs lymphocytes, and could have a broad therapeutic potential in particular for autoimmune diseases (1). Indeed, in vitro IL-2 expands Tregs cells and blocks the differentiation of CD4+ naïve T cells into follicular helper or proinflammatory helper Th17 cells (2, 3). Considering the quantitative and functional deficit of Tregs cells in various autoimmune diseases, ld-IL2 therapy could be an interesting targeted therapy (4–11). Here we aimed to describe the off-label use, the efficacy and the safety of ld-IL2 therapy in patients with systemic autoimmune diseases.

This was a retrospective from Saint Antoine Department of Internal Medicine including patients treated with ld-IL2. Twelve patients received ld-IL2 treatment during the study time: SLE (n=5), Sjögren’s syndrome (n=6) and systemic sclerosis (n=2). The median age was 45 years (ranges, 37-59), all patients were women (Table I). The ld-IL2 was used for steroid-dependent or refractory disease and for intolerant or refractory to DMARDs disease in 6 cases (50%) each. The ld-IL2 was used with 5 days induction therapy at 1 M UI in 4 cases, followed by 1 M UI dose bi-monthly and in 8 cases bi-monthly without induction regimen. The median duration of ld-IL2 treatment was 6.5 months (range: 6–12). Combined steroids and/or other immunosuppressive drugs were used in 6 (50%) and 8 (66%) cases, respectively.

A significant improvement of subjective pain and subjective disease activity (VAS (0–100)) were noted at 6 months after ld-IL2 therapy; pain (from 80 [60–80] to 45 [18–50]; p=0.02), disease activity (VAS (0–100)) from 90 [80–100] to, 40 [15–50]; p=0.02) and fatigue (from 90 [80–94] to 60 [50–65]; p=0.15) (Table II, Fig. 1). Joint involvement was significantly less frequent under 6 months of ld-IL2 therapy: 8 (67%) at baseline vs. 3 (25%) cases at 6 months (p<0.046) and there was a trend for skin improvement (5 (42%) at baseline vs. 1 (8%) case at 6 months; p=0.08). The median amounts of prednisone equivalent were not significantly decreased under ld-IL2 (7 mg/day [from 5–10] at baseline to 5 mg/day [5, 0.14]) and C-reactive protein levels were stable.

Among 5 patients with SLE, all have SLE with skin and joint involvements, without any case of kidney, CNS or other severe form of SLE. All patients were previously treated and failed at least to the combination of low dose steroids and hydroxychloroquine, and 3 previously received methotrexate (60%). The median SLEDAI score have significantly decreased from M0, 4.00

<table>
<thead>
<tr>
<th>Disease</th>
<th>Systemic lupus erythematosus, n (%)</th>
<th>Sjögren’s syndrome, n (%)</th>
<th>Systemic sclerosis, n (%)</th>
<th>Organ damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin, n (%)</td>
<td>5 (42%)</td>
<td>6 (50%)</td>
<td>2 (17%)</td>
<td></td>
</tr>
<tr>
<td>Joints, n (%)</td>
<td>8 (67%)</td>
<td>2 (17%)</td>
<td>2 (17%)</td>
<td></td>
</tr>
<tr>
<td>Peripheral nervous system, n (%)</td>
<td>2 (17%)</td>
<td>2 (17%)</td>
<td>2 (17%)</td>
<td></td>
</tr>
<tr>
<td>Digestive, n (%)</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
<td>1 (8%)</td>
<td></td>
</tr>
<tr>
<td>Heart, n (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Lung, n (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Kidney, n (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

Medications

- Corticosteroids, n (%) 6 (50%)
- Corticosteroid amounts (mg/day), median (range) 7 [5.0–9.8]

**Fig. 1.** Clinical parameters at baseline, under 3 and 6 months of ld-IL2 therapy.

[4.00–6.00] to M3 at 0.00 [0.00–2.00] and M6 at 0.00 [0.00–2.00] (Test de Friedman p=0.012). Complete skin and joint responses were noted in all cases under 6 months of ld-IL2, and 1 patient discontinued the steroids.

In patients with systemic sclerosis (one diffuse and one limited SSc), ld-IL2 was ini-
Letters to the Editors

Re: Low-dose interleukin-2 therapy for autoimmune and inflammatory diseases.

In this study we describe the use of off-label ld-IL2 therapy in patients with autoimmune systemic diseases and mild active disease. Among 6 patients with Sjögren’s syndrome, two patients (33%) had SSA/SSB autoantibodies and focus score >1 was noted in 5 patients (83%). Extraglandular features were present in all patients, with joint involvement (arthralgia without arthritis) in 5 patients (83%) and a multiple-sclerosis like central nervous system involvement in one case. The median number of tender joints significantly decreased from 10.0 [8.0–12.0] at baseline to 4.0 [0.0–7.0] at 3 months and 4.0 [0.0–4.0] at 6 months (Test de Friedman: \( p=0.024 \)). Under ld-IL2, joint complete improvement was noted in 2 cases (40%). The median ESSDAI score was not significantly changed under ld-IL2 therapy: 2 (range: 1–4) at initiation and 2 (range: 1–3) under 6-month ld-IL2 therapy (\( p=0.368 \)). During the median follow up of 6.5 months (range: 6–12), there was 5 adverse events without any severe case and none needed the ld-IL2 discontinuation. The adverse events were reactions at the site of infusion (n=4) and one episode of flu-like syndrome. In this study we describe the use of off-label ld-IL2 in patients with not-severe and mild active autoimmune diseases. Indeed, none from our patients with SLE, Sjögren’s syndrome and systemic sclerosis have a life-threatening organ involvement, and all were mostly concerned by joint and skin involvement. In this particular subset of patients, independently from the underlying autoimmune disease, a global improvement in subjective disease activity and pain perceptions was significantly noted under 6-month ld-IL2 therapy. Our data are consistent with previous reports, and in particular data from the TRANSREG study (4).

In conclusion, our study showed that ld-IL2 therapy allows an improvement of patients with autoimmune systemic diseases and mild active disease.

O. AL-TABA\(^1\), MD
S. HAMBOUN\(^1\), MD
C. LEPLAY\(^1\), PharmD
O. FAÎN\(^1\), MD, PhD
D. KLATZMANN\(^2\), MD, PhD
A. MEKINIAN\(^3,4\), MD, PhD

\(^1\)Department of Internal Medicine, \(^2\)Department of Pharmacy, Sorbonne Université, Assistance Publique – Hôpitaux de Paris, Hôpital Saint-Antoine, Paris;
\(^3\)Inflammation-Immunopathology-Biotherapy Department (i2B), AP-HP, Pitié-Salpêtrière Hospital, Paris;
\(^4\)Immunology-Immunopathology-Immunotherapy (i3), Sorbonne Université, INSERM, Paris, France.

Please address correspondence to:
Arsène Mekinian,
Department of Internal Medicine, AP-HP, Hôpital Saint Antoine, 75012 Paris, France.
E-mail: arsene.mekinian@aphp.fr
Competing interests: none declared.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2022.

References