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Case Series

The role of interleukin-17 in spondyloarthropathies and systemic lupus erythematosus: Two clinical cases in real

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Abstract

Spondyloarthropathies are known to affect the interleukin (IL)-17 activation pathway as a basis of their pathology, as is apparent from the literature. Recent studies established the vital role of IL-17 in the treatment of Systemic Lupus Erythematosus (SLE). This article aims to demonstrate the efficacy and safety of IL-17 in the treatment of both spondyloarthropathies and SLE by presenting two cases.

The first case concerns a 30-year-old woman who was initially diagnosed with SLE. In the course of the disease, she developed spondyloarthritis and genital psoriasis. She was initially medicated with secukinumab but maintained severe genital psoriasis, the reason it was changed to ixekizumab with great improvement.

The second case refers to a 40-year-old woman who previously had spondyloarthropathy with D12 enthesitis and sacroiliitis. Initial treatment with adalimumab led to a lupus-like syndrome, with persistent high systemic inflammatory response syndrome and extreme fatigue. Because of the recrudescence of axial complaints, secukinumab was started and the patient evolved with a global clinical response.

Thus, the authors present two cases of spondyloarthropathy and SLE that document the efficacy and safety of IL- 17 blockers, which can lead to the incorporation of these agents in the treatment of SLE.

Introduction

Spondyloarthropathies, including Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), and Crohn's disease, have been known to influence the interleukin (IL)-17 activation pathways at the base of their pathology.

IL-17A is a homodimeric disulfide-linked glycoprotein with a potent inflammatory effect. The IL-17A signal influences various cells and improves the secretion of other pro-inflammatory mediators (such as Tumor Necrosis Factor (TNF), IL-6, and IL-1) as well as colony-stimulating factors [1]. IL-17 protects the host against pathogens and functions as an epithelial barrier (such as the skin or intestine). The effects of IL-17 at the bone level are well documented, both for its action on osteoclasts and osteoblasts, as well as on enthesitis. Entheseal inflammation, a relevant component in PsA or AS, could be a result of the clonal expansion of IL-17-producing Th17 in male mice [1]. Furthermore, clinical evidence demonstrates the presence of IL-17-producing cells in synovial tissues. Similarly, an increase in the amount of IL-17-producing cells and serum levels at the initial stage of the disease has been greater in patients with AS compared with healthy patients; a positive correlation is observed between serum IL-17 concentrations and disorder activity in AS [1].

Thus, the use of specific antibodies for IL-17 (such as secukinumab or ixekizumab) is increasingly being perceived to improve inflammation in patients with PSA. Application of IL-17 blockers for this purpose has already been proposed

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in the Assessment in AS and the European League Against Rheumatism (EULAR) guidelines [2]. In this study, compared with placebo, secukinumab was clinically more effective and reduced inflammation (by blood biomarkers and imaging). Subsequently, the efficacy of secukinumab was proved in MEASURE studies 1 and 2 [3,4].

The most recently approved drug, ixekizumab, has an efficacy and safety profile similar to secukinumab. COAST-V was the first study that was launched for ixekizumab, and COAST-W [5,6] was the second study in which the efficacy of ixekizumab was compared with that of the placebo (the first study had an additional comparator arm with adalimumab). In both these studies, ixekizumab demonstrated a better clinical response.

Unfortunately, no information can better prove the efficacy or safety of IL-17 blockers against TNF inhibitors or contrariwise, as demonstrated in a face-to-face trial published in 2020 [7]. Another point in favor of the use of IL-17-blocking drugs instead of the use of TNF inhibitors is the well-documented induction of lupus-like syndromes described in patients treated with TNF inhibitors [8].

IL-17 blockers have demonstrated adequate efficacy against SLE in terms of its pathology in recent years. Increased IL-17 expression has been reported in animal models, such as the BXD2 mouse, an animal with lupus that spontaneously presents joint and renal involvement, as well as serum antibodies [9], this model presents high serum levels of IL-17 and an increased number of IL-17+ cells in the spleen with the formation of germinal centers [10]. In a real-life setting, as observed in spondyloarthropathies, T cells that produce IL-17 appear in the plasma of patients with SLE [11,12]. Several studies have reported that the plasma level of IL-17 correlates with the severity of SLE and disease activity in SLE [12-16], which is similar to spondyloarthropathies.

IL-17 appears to reduce the manifestations of lupus in animal models [10]. These effects have not yet been explored in clinical trials with humans, with the exception of lupus nephritis.

Thus, given the current scientific evidence, the authors present two cases with spondyloarthropathy and SLE that document the efficacy and safety of IL-17 blockers. We highlight that verbal consent was obtained from patients presented in this article.

Case presentation

Case one

The first case is a 30-year-old woman with a family history of rheumatoid arthritis and cutaneous psoriasis. Her initial clinical symptoms were intense fatigue, photosensitivity, polyarthritis of small joints (with associated dactylitis) and pathological alopecia. She was analytically positive for antinuclear antibodies, with a titer of 1/1280. She was suspected of SLE and thus started on hydroxychloroquine and nonsteroidal anti-inflammatory therapy.

The disease evolved with severe enthesitis in December 2018, with new cutaneous psoriasis and anemia of inflammatory characteristics. Spondyloarthritis was assumed in a patient undergoing high-dose anti-inflammatory therapy at this time. Thus, following a team discussion, IL-17 blocker (secukinumab) was started in February 2019 (150mg monthly). After 2 months of treatment, cutaneous psoriasis and enthesitis improved.

However, gastrointestinal intolerance to antimalarial and recrudescence of cutaneous psoriasis was verified after 5 months of therapy; therefore, the dose of the initiated drug was increased to 300mg every month. Topical therapy was still required for perineal psoriasis as the patient maintained local discomfort and recurrent and new-onset sacroiliitis even after 3 months of dose increase. Since antimalarial drugs are associated with plaque-type psoriasis exacerbations, hydroxychloroquine treatment was suspended. In May 2020 (15 months after starting anti-IL17 therapy), peripheral arthritis relapsed, maintaining only partial cutaneous remission; thus, the treatment was combined with cyclosporine, and improvement in cutaneous psoriasis was maintained, but the complete improvement was not noted. Therefore, in September 2020, we proposed that ixekizumab (induction scheme 160mg, followed by 80 mg monthly) be administered to the patient with genital psoriasis having SLE and psoriatic spondyloarthropathy. We combined cyclosporine in a weaning scheme (to avoid the rebound effect) with ixecizumab and, after three months of therapy, there was an improvement in enthesitis, inflammatory markers, and genital psoriasis.

Case two

The second case is a 40-year-old woman with spondyloarthropathy; she had D12 enthesitis and sacroiliitis (with only radiological, grade II) with positivity for HLA B27. She completed three cycles of infliximab (5mg/kg monthly) with an initially complete clinical response but relapsed in 5 months with the need to restart therapy. Allergic reaction with febrile peak and inflammation at the infliximab administration site had led to its suspension. Given frequent refractoriness (new flare in <2 months), the medication was changed to adalimumab (40mg every 15days). We highlight an episode of erythema nodosum in July 2010, resolving with corticotherapy and colchicine.

She remained in clinical remission from the joint component, although extreme fatigue appeared to be associated with persistent high systemic inflammatory response syndrome; furthermore, in 2014, persistent mild normocytic normochromic anemia was assumed to fit into chronic diseases. In December 2015, new immunological evaluation was required, and antinuclear antibodies in 1 of 320 titers with nucleolar-mottled pattern and positive Ku antibodies were found in a patient with positive anti-cardiolipin and anti-beta-2 glycoprotein 1 (both Immunoglobulin G, IgG) antibody background (framed in analytical anti-phospholipid antibody syndrome, without clinic). In addition, since her diagnosis (2010), she was on acetylsalicylic acid and had an episode of erythema nodosum. Thus, the patient was diagnosed with a lupus-like syndrome associated with adalimumab, with a suspended TNF inhibitor.

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In a 2016 analytical study, positive anti-double-stranded DNA (dsDNA) emerged, and hydroxychloroquine was thus initiated; thus, a diagnosis of SLE was made.

Despite the clinical systemic improvement (fatigue), the recrudescence of axial complaints was observed, which was not previously verified; therefore, biological therapy was restarted with the administration of secukinumab (150mg in an induction scheme for 3 months, monthly, and finally every 6 weeks) in December 2016. The patient remains on therapy to date with good clinical and immunological responses. Table 1 demonstrates the analytical evolution over the disease course.

Discussion

The first case demonstrates the role of IL-17 blockers both in spondyloarthropathies and SLE, as well as in genital psoriasis. Therefore, ixekizumab can be used for the treatment of psoriatic arthritis because its efficacy has already been reported in some clinical trials, as documented in the original article "*Treatment of psoriatic arthritis complicated by systemic lupus erythematosus with the IL-17 blocker secukinumab and an analysis of the serum cytokine profile*" published by Sato, et al. in 2020 in Modern Rheumatology Case Reports [17]. Drug safety was also evident with low incidence rates of adverse events at <10% (only severe adverse events were recorded at 6.0 per 100 patient-years) and death at 0.3 per 100 patient-years [17]. This has also been proven for patients with inadequate response to TNF inhibitors, including clinical improvement beyond 1 year of treatment as documented in the SPIRIT-P2 study (Genovese, et al. Rheumatology, 2018) [18]. Regarding genital psoriasis, the effects of ixekizumab on moderate-to-severe plaque psoriasis have been increasingly documented [19]. This is consistent for both symptoms and sexual activity, as published by Yosipovitch, et al. in The Journal of Sexual Medicine (2018) [20].

Regarding spondyloarthropathies (present in both cases), IL-17 blockade is safe for short-term treatment (especially in its axial form), although long-term data should be further studied. IL-17 blockers did not increase the frequency of achieving the leukocyte series or appearance of fungal infections when these only slightly occurred [1]. No association was observed between the onset of mycobacterial infection and the blockade of biological activity of IL-17A in humans [21]. These adverse events were not observed in patients presented in this study. The authors highlight the importance of therapy switch in a patient with axial complaints, namely, with enthesitis, as already well documented in the literature [1].

Regarding the safety profile of the use of IL-17 blockers in SLE, there are no published studies yet; however, two clinical trials are ongoing: one that focuses on symptomatic relief in lupus but in its discoid form and another on active lupus nephritis (NCT03866317 and NCT04181762). These could be the guiding principles for concrete studies in SLE.

The cases presented in this study show the potential efficacy of IL-17 blockers in SLE, namely, when in association with spondyloarthropathies, as in the case reported in the article published in 2020 by Sato, et al. [17]. This article documented the case of a patient with an initial diagnosis of psoriasis, which progressed to psoriatic arthritis and was later diagnosed with SLE (nephritis and marker elevation – positivity of antinuclear antibodies and anti-ds DNA antibodies and lymphocytopenia). It was initially treated with methotrexate, later with adalimumab, without obvious effects. Adjusted therapy with secukinumab improved cutaneous, articular, and renal conditions without reducing the markers, the generally considered a good result. This publication is similar to those in our cases.

Table 1: Analytical evolution along the course of the disease in case 2.

Parameter	RV* and units	Diagnosis (2010)	July 2010	December 2010	January 2014	December 2015	March 2016	December 2016	August 2020	April 2021
Hemoglobin	12–15 g/dL	12.2	11.7	11.6	11,6	10.8	10.4	11,1	12.2	---
Erythrocyte sedimentation rate	0–19 mm	24	28	44	69	77	86	59	33	27
C-reactive Protein	0–5, mg/L	1.69	---	3	17,90	11.81	12.48	5.3	0.56	0.83
Antinuclear Antibodies	<1/80	Negative	---	---	---	1/320 titer with nucleolar- mottled pattern	---	---	---	---
Anti-double stranded DNA	<15 UI/mL	---	---	---	---	---	37	39	11	14
Anti- Cardiolipin IgM	<20 MPL/mL	12.2	24.4	---	---	---	---	---	---	---
Anti- Cardiolipin IgG	<20 GPL/mL	51	55.6	---	---	---	---	---	---	---
Anti-Beta-2 Glycoprotein 1 IgM	<20 U/mL	7.6	5.1	---	---	---	---	---	---	---
Anti-Beta-2 Glycoprotein 1 IgG	<20 U/mL	27.1	21.5	---	---	---	---	---	---	---
Anti-Ku antibodies		---	---	---	---	Positive	---	---	---	---

*RV - Referenced Value

Description: As can be seen, after the introduction of secukinumab the inflammatory parameters decreased and there was a reduction in the titer of anti-dsDNA, contributing factors for the control of the disease.

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Conclusion

Thus, the two cases presented here are, in a way, in line with already abundantly reported data on the efficacy of IL-17 blockade in spondyloarthropathies. Case 1 also adds to the relative efficacy in specific genital psoriasis. Case 2 even shows refractoriness to TNF inhibitor and clinical improvement after introducing IL-17 blocker. In both cases there were no adverse effects or complications associated with the use of IL-17 blockers. Despite having satisfactory results in animal models, studies of the efficacy and safety of IL-17 blockers in SLE in real life are urgently required. However, clinical trials that may promote the on-label use of these drugs are ongoing, and they can allow their introduction in future guidelines. With this article, the authors consider that its use in our patients could be a warning for other centers to explore this issue.

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