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Uveitis – Possible adverse reaction to secukinumab in a patient with rehabilitation treatment for ankylosing spondylitis (case report)

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Abstract

Introduction. Ankylosing spondylitis (AS) is a chronic inflammatory disease that predominantly affects the spine, but also peripheral joints, the major characteristic of the disease being the early involvement of the sacroiliac joint. The most common extra skeletal manifestations are ocular disorders and appear to 25-30% of the patients, being more frequent to HLA B27 positive patients. Episodes of previous acute uveitis, known as iridocyclitis, may precede or may occur during or after inflammatory joint manifestations. **Materials and Methods.** We present a 41-year-old patient diagnosed 11 years ago with Ankylosing spondylitis, on its axial form, without extra-articular manifestations, periodically treated with anti-inflammatory drugs and balneary treatment, but with inefficient clinic and biological response. Since November 2019, his treatment with Secukinumab, started to improve the clinic and paraclinical symptoms. Secukinumab is a fully human monoclonal antibody, the first care that selectively targets IL-17A, an essential cytokine treatment that produces inflammation, and bone remodeling, characteristic of AS. **Results.** In January 2020, the patient presents increased pain and redness in the right eye area, subsequently diagnosed as anterior acute uveitis. **Conclusions.** This anterior acute uveitis, may be an extra-articular manifestation in the context of the natural evolution of the disease insufficiently controlled by the recently introduced therapy, or it may be an adverse reaction to Secukinumab, being known that the optic malfunction is a less common side effect.

Keywords: *Ankylosing Spondylitis, Uveitis, Secukinumab, extra-articular manifestations, rehabilitation, treatment,*

Introduction

Ankylosing Spondylitis (AS) is a part of the spondyloarthropathy group and it is a chronic inflammatory disease that predominantly affects the spine. On the mixed forms of the disease, it can also affect the peripheral joints, in the form of an asymmetric oligoarthritis of the lower limbs.

The major characteristic of the disease is the early involvement of the sacroiliac joints.

The AS chronic inflammatory process is localized both skeletal and extra skeletal and it is responsible for the occurrence of erosions and subsequent, bone proliferation (1,2).

For a long time, the AS diagnosis was formulated based on the criteria from New York (1966), modified in 1984 (table 1). Based on those criteria, the diagnosis was primarily based on the presence of sacroiliitis on standard radiographic examination, which had implications for when the diagnosis could be specified. The radiographic visualization of sacroiliitis is belated, many studies showing that between the time of the first clinical symptom occurrence and the encountering of the all New York diagnostic criteria can take around 8-10 years (3).

AS is defined, if the fulfillment of the radiological criterion is associated with at least one clinical criterion. In the case of the patients who did not meet enough criteria for the diagnosis of one disease, but who could be integrated in the spondyloarthritis group, Zeidler (1992) suggested the term of undifferentiated spondyloarthritis.

Undifferentiated spondyloarthritis stands for either an early stage of a defined spondyloarthritis, whose clinical picture will develop later, or a forme fruste of a defined spondyloarthritis.

The ASAS Classification criteria that confirm the diagnosis for axial Spondyloarthritis.

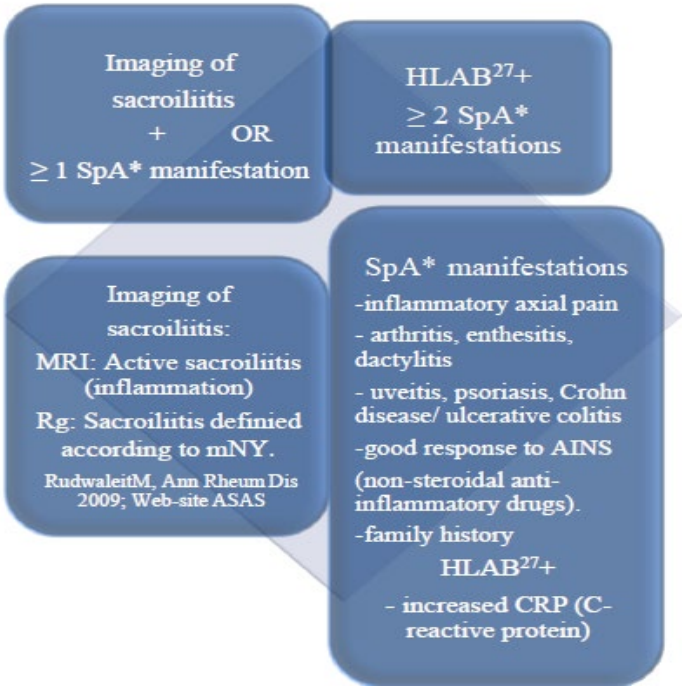


Fig. 1. ASAS Classification criteria - Axial Spondyloarthritis

Table 1. Diagnostic criteria for Ankylosing Spondylitis (Van der Linden col, 1984)
I Clinical criteria
a) Low back pain and morning stiffness lasting more than 3 months that improves with physical exertion and does not disappear at rest.
b) Limiting the movement of the lumbar spine in the sagittal and frontal planes
c) Limiting chest expansion as against the normal corrected values
II Radiological criteria
Sacroiliitis > 2nd grade bilateral or 3rd – 4th unilateral Sacroiliitis

The disease has a long evolution with exacerbations and spontaneous or therapeutic remissions. The earlier the commencement of the disease, the more severe the evolution. The presence of extra articular manifestations such as acute irritation, secondary amyloidosis or a treatment-resistant evolution obscures the prognosis of the disease.

The therapeutic objectives involves the relief of pain, reducing the inflammation, maintaining the mobility of the spine and preventing ankylosis.

Recommending number 5 ASAS/EULAR4 for axial AS management draws attention on the fact that the non-steroidal anti-inflammatory drugs (AINS), including the coxibs, represent the first line of treatment for the patients with AS with pain and stiffness. However, the cardiovascular, gastrointestinal and renal risks should be considered when prescribing AINS (non-steroidal anti-inflammatory drugs).

The Anti-TNFα biological therapy has changed the prognostic of the patients with AS. There are specified indications of the ASAS group of experts regarding the use of the biological therapy in axial AS and SpA. The anti-TNFα agents are: anti-TNFα monoclonal antibodies (Infliximab, Adalimumab, Golimumab, Certolizumab) and TNFα soluble receptor (Etanercept)

Recently, it was approved a new anti IL-17 biological agent, Sekukinumab. In AS, the biological agents are used in mono- therapy. Their early use, before the appearance of bone erosions can prevent the appearance of syndesmophytes and other osteoproliferations. The biological agents must be closely monitored to prevent the main adverse effects (risk of infection, risk of developing neoplasms, risk of deterioration of heart failure, risk of demyelinating disease, risk of allergic reactions, risk of immunogenicity) (5).

Objectives

The purpose of this case presentation is to demonstrate the importance of interdisciplinary in therapeutic decision-making, especially in the case of a newly introduced drug when the issue of a possible adverse reaction occurs.

Materials and methods

We present the case of a patient named R.C., a 41- years-old person, diagnosed 11 years ago with axial ankylosing spondylitis, IIIrd stage radiological, having the positive Antigen HLA B27, with no history of extra-articular manifestations.

When the first examination was done (March 2019), the patient was hospitalized at the Balneal and Rehabilitation Sanatorium of Techirghiol for rehabilitation treatment.

The clinical examination showed a young patient, with significant modifications of the vertebral statics (accentuation of dorsal kyphosis, lumbar rectitude) and of the vertebral dynamics (cervical rotations that are limited analgesic, cirtometric index = 1cm, Schober test = + 2cm).

Paraclinical: marked biological inflammation syndrome (VSH 48 vs 15mm/h, PCR 24 vs. 5mg/L).

BASDAI score > 6 persistently, VAS (visual analogue scale) = 8, daily necessity of AINS (non- steroidal anti-inflammatory drugs), moderate functional deficit affecting the quality of life on the professional level, the patient being a police officer.

From the moment of diagnosis and up to date, the patient has done treatments with various AINS (non- steroidal anti-inflammatory drugs), pain relievers and Balneology & Physiotherapy periodically (at 6 months), but with an unsatisfactory clinical and biological response.

In November 2019, according to the initiation protocol criteria of the biological therapy, we initiated the treatment with Secukinumab (Cosentyx), 150 mg / week subcutaneously for 4 weeks (1 injection in week no. 0, 1, 2 and 3)

subsequently, 150 mg/ month subcutaneously (1 injection in each month starting with week no. 4) with significant improvement of the clinical and paraclinical symptoms, even after the first 6 weeks of initiation.

The biological therapy was initiated in accordance with the national protocol of 2017, the patient failing at least 2 AINS (non-steroidal anti-inflammatory drugs) at maximum or tolerated doses for a period of 6 weeks each, the form of the disease being active (BASDAI> 6 and increased values of VSH și PCR), we have performed the mandatory screening for pulmonary tuberculosis, consisting of Quantiferon and chest X-rays and also we have determined the liver viral markers.

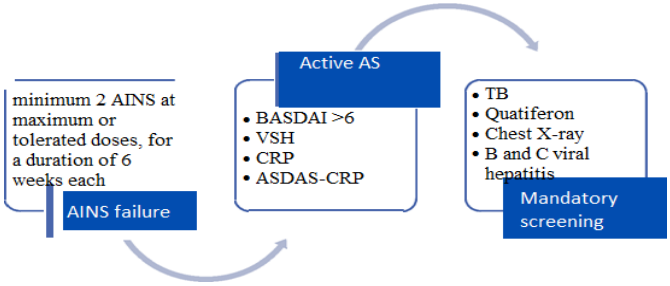


Fig 2. National Protocol 2019

As predictors of the response to the treatment with biological therapy, following an inadequate response to AINS (non-steroidal anti-inflammatory drugs), we list: young patients, males, the early diagnosis, initially increased PCR, high BASDAI, low BASFI, MRI inflammation and positive HLAB27.

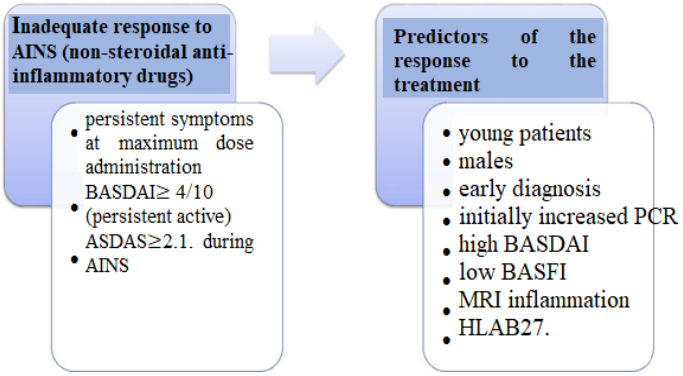


Fig. 3. Predictors of the response to the treatment

Cosentyx is an anti IL17A monoclonal antibody completely human, being the first treatment that selectively targets IL17A, being an essential cytokine that produces inflammation, enthesitis and bone remodeling characteristic of AS.

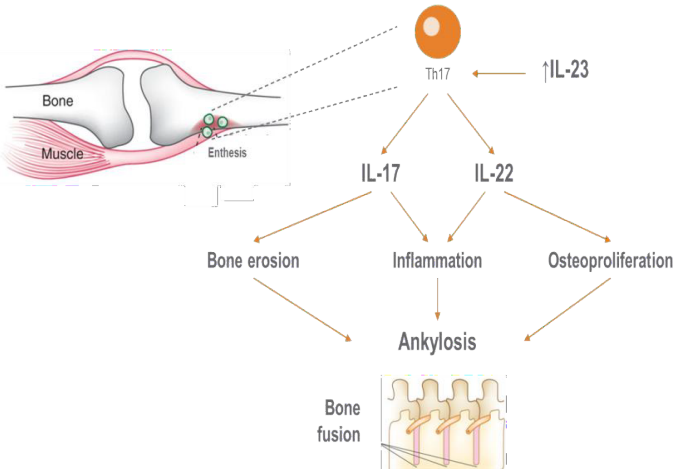


Fig. 4. IL17A Pathophysiology

IL17A may play an essential role in bone proliferation in AS, because bone remodeling may be related to the IL17A effect, which interferes with osteogenesis and bone homeostasis leading to osteoclast formation. The inflammatory enthesitis is mediated by resident T cells, which are producing IL-17A, being linked to the formation of new bone6.

At 6 weeks after initiating the treatment with Secukinumab, the patient showed significant improvement in clinical and paraclinical symptoms: VAS scale was 4 versus 8, BASDAI score = 4.0 versus 8.2, PCR = 8 versus 24 mg / L when the treatment was initiated. The patient no longer needed AINS (non-steroidal anti-inflammatory drugs) and the quality of life increased both professionally and personally.

In January 2020 (8 weeks after starting with Secukinumab), the patient presented with severe pain and redness in the right eye, later diagnosed as previous acute uveitis (Fig 5).

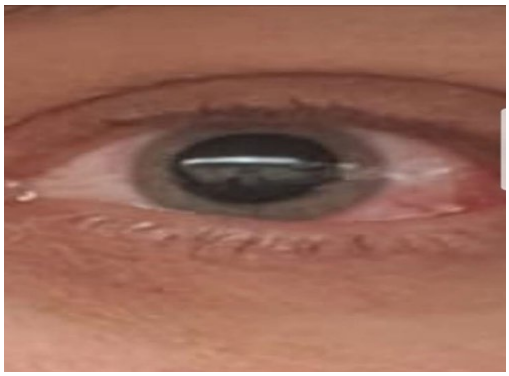


Fig. 5. January 2020

The image shows the changes in iridocyclitis, when the patient was already following the treatment recommended by an ophthalmologist.

What issues are being raised at the moment? Is it an acute episode of anterior uveitis as an extra articular manifestation in ankylosing spondylitis? Or is it an adverse reaction to Secukinumab treatment? Can we consider AS a systemic disease?

This has become a certainty given the multitude of extra articular manifestations described in spondylarthritis, among which we can list: heart, skin, lung, kidney, gastrointestinal, osteoporosis, neurological and ocular impairment.

Fig. 6. Extra-articular manifestations in SpA

In the case of the ocular impairment among the patients with spondylitis, uveitis is the most common form of the disease, being described in 20-30% of cases, It can be anterior (affecting the iris and / or the ciliary body), intermediate (affecting the vitreous humor and / or the peripheral retina), posterior (affecting the choroid and / or retina) or panuveitis affecting all the above components.
Conjunctivitis (inflammation of the conjunctival membrane) and episcleritis (inflammation of the episclera) are two other possible ocular impairments in the extra articular manifestations of spondylarthritis.
In a percentage of 25-40% in patients with spondylarthritis, they have more than one episode of previous acute uveitis, the incidence being higher in the patients with HLA B27 positive. There is no clear relationship with the joint activity of the disease. The most common complication is the appearance of synechiae. Under treatment, the attacks decrease after 2-3 months and in the absence of treatment, they progresses rapidly to blindness, which can be irreversible.

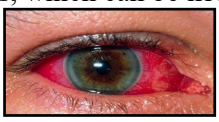
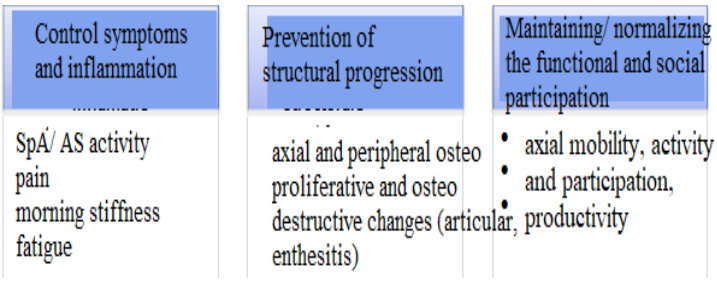


Fig. 7. Acute Anterior Uveitis

The posterior uveitis associated with the psoriatic arthritis or enteropathic spondylitis is more frequently chronic and bilateral and often involves the posterior elements.
The treatment is individualized according to the current manifestations of spondyloarthritis (axial, peripheral, extra articular), general clinical status (age, sex, comorbidities, concomitant medication, psychosocial factors), as well as current symptoms (clinical picture and prognostic factors negative).

	Any Secukinumab 150 mg s.c. *(N = 263)	Any Secukinumab 75 mg s.c. *(N = 179)	Accumulated Secukinumab *(N = 360)
Exposure (days), average (DS)	1085,2 (699,27)	1314 (523,72)	1446,1 (631,21)
Death[#], n (%)	1 (0,4)	2 (1,1)	3 (0,8)
Interruption because of RA, n (%)	23 (8,7)	13 (7,3)	36 (10,0)
Any RA, n (%)	204 (77,6)	154 (86,0)	319 (88,6)
Any serious RA, n (%)	33 (12,5)	36 (20,1)	66 (18,3)
The most frequent RA, n (EAIR)			
Nasopharyngitis	63 (10,6)	45 (8,6)	102 (9,3)
Headache	29 (4,2)	26 (4,5)	54 (4,3)
Diarrhea	30 (4,3)	26 (4,7)	53 (4,3)
Upper respiratory tract infection	21 (2,9)	29 (5,3)	49 (3,9)
RA of interest, n (EAIR)			
Crohn Disease	2 (0,3)	5 (0,8)	7 (0,6)
Infections with *Candidiasis*	3 (0,4)	2 (0,3)	5 (0,4)
Ulcerative colitis	1 (0,1)	1 (0,2)	2 (0,1)
MACE	4 (0,5)	5 (0,8)	9 (0,6)
Malignancies	5 (0,6)	2 (0,3)	7 (0,5)
Uveitis	**16 (2,1)**	**10 (1,6)**	**24 (1,8)**

Ocular impairment in spondylitis can be acute, it is unilateral, with photophobia, blurred vision, hyper lacrimation and with a duration of 6-12 weeks or it can be chronic, being bilateral, recurrent and with posterior synechiae, cataracts, hypopyon, glaucoma and vision loss (7).
Taking into consideration the ASAS/ EULAR recommendations, the main objective in the treatment of spondyloarthritis is to maximize the quality of patients' life on long term by controlling the symptoms and the inflammation, preventing structural progression and maintaining or normalizing the functional and social participation8. The therapeutic target is the clinical remission or the low-activity disease status. It requires a multidisciplinary approach (9-11).



Fig, 8. ASAS/EULAR Recommendations

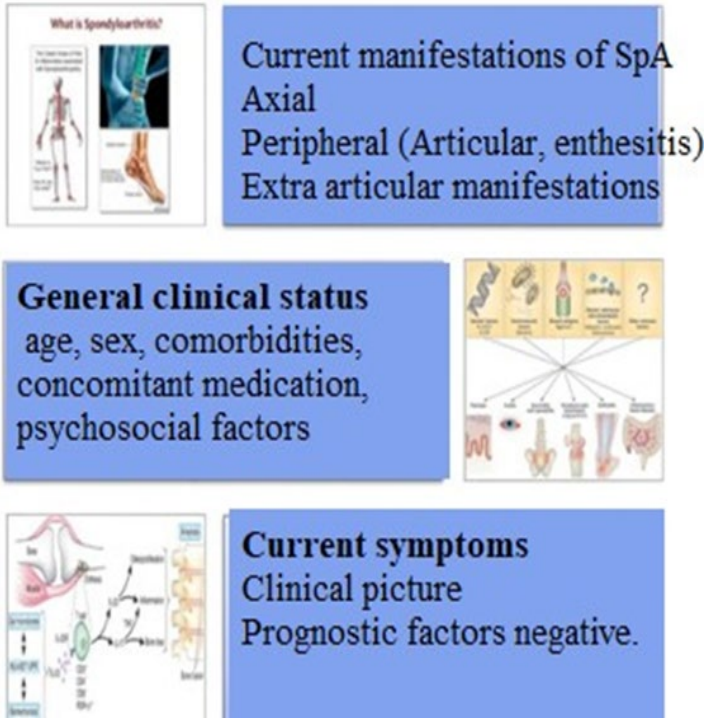


Fig.. 9. Choosing the therapeutical strategy

According to the studies, the medication administered to the patient, respectively Cosentyx, has a favorable and constant safety profile for a period of 5 years. The study shows that uveitis was described in a percentage of 16% as an adverse reaction to Secukinumab at a dose of 150 mg (recommended dose in AS) 6.

Back to the case. The therapeutic attitude was as follows: through an interdisciplinary consultation, the ophthalmologist properly treated the previous episode of acute uveitis until complete remission and without its recurrence in the next 6 months. We continued the treatment with Secukinumab according to the administration protocol, considering the episode of unilateral uveitis as an extra articular manifestation in the context of ankylosing spondylitis, the disease being insufficiently controlled by the recently initiated treatment.

Conclusions

The peculiarity of this case is that in a patient with AS for more than 10 years, without extra articular manifestations until that moment, the episode of iridocyclitis occurred shortly after the initiation of the treatment with an anti-IL biological agent.

Spondyloarthropathies are systemic diseases with genetic substrate, with auto inflammatory and autoimmune elements; they are directed by cytokines such as: TNF, IL 17, IL 23, etc.; they have articular, cutaneous, digestive, pulmonary, renal manifestations, etc.; the extra articular manifestations are frequent and important in premature and established SpA; the clinical and imaging examination (MSUS, colonoscopy, X-ray, etc.) require a multidisciplinary approach; the treatment may be common or specific according to each case.

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