CLINICAL PRACTICE

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Ankylosing spondylitis and cardiovascular risk – Case report

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Abstract: *Introduction: Ankylosing spondylitis (AS) is a chronic progressive inflammatory disease of the axial skeleton and peripheral joints associated with HLA B27 antigen and with the predominance of the male gender (with an average between 20 and 30 years old).*
Case presentation
A 48 years old male patient was admitted to our clinic, having a long history regarding this disease since he was 16.
This patient has switched 3 therapies with anti TNF alpha agents until now, and we hope to obtain a good response for a long time.
During the treatment with Etanercept he presented an acute anterior uveitis which had a good response to therapy.
Conclusion: The ankylosing spondylitis management is complicated when we have the possibility to choose only three anti TNF alpha agents. If a patient does not respond to the first or second agent we are constrained to follow the last one. Therefore the principal problem regarding this special case is that the patient is non responder at the last agent. So the question that arises is witch will be the next therapy for this patient?

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic progressive inflammatory disease of the axial skeleton and peripheral joints – asymmetric.

Its major characteristic is the early damage of the sacroiliac joint, ascending to ankylosis. The incidence is increased for males between 20 and 30 years old, thus most of the patients are associating a HLA B27 antigen. The existence of cardiovascular risk due to inflammatory rheumatic diseases is known for decades but the real significance and therapy designed to control this risk has been recently evaluated.

Systemic inflammation because of inflammatory rheumatic diseases accelerates atherosclerosis and destabilizes plaque of atheroma, contributing to an increased frequency of fatal cardiovascular events such as myocardial heart attacks and strokes. The ankylosing spondylitis cardiovascular events include: aortic insufficiency, heart muscle damage (dilatation/hypertrophy), nerve impulse conduction disorders, pericarditis, and accelerated atherosclerosis.

Anti TNF-alpha therapy leads to a decrease of the disease activity score (BASDAI) and also the nonspecific inflammatory syndrome.

The anti TNF approved drugs which are currently in clinical practice are:

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1. Infliximab (*Remicade®*) – chimeric monoclonal antibody anti-TNF alpha;
2. Adalimumab (*Humira®*) – fully human monoclonal antibody anti –TNF alpha;
3. Etanercept (*Enbrel®*) – a fusion protein between the type 2 p75 receptor of TNF and an IgG1 Fc fragment.

CASE PRESENTATION

We present the case of a man, A.I., 48 years old, from urban medium, nonsmoker, having an insignificant family history, diagnosed since 1982 when he was 16 years old with juvenile arthritis.

He came for the last hospitalization, for clinical and biological reassessment, with ankles light arthralgias.

From his medical history we know that the disease has started when he was 16 years, with ankles and knees arthritics, at radiocarpal joints, at bilateral elbows, acute back pain and fever. The patient was diagnosed with juvenile arthritis and treated with Sulphasalazine 6 grams and nonsteroidal anti-inflammatory drugs. Under this treatment he had a slightly favorable evolution with partial improvement of symptoms. After 2 years of treatment disease flares have appeared, therefore the dose of Sulphasalazine at 8 grams/day was increased and a quantity of Methotrexate 7.5 mg/week was also added. After 1 year his clinical and biological evolution became favorable and the dose of Sulphasalazine was reduced to 4 grams/day, keeping Methotrexate and nonsteroidal anti-inflammatory drugs at the same dose. In 1998 he was diagnosed with ankylosing spondylitis according to the New York criteria and the association of HLA-B27 antigen. The patient gave up Methotrexate, the swelling and pain in large joints persisted so we increased the Sulphasalazine dose to 8 grams/day. The patient has annually done physio-kinesiotherapy. In 2009 it was decided to initiate biological therapy criteria (low back pain and morning stiffness, bilateral sacroiliitis grade 4, BASDAI 8.6) according to Guidelines for the treatment of ankylosing spondylitis.

In March 2009, the Infliximab (*Remicade®* 100 mg / fl) 5 mg/kg treatment was initiated. After a loading with Infliximab at 0, 6, 12 weeks, the patient had a clinically and biologically favorable development for 18 months.

Figure 1: Indications of biological therapies in ankylosing spondylitis by therapeutics protocols

Ankylosing spondylitis certain diagnostic according to the criteria of New York 1984:
• Low back pain and morning stiffness more than 3 months, being improved with effort and does not disappear at rest • Movement limitation of lumbar spine in sagital and frontal planes • Limitation of chest expansion • Unilateral or bilateral sacroiliitis grade 3-4 grade 2-4 (imaging criteria). • Diagnosis involves the imaging criteria presence (radiology, MRI) associated to at least one clinical criteria.
Active and severe disease
• BASDAI ≥ 6 for at least 4 weeks • Erythrocyte sedimentation rate > 28 mm/h • C reactive protein > 20 mg/L and 3 x VN (quantitated)
The failure of traditional therapies
•At least 2 nonsteroidal anti-inflammatory drugs continuously administrated for at least 3 months, at maximum recommended doses or tolerated for patients with axial forms • Patients with severe axial do not need a remitting (Sulphasalazine) before the biological therapy • Nonsteroidal anti-inflammatory drugs and Sulphasalazine in peripheral forms, at least 4 months of treatment at the maximum tolerated dose (3 g/d) • Ineffective response to at least one local administration of a corticosteroid injection in peripheral arthritis and/or active enthesopathies, if indicated.
The presence of hip joint damage and extra-articular manifestations are additional factors allowing anti-TNF therapy administration at a lower score of disease activity, with BASDAI ≥4

At the end of the year he suffered an acute infero-lateral myocardial infarction. The patient was hospitalized in the cardiology department, a coronary angiography was performed which revealed a 80-90% anterior descending artery stenosis, to the distal 50-60% left coronary artery stenosis, 80% stenosis in the origin of the AC, 90% oblique median artery stenosis.

The biological therapy was stopped and a surgical intervention was performed with a triple coronary artery bypass graft with autologous saphenous vein.

A carotid Doppler ultrasound was performed showing that carotid vascular system was without hemodynamically significant stenosis. Cardiac ultrasound revealed (left ventricular hypertrophy with anterolateral myocardial contractility low post, left ventricular ejection fraction 55%). Three months postoperatively the biological therapy with *Remicade®* was restarted but the second adverse reactions has occurred (generalized rash, severe hypotension). The patient received Sulphasalazine 6 grams/day, painkiller, intermittent nonsteroidal anti-inflammatory drugs and cardiological medication. Biological evaluation showed a mixed dyslipidemia, associating a grade 1 obesity.

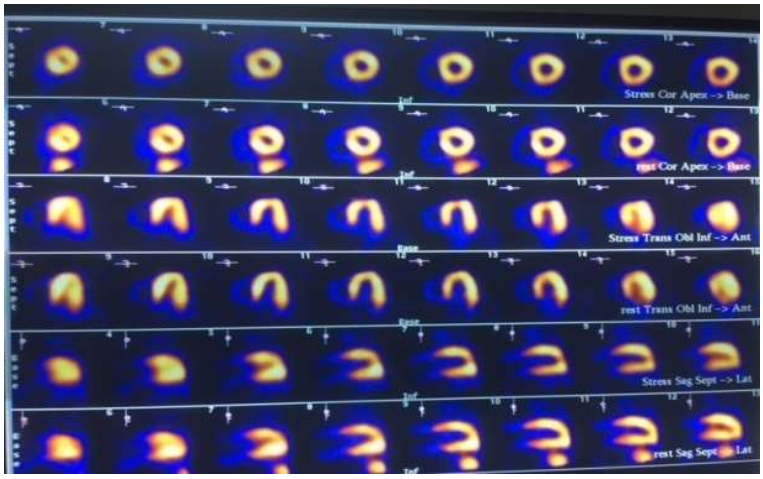
Rheumatic symptoms were significantly exacerbated (peripheral arthritis and low back pain, intense predominantly nocturnal), thus it was decided to initiate therapy with another anti-TNF alpha (*switch*) respectively Adalimumab (*Humira®*). In February 2011 a first dose of Adalimumab – *Humira®* 40 mg/2 weeks sc was administrated.

After 6 months of biological treatment with Humira, the following peripheral arthritis, acute lombalgy and inflammatory syndrome have persisted, BASDAI score was 8.1 and anginous pain occurs during small efforts. The angiography was repeated after which angioplasty was performed. Cardiac ultrasound is performed together with control cardiac stress tests, highlighting a grade 2 mitral regurgitation, posterior mitral ring atheromatosis, hypokinesia in the left ventricle lower part. Our patient had high blood pressure values being diagnosed with a 2 grade essential hypertension, thus instituting a antihypertensive therapy treatment. Therapeutics commission (rheumatologist – cardiologist) has decided to interrupt the biological therapy, considering the patient as being non responder according to the guide treatment ankylosing spondylitis criteria. The patient has continued the background therapy with Sulphasalazine 8 grams/day, pain relievers and cardiological medication.

Persistent inflammatory syndrome associated with peripheral arthritis (*de novo*, costo-vertebral arthritis and intense bilateral talalgia), BASDAI score was 9.1, has imposed a board therapeutic meeting whose opinion was to switch on the last anti TNF alpha, which remained the only therapeutic option, Etanercept (*Enbrel®* 50 mg/week).

Before the Enbrel therapy initiation a whole-body bone scintigraphy was performed (osteogenic lumbar spine and right acetabulum reactions), CT abdominal-pelvic (grade I hydronephrosis left kidney, left kidney chronic pyelonephritis) and TB QuantiFERON test (negative) to exclude a subclinical tuberculosis infection.

Figure 2: Myocardial Perfusion Scintigraphy



After 3 months the patient has presented a favorable evolution with a significant remission of the biological inflammatory syndrome, the peripheral joint tumefactions, persistence of a moderate intensity arthralgia and improvement of overall mobility. The patient was cardiologically reassessed, renal without the evidence of evolutionary elements. An angiocoronarography control was conducted (with 50% restenosis of the anterior descending artery stent), together with a myocardial treacherous tomoscintigraphy ECG synchronized (infero-septal dyskinesia level and decreased left ventricular ejection fraction regional effort – stress left ventricular ejection fraction 49%, resting left ventricular ejection fraction 60 %).

In 2014 the patient experienced an episode of acute anterior uveitis treated with corticosteroids and local mydriatic.

At the last hospitalization in February 2016 the clinical and biological evolution of the patient was favorable, the BASDAI score was 1.6. The treatment include *Enbrel®* the 50 mg/week, Sulphasalazine 1.5 grams/day, and nonsteroidal anti-inflammatory drugs intermittently. The patient is monitored at every 3 months by the rheumatologist and cardiologist and monthly by the family physician evidence the early possible complications.

Particularities of the case

1. Patient with juvenile arthritis, with ankylosing spondylitis evolution and complexes cardiovascular complications;

2. Lack of response to anti-TNF alpha 2 (*Remicade®*- side effects and *Humira®* - non responder);

3. Favorable answer and sustained to the 3rd anti TNF alpha (*Enbrel®*) after 3 years of treatment.

CONCLUSIONS

The introduction of TNF-alpha anti agents in treatment guidelines of ankylosing spondylitis, has revolutionized the therapy of patients with this disease, efficiency confirmed by numerous international clinical trials.

Anti TNF-alpha agents by reducing systemic inflammation creates a real cardiovascular protection for patients with ankylosing spondylitis, aspect highlighted for the case of our patient who has presented progressive cardiovascular events.

The complexity of the presented case is revealed by the associated comorbidities (cardiovascular, ocular, osteoarticular), which responded favorably after two switches of anti TNF-alpha concluding that switch between anti TNF alpha may be an effective therapeutic option in controlling the underlying disease and its complications.

Debut at the young age and association with HLA B 27 antigen are unfavorable prognostic factors for cardiovascular complications.

Interdisciplinary collaboration (rheumatologist, ophthalmologist, and cardiologist) is important for the management of patients with ankylosing spondylitis.

The evolution of this ankylosing spondylitis case is to be followed and the initiation in case of non-responder to *Enbrel®*, with a anti IL type 17 therapy, with sustained international studies having very good results in controlling this disease.

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