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# Significance of uveitis in patients with ankylosing spondylitis – Report from the Romanian Centre of Rheumatic Diseases

Mihaela AGACHE, MD[a]; Costin-Traian MITULESCU, MD[b];
Monica DIMANCESCU, MD[a]; Ana-Maria DASCALU, MD[b];
Liliana VOINEA, MD, PhD[b]; Violeta-Claudia BOJINCA, MD, PhD[a];
Denisa PREDETEANU, MD, PhD[a]; Ruxandra IONESCU, MD, PhD[a]

[a]Research Centre of Rheumatic Diseases, "Sf. Maria" Clinical Hospital, Bucharest, Romania
[b]Ophtalmology Department, Emergency University Hospital,
"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

*ABSTRACT*

***Background.*** *Ankylosing Spondylitis (AS) is a chronic systemic inflammatory rheumatic disease that primarily affects the axial skeleton and leads to limitation of spinal mobility. Acute anterior uveitis is the most common extraspinal lesion of AS occurring in the course of the disease. Uveitis can lead to serious complications that can compromise the visual function. Because of recent promising data concerning the effects of anti tumor necrosis factor (TNF) therapy not only on AS but also on refractory uveitis it is important to determine the uveitis baseline prevalence and characteristics related also with clinical and biological markers.*

***Aims.*** *The aims of the study were to evaluate the prevalence of uveitis and to establish several associations with clinical and paraclinical parameters in Romanian patients with AS.*

***Design.*** *A retrospective clinical study was carried out on a group of 104 patients diagnosed with AS and admitted to "Sf. Maria" Clinical Hospital between January and December 2007.*

***Methods.*** *The following parameters were taken out of the patients' files: demographic data, duration of the disease, axial and/or peripheral involvement, the presence of HLA-B27 antigen, inflammation biological markers, followed treatments, activity and functionality scores BASDAI/BASFI, ocular involvement passively reported by the patients and confirmed by ophtalmological exams.*

***Results.*** *The global prevalence of uveitis in patients with AS was 14.42% with a mean disease duration of 9.7 years. Uveitis was associated with uni/bilateral coxitis. The uveitis were predominant HLA B27 positive, unilateral and recurrent.*

***Conclusions.*** *The prevalence and characteristics of uveitis in Romanian patients with AS are comparable to the data in literature. It was demonstrated an association between uveitis and coxitis both of them being features of the disease severity. The similarities and differences in the pathogenesis of uveitis and arthritis remain a topic for further discussion and research.*

**Key words:** ankylosing spondylitis, uveitis, $TNF_{\alpha}$ inhibitors

*Address for correspondence:*
Denisa Predeteanu, MD, PhD, "Sf. Maria" Clinical Hospital, 37-39 Ion Mihalache Blvd, District 1, Bucharest Romania, Zip Code 0111172
email address: dpredet@rdslink.ro

## 1. INTRODUCTION

Ankylosing spondylitis (AS) is the prototypical form of seronegative spondylarthropaties, a group of disorders that involves chronic inflammation of the sacroiliac joints and spine leading to progressive stiffening of the spine and ankylosis. In addition with AS, in the group of seronegative spondylarthropaties are included psoriatic arthritis, reactive arthritis, entheropathic arthritis and undifferentiated spondylarthropaties.

The prevalence of AS ranges from 0.1% to 6.0% across different populations. The etiology of the disease is unknown; there is a genetic susceptibility associated with human leukocyte antigen (HLA)-B27. The principal musculoskeletal lesions associated with AS are sacroiliitis, synovitis and enthesithis. The ocular, intestinal, pulmonary and neurological complications make it a multisystemic disease (1).

AS represents a major health problem due to the gradual and severe limitation of patients' mobility and the high social and financial costs.

One of the most frequent extraarticular manifestations of AS is uveitis. Current International Uveitis Study Group (CIUSG) classification system is based on the anatomical location of the inflammation: anterior uveitis (iris and ciliary body), posterior uveitis (choroidea and retina) and panuveitis (generalised inflammation) (2). Anterior uveitis commonly occurs in spondylarthropathies and sarcoidosis. Posterior uveitis (choroiditis or retinitis) is commonly associated with infection, sarcoidosis, and Behçet's disease. Patients with uveitis present a red, painful, photophobic eye and have blurred vision. Similar to the diagnosis of various forms of arthritis, the diagnosis of uveitis can be made by historical features (e.g., onset), physical findings (anterior vs. posterior uveitis), and response to therapy. Anterior uveitis is easily identified by the ophthalmologist using a slit lamp examination (3). Untreated or inadequately treated uveitis may lead rapidly serious sequelae such as synechiae formation, irregularity of pupil, cataracts, macular oedema, optic nerve oedema with loss of vision and even loss of eye. However, treatment must be administered carefully because of well-known side effects of corticosteroids in the eye, including cataracts and secondary glaucoma with permanent damage of the optic nerve (4).

Data concerning the prevalence and characteristics of uveitis in patients with AS reported a prevalence of 30-50% (5). The occurrence of uveitis typically does not coincide with flare of arthritis. Uveitis can appear both before and after the onset of osteoarticular symptoms and may need a change in their basal treatment.

Recently, the new treatment of AS with biological agents anti tumour necrosis factor (TNF) was proven effective not only for the rheumatic disease but also for ophtalmological manifestation. ❑

## 2. PATIENTS AND METHODS

This is a retrospective clinical study carried out on a group of 104 patients with AS diagnosed according to modified New York criteria and admitted to "Sf. Maria" Clinical Hospital between January and December 2007. The following parameters were taken out of the patients' files: demographic data (age, sex), duration of the disease, axial and/or peripheral involvement, the presence of HLA-27 antigen, inflammation biological markers (ESR, CRP, and fibrinogen), followed treatments and activity and functionality scores (Bath Ankylosing Spondylitis Disease Activity Index /BASDAI and Bath Ankylosing Spondylitis Functional Index / BASFI). Ocular involvement passively reported by the patients and confirmed by ophthalmological exams was also reported.

## 3. RESULTS

The study was carried out on a group of **104** patients diagnosed with AS according to modified New York criteria. Of these, **82** (78.8%) patients were men, the sex ratio M/F being **3.73 /1.**

Of the entire group, **93** (89.43%) patients had primary AS and **11** (10.57%) patients had secondary AS following psoriatic arthritis and reactive arthritis. **61**(58.65%) patients presented only axial involvement and **43** (41.35%) patients presented both axial and peripheral involvement – 18 (41.86%) having oligoarthritis and 25 (58.14%) having poliarthritis. HLA-B27 was positive in **58** (92.06%) patients (63/104 available). The characteristics of the study group are presented in the Table 1.

Regarding the current treatment the most used were DMARDs: Sulfasalazine 48 patients (46.15%) patients, Methotrexat 5 patients

| | mean | standard deviation | median | minimum | maximum |
|---|---|---|---|---|---|
| Age (years) | 41.15 | 13.07 | 39.00 | 19 | 73 |
| Disease duration (years) | 9.75 | 9.99 | 5.00 | 0 | 40 |
| ESR (NV: <10 mm/h) | 37.29 | 25.84 | 31.00 | 4 | 120 |
| CRP (NV: <2 mg/l) | 26.46 | 34.79 | 16.05 | 0.16 | 195 |
| Fibrinogen (NV: 200-400mg/dl) | 459.43 | 124.173 | 443.00 | 203 | 837 |
| BASDAI | 6.32 | 2.31 | 6.8 | 2 | 9.7 |
| BASFI | 5.69 | 2.36 | 6.1 | 1.5 | 10 |

**TABLE 1.** Characteristics of the patients group

(4.8%), combination Methotrexat and Sulfasalazine 14 (13.46%) patients. 13 (12.5%) patients were on biological treatment associated or not to conventional treatment: 9 patients (39.23%) patients were on Infliximab, 4 patients (30.76%) patients were on Adalimumab and 1 patients (7.69 %) patient was on Etanercept.

In the study group, **15** patients had uveitis, the prevalence of uveitis being **14.42%**. The characteristics of uveitis are presented in the Table 2.

The prevalence of the genetic marker HLA-B27 was **92.59%** in patients with AS without uveitis (54/89 available) and **88.88 %** in patients with AS and uveitis (9/15 available), but the differences were not statistical significant (p=0.709). Generally, the first episode of uveitis appeared after the onset of AS, only in three patients the first episode of uveitis was before the onset of AS.

Between those 15 patients with uveitis, 4 were on biological treatment. Two of them had flares of uveitis even after the initiation of the biological treatment with Infliximab. The cure of the episodes was obtained with local treatment and didn't require changing the doze or the timing of the biological treatment.

In our study, coxitis was present in **26** patients (25%) patients: unilateral 5 patients (19.23%) patients, bilateral 21 patients (80.76%) patients. Generally, uni/bilateral coxitis is found in young patients, affecting life quality and necessiting articular replacement. In our case the mean age of patients with coxitis was 38.25 (±13.51) years, the youngest patient being 19 years with bilateral coxitis. 10 patients (38.45%) patients with coxitis had hip articular replacement. We found an association between uveitis and uni/bilateral coxitis (p=0.001), both of them being features of the disease severity.

The disease activity and functional indexes (BASDAI=6.32, BASFI=5,69) on a scale 0-10 showed an intense activity and an important functional disability of the AS. Inflammation biological markers correlated positively with BASDAI and BASFI indices. As expected BASFI correlated positively with disease duration (Table 3).

The inflammation biological parameters (CRP, ESR, fibrinogen) were generally elevated, indicated a high activity of the disease. But between the two groups of patients: with uveitis and without uveitis we didn't find significant

| Prevalence of uveitis (mean disease duration 9.7 years) | 15 (14.42 %) |
|---|---|
| HLA B27 positive | 92.06% |
| First episode of uveitis prior to the onset of AS | 20% |
| Unilateral uveitis | 55.6% |
| Recurrent uveitis | 66.6% |
| Sequelae (posterior sinechia) | 13.3% |

**TABLE 2.** Characteristics of uveitis

| Epidemiological association | p | Pearson's correlation coefficent |
|---|---|---|
| Coxitis-uveitis | 0.001 | 0.329 |
| Coxitis – CRP | 0.027 | 0.226 |
| Disease duration-BASFI | 0.022 | 0.425 |
| BASDAI-ESR | 0.002 | 0.522 |
| BASDAI-CRP | 0.011 | 0.435 |
| BASDAI-fibrinogen | 0.002 | 0.538 |
| BASFI-ESR | 0.000 | 0.606 |
| BASFI-CRP | 0.085 | 0.326 |
| BASFI-fibrinogen | 0.003 | 0.542 |

**TABLE 3.** Epidemiological association

| | Uveitis | Without uveitis | Sig (2-tailed) |
|---|---|---|---|
| Age | 43.20 | 40.66 | 0.493 |
| Disease duration | 12.14 | 9.49 | 0.365 |
| HLAB27 + | 88,88% | 92,59% | 0.709 |
| ESR | 40.13 | 36.84 | 0.654 |
| CRP | 25.19 | 26.97 | 0.862 |
| Fibrinogen | 483.71 | 455.73 | 0.445 |
| BASDAI | 5.89 | 6.63 | 0.417 |
| BASFI | 5.82 | 5.75 | 0.942 |

**TABEL 4.** Characteristics of patients with and without uveitis

differences. This confirms the fact that eye inflammation evolved independently, alternating acute and remission periods without correlations with the evolution of the disease at a systemic level. ❑

## DISCUSSIONS

### Prevalence

In patients with AS the prevalence of uveitis is approximately **30%** and the typical pattern of it is frequently **acute, anterior, unilateral, recurrent** and **responsive to local treatment**. A recent study regarding the prevalence and characteristics of uveitis in patients with seronegative spondylarthropaties has reported a mean prevalence of **32.7%** varying with the type of the disease. The prevalence was directly proportional to the increase in disease duration: for mean disease duration of less than 5 years, the prevalence of uveitis was 12.3% while for mean disease duration for more than 30 years, the prevalence of uveitis was 43%. Likewise, the prevalence of uveitis was higher in patients with HLA-B27 positive compared to HLA-B27 negative with an odd ration 4.2 (6).

In our study the prevalence of uveitis in Romanian patients with AS is **14%.** The prevalence of genetic marker HLA-B27 was high in both groups of patients (with uveitis or without uveitis).

### Pathogenesis

The similarities and differences in the pathogenesis of arthritis and uveitis remain a topic for future discussion and research.

The pathogenic mechanism responsible both for articular and ocular involvement in patients with AS is autoimmune in nature with specific antibodies against the "self" structures of the organism and with the increase of specific mediators of inflammation. The intimate molecular mechanism triggering the pathological cascade has not been yet fully understood. Apparently, **once the first episode has set on, the inflammation of the eye develops on its own with periods of activation and remission, without any correlations with the progress of the disease at a systemic level.**

HLA-B27 is an independent risk factor not only for articular disease but also for extraarticular disease such as uveitis with more frequent, more severe, and more vision-threatening episodes of uveitis (7). Although human leukocyte antigen (HLA) B27 has been directly implicated in the pathogenesis of AS, additional evidence favours the involvement of an additional genetic factor(s). In a population of AS patients selected for a history of acute anterior uveitis (AAU), the authors demonstrated a phenotypic association between polymorphism in an HLA-linked proteasome subunit gene, LMP2, and the development of anterior uveitis and peripheral arthritis (8).

TNF is known to play a key role in ocular inflammation as shown by animal studies and its detection in the ocular fluids of inflamed eyes in man (9).

### Treatment

In patients with AS the classical treatment of uveitis includes local administration of cycloplegic drugs and glucocorticoids in association with general administration of nonsteroidal anti-inflammatory drugs and glucocorticoids. In more severe cases, unresponsive to treatment or requiring the maintenance of an increased dosage of glucocorticoids, immunosuppressive medication is recommended (like: cyclophosphamide, chlorambucil, azathioprine and methotrexate, mycophenolate mofetil, cyclosporin A) (10).

The new biological therapies in use are TNFα inhibitors, interferon α and immunoglobulins iv. These are more effective but at the same time they are more aggressive and associated with not only severe complications (TB, a decrease in the antiinfection defence mechanisms, neoplasic disease) but also having a higher cost.

There are proofs as to beneficial effect of TNF inhibitors in the treatment of unresponsive uveitis to conventional therapy in patients with AS (11-13). Anti-TNFα monoclonal antibodies (Infliximab, Adalimumab) induce a decrease in the recurrence rate of resistant uveitis in patients with AS (14-15). Soluble receptors for TNF (Etanercept) are less effective in the treatment of uveitis in patients with AS and even can cause uveitis in previously asymptomatic patients with AS (16-19). In all these cases the characteristics of uveitis are atypical for AS: although Etanercept-induced uveitis is initially unilateral, its evolution becomes more severe with bilateral involvement of the eyes. It does not respond to classical therapy, only to the discontinuation of the biological agent.

In a prospective trial with Infliximab the side effects noted in the cohort of patients were far more than what is described in the literature for other autoimmune disease. Suhler and colab. reported serious adverse events that were potentially related to Infliximab included pulmonary embolus, congestive heart failure, lupus-like reaction in 2 patients, and vitreous hemorrhage in 2 patients. Antinuclear antibodies developed in 15 of 20 enrolled patients receiving 3 or more infusions (20).

The differences between biological agents could be related to their different molecular structure, with different permeability in the blood ocular barrier.

The rheumatologist and the ophthalmologist need to work together in patients with spondylarthropaties and uveitis. The general opinion is that routine screening for uveitis is not necessary. In adults who do not have any ophthalmic complaints, probably there is no ophthalmic disease. The rheumatologist is generally very familiar with the medications that are used to treat uveitis, except for the topical agents. But the ophthalmologist has to do the history, the local exam and some laboratory tests to rule out an infectious cause for uveitis and to determine the response to therapy.

Taking into account, the new approved treatment for AS with biological agents anti tumour necrosis factor (TNF) in our country, we consider necessary to extend the research to determine a national multicentric prevalence and characteristics of uveitis associated AS because resistant uveitis can benefit of this treatment.

## CONCLUSION

1. The prevalence of uveitis in Romanian patients with AS is lower comparable to the data in literature but its characteristics are the same.
2. We found an association between uveitis and coxitis both of them being disease severity features.
3. There is a necessity for rheumatologists and ophthalmologists to design a standardised interdisciplinary model of therapeutic approach of the uveitis in patients with AS.

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