

Analysis of the frequency of uveitis in spondyloarthritis patients and associations with clinical parameters of the disease

Análise da frequência de uveítes em pacientes com espondiloartrites, suas complicações e associação com parâmetros clínicos da doença

Isabela Miyazaki Solano Vale¹, Ivânio Alves Pereira², Mariana de Souza Mastella¹

ABSTRACT

Objective: Acute anterior uveitis (AAU) is the most common extra-articular manifestation of spondyloarthritis. The aim of this study is to analyze if the presence of uveitis is associated with a different clinical manifestation, laboratorial, radiological and therapeutic among spondyloarthritis patients. **Methods:** This was an observational retrospective study with 153 patients with spondyloarthritis attended in the period from 1997 to 2017 in Florianópolis, Brazil. It was analyzed demographic, laboratorial, clinical and therapeutic data in spondyloarthritis patients with or without uveitis. **Results:** 26,8% of the patients with spondyloarthritis presented uveitis. The presence of complications was rare, with cataract occurring in only four patients and glaucoma in two of them. A higher frequency of acute anterior uveitis in males ($p = 0.06$) was observed in patients with a family history ($p = 0.19$) and HLA-B27 positive ($p = 0.14$). Patients with spondyloarthritis and uveitis more frequently used anti-TNF ($p = 0.04$) and presented sacroiliitis on imaging tests ($p = 0.02$). There was no association between uveitis and cardiovascular ($p = 0.44$), cutaneous ($p = 0.13$) or gastrointestinal involvement ($p = 0.10$). **Conclusion:** Uveitis in patients with spondyloarthritis is common, predominantly in males, and more frequently in HLA-B27 positive patients. The use of immunobiological agents such as anti-TNF is common in patients with uveitis.

Keywords: Uveitis; Anterior uveitis; Spondyloarthritis, ankylosing; Spondylitis; Anti-TNF

RESUMO

Objetivo: A uveíte anterior aguda é a principal manifestação extra-articular na espondiloartrite. O objetivo deste estudo foi analisar se a presença da uveíte se associa com diferentes manifestações clínicas, laboratoriais, radiológicas e a terapêutica nos pacientes com espondiloartrite. **Métodos:** Estudo observacional retrospectivo realizado com 153 pacientes portadores de espondiloartrite atendidos no período de 1997 a 2017 na Grande Florianópolis, Brasil. Foram analisados dados demográficos, laboratoriais, clínicos e do tratamento de pacientes com espondiloartrite em relação a presença ou não de uveíte. **Resultados:** A uveíte foi encontrada em 26,8% dos pacientes. A presença de complicações foi rara, ocorrendo catarata em somente quatro pacientes e glaucoma em dois deles. Foi observada uma tendência a maior frequência de uveíte anterior aguda no sexo masculino ($p=0,06$), nos pacientes com história familiar ($p=0,19$) e HLA-B27 positivos ($p=0,14$). Pacientes com espondiloartrite e uveíte mais frequentemente usavam anti-TNF ($p=0,04$) e apresentavam sacroiliite em exames de imagem ($p=0,02$). Não observou-se associação entre a uveíte e o acometimento cardiovascular ($p=0,44$), cutâneo ($p=0,13$) ou gastrointestinal ($p=0,10$). **Conclusão:** A uveíte que ocorre em pacientes com espondiloartrite é comum, tem predomínio no sexo masculino e é mais frequente em pacientes com HLA-B27 positivo. O uso de imunobiológicos como o anti-TNF é frequente nos pacientes com uveíte.

Descritores: Uveíte; uveíte anterior, Espondiloartrite; Espondilite anquilosante; Anti-TNF

¹ Academic Course in Medicine, Universidade do Sul de Santa Catarina, Tubarão, SC, Brazil.

² Universidade do Sul de Santa Catarina, Tubarão, SC, Brazil.

The authors declare no conflict of interests.

Received for publication 05/11/2017 - Accepted for publication 13/01/2018.

INTRODUCTION

Spondyloarthritis (SpA) comprises a set of diseases such as Ankylosing Spondylitis (AS), nonradiographic SpA, reactive arthritis, psoriatic arthritis, and enteropathic arthritis. The term proposed in 1974 by Moll and Wright aimed at demonstrating the strong association between non-rheumatoid disorders previously described separately.⁽¹⁾

AS is the main subtype and prototype of the SpA in this heterogeneous group, which can lead to functional and structural impairments, and significantly reduce the quality of life of the patient.^(2,3)

The onset of the disease usually occurs between the 2nd and 3rd decades of life, and men are more affected than women in the ratio of 2-3:1.⁽⁴⁾ The pattern of the disease varies according to gender, being more severe in men and with a later onset in women.⁽⁵⁾

The overall prevalence of SpA ranges from 0.20% -1.61%, and it is known that this difference is due to the higher frequency in some ethnic groups and certain geographic regions, and some of this is due to the difference in the prevalence of HLA-B27.^(6,7)

The main symptom of SpA is lumbar pain of inflammatory pattern, which usually has insidious onset and is reported in the lower back or glutes.⁽⁸⁾ In addition, peripheral enthesopathies, asymmetric peripheral oligoarthritis (especially in large lower limb joints), and extra-articular involvement such as anterior uveitis, psoriasis, and chronic inflammatory bowel disease may be present.⁽³⁾ The most relevant laboratory tests for the diagnosis of SpA are HLA B27 and C-Reactive Protein (CRP), the first being important in the early detection of SpA.⁽⁹⁾

For decades, the treatment of patients with AS comprised mainly the use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs) and physiotherapy.⁽¹⁰⁾ The use of synthetic DMARD, such as methotrexate, leflunomide, and sulfasalasin in the treatment of SpA was ineffective, especially in patients with axial disease.⁽³⁾

In recent years, the greatest revolution in the treatment of SpA was the use of Tumor Necrosis Factor (TNF) Inhibitors, since they have exponentially improved the treatment of the clinical manifestations of the disease. Different studies have shown a representative improvement in pain, function and inflammatory markers with the use of biologicals, in particular anti-TNF, such as adalimumab, etanercept and infliximab.⁽¹¹⁻¹⁵⁾

Several rheumatic diseases present ocular involvement, and they present in varied prevalences, with the main types being uveitis, conjunctivitis, scleritis, vasculitis in the retina, dry eye syndrome, inflammation of the orbit, and neuro-ophthalmological manifestations.⁽¹⁶⁾

Among the extra-ocular manifestations of patients with SpA, the most common is Acute Anterior Uveitis (AAU). The prevalence of AAU in patients with AS is 30 to 40%.^(17,18) The ocular inflammation in SpA is restricted to the uvea and is usually unilateral, and may alternate from one eye to the other. Typical eye attacks are abrupt and present severe pain, limbal hyperemia, visual impairment and photophobia.⁽¹⁹⁾

Although the high occurrence of uveitis among patients with SpA is known, the understanding of the predictive factors in its development is limited. Factors such as age of onset, gender, duration of disease, and HLA-B27 positivity have already been strongly associated to the clinical course of the SpA.⁽²⁰⁻²²⁾ One

aspect in need to be better understood is whether the presence of AAU in patients with spondyloarthritis is associated to the different clinical expression of the disease in relation to the clinical and laboratory manifestations and the therapeutics used.

METHODS

This is a retrospective observational study performed in two care centers for patients with rheumatic diseases in Grande Florianópolis during the period from 1997 to 2017 including patients with axial and/or peripheral spondyloarthritis or ankylosing spondylitis. The study was approved by the Research Ethics Committee (CEP) - UNISUL under number 49299415.7.2006.5369.

The diagnosis of AS was established using the modified New York criteria and the axial and peripheral SpA criteria based on the classification criteria of the ASAS group for spondyloarthritis. The diagnosis of uveitis was based on previous ophthalmologic evaluation.

All patients with other associated pathologies determining the appearance of uveitis, such as Behcet's disease, sarcoidosis, toxoplasmosis, and juvenile idiopathic arthritis were excluded.

Patients' medical records were reviewed in order to collect data such as uveitis and other ocular complications (glaucoma, cataract, visual loss, eye surgery), arthritis and enthesitis and their respective sites of involvement, gastrointestinal (inflammatory bowel disease), cutaneous (psoriasis, erythema nodosum, pyoderma gangrenosum), or cardiovascular (aortitis, arrhythmias, valve insufficiency) involvement, and the type of treatment used by the patients.

Pearson's chi-square test (χ^2), Fischer's exact test, and Student's t-test were used to verify the association of the variables of interest, and p values ≤ 0.05 were considered statistically significant.

RESULTS

Among 153 patients with spondylarthritis, 71 (46.4%) were female and 82 (53.6%) were male. In the group of patients with uveitis, the prevalence of men was 65.8%. The average age at diagnosis was 36 years, and the average disease time was 26 years. Positive family history was present in 15.7% of the cases. Of the 108 patients who performed HLA-B27, 71.2% were positive in the test. The average values of HSV and CRP at the first appointment were 33 mm/h and 21.2 mg/l, respectively.

Peripheral involvement was observed in 68% of patients, with the knee being the most affected site in arthritis, and plantar fasciitis in the enthesitis. Sacroiliitis was detected in 84.3% of the imaging exams performed (RX, CT and MRI). The presence of uveitis was associated to the findings of sacroiliitis in the imaging exams (95.1%), with statistical significance ($p = 0.02$).

Table 1 shows the clinical, demographic, laboratory and radiographic aspects of patients with spondylarthritis in relation to the presence of uveitis.

When analyzing extra-articular manifestations in patients with uveitis, gastrointestinal involvement was observed in 17.0% of patients, followed by cutaneous and cardiovascular involvement in 7.3%. Uveitis was present in 26.8% of cases. All patients in the present study had previous, acute and unilateral uveitis. The association between the presence of uveitis and extra-articular manifestations was not statistically significant.

As for the ocular complications of patients with spondyloarthritis in the presence of uveitis, cataract was the most frequent (9.7%) followed by glaucoma (4.8%), and these results are described in table 2.

Table 1
Clinical, demographic, laboratory and radiographic aspects in 153 patients with spondyloarthritis in the presence or absence of uveitis

Variables	With uveitis n=41 n (%)	Without uveitis n=112 n (%)	p Value
Age	49	47	0.63
Gender			
Female	14 (34.1)	27 (65.8)	
Male	57 (50.8)	55 (49.1)	0.06
Family history	9 (21.9)	15 (13.3)	0.19
HLA B27 positive	29 (78.3)	48 (67.6)	0.14
Current smoking	2 (4.8)	8 (7.1)	0.61
Sacroiliitis in image (RX, TC or MRI)	39 (95.1)	90 (80.3)	0.02
Peripheral involvement	33 (80.4)	71 (63.3)	0.07
Peripheral arthritis	22 (53.6)	64 (57.1)	0.70
Enthesitis	18 (43.9)	39 (34.8)	0.30
Gastroint. involvement	17 (17.07)	30 (26.7)	0.10
Cutaneous involvement	3 (7.3)	20 (17.8)	0.13
Cardiovascular involvement	3 (7.3)	5 (4.4)	0.44

Table 2
Ocular complications in 41 patients with uveitis and spondyloarthritis

Variables	Frequency n (%)
Cataracts	4 (9.7)
Glaucoma	2 (4.8)
Visual loss	1 (2.4)
Ocular surgery	2 (4.8)

Regarding drug therapy, 96.1% of the patients used NSAIDs, and 78.4% used DMARDs. Anti-TNF was used by 68% of patients with spondyloarthritis, and in the group of uveitis the percentage was higher (80.4%), giving a significant difference ($p = 0.04$). Among the biologicals, monoclonal antibodies such as adalimumab and infliximab were more used when compared to the soluble TNF receptor, etanercept. The most used biological therapy was adalimumab (49%), followed by infliximab (24.8%). As for the number of anti-TNF used since the diagnosis, 56.7% of the patients used only one type of drug, whereas 40% used two or more sequentially. Table 3 shows the frequency and type of treatment used.

Table 3
Frequency and type of treatment used in 153 patients with spondyloarthritis

Variáveis	With uveitis n=41 n (%)	Without uveitis n=112 n (%)	P-value
Use of NSAIDs	41 (100)	106 (94.6)	0.13
Use of DMARDs	31 (75.6)	89 (79.4)	0.60
Methotrexate	27 (65.8)	78 (69.6)	0.65
SSZ	16 (39)	39 (34.8)	0.55
Leflunomide	1 (2.4)	6 (5.3)	0.67
Use of anti-TNF	33 (80.4)	71 (63.3)	0.04

DISCUSSION

For a better understanding of the course of spondyloarthritis, a greater understanding of the role of extra-articular manifestations is needed. In this context, the evaluation of uveitis is extremely important because of its greater frequency when compared to other manifestations such as cutaneous, intestinal and cardiovascular involvement.⁽²³⁾ Initially, it is important to report that the current study was performed in a population of patients with spondylarthritis with clinical and epidemiological characteristics consistent with the classic description of spondyloarthritis: male predominance, HLA-B27 positive,⁽²⁴⁾ and AAU as the main extra-articular manifestation.^(2,3,25)

The frequency of HLA B27 positive in this study was higher in the population with uveitis, although not statistically significant. The predominance of males in patients with uveitis was also observed, as Braakenburg et al. and Mitulescu et al. found. However, there was no statistical significance.^(26,27) Some factors may justify this difference, such as the higher frequency of HLA-B27⁽²⁸⁾ in males and a more severe clinical expression of the disease in males.⁽⁵⁾

Uveitis due to spondylarthritis is usually anterior, acute, recurrent, unilateral, alternating, and with a low degree of complication.⁽²⁹⁾ In order to confirm this data, all patients in the present study presenting uveitis had a unilateral, acute and recurrent presentation, only four of them evolved with cataract, and only two patients had complications such as increased intraocular pressure. Data analysis from the literature regarding the complication rate of uveitis not associated to spondyloarthritis shows that the chance of complications in this group is higher.^(30,31)

Peripheral involvement of the SpA characterized by the presence of peripheral arthritis and/or enthesitis was more frequent in the subpopulation of patients with uveitis, with a trend towards statistical significance. Muñoz-Fernández and colleagues, in a cross-sectional study conducted in Spain with 100 patients, found an association between the finding of enthesitis in AAU patients and the presence of the HLA-B27 gene, even in the absence of a diagnosis of spondyloarthritis.⁽³²⁾ The authors have suggested the existence of an abortive or incomplete form of spondyloarthritis that expresses by the finding of extra-articular manifestation in patients with genetic predisposition, even in the absence of sacroiliitis or other involvement of the axial skeleton. Similar to this finding, our study demonstrated an increased prevalence of enthesitis in patients with uveitis, but this association did not show statistical significance.

The analysis of the presence of sacroiliitis in the imaging exams showed a higher frequency of this finding in patients with uveitis. This fact may be associated to a greater axial involvement in patients with uveitis.⁽³³⁾ When we verify the frequency of uveitis in the different spondyloarthritis, it is known that AS, which is characterized by the presence of radiographic axial involvement, is more associated to the presence of uveitis.^(18,34) In our study, there was no separation of cases of AS and non-radiographic SpA. However, a recent meta-analysis comparing AS and non-radiographic axial SpA did not find differences in the clinical expression, except that patients with AS had a higher frequency of uveitis.⁽³⁵⁾

In the current study, there was no association between the presence of uveitis in patients with spondylarthritis and other extra-articular manifestations such as gastrointestinal, cutaneous and cardiovascular involvement. Cantini and colleagues, in a case-control study conducted in Italy, found a lower frequency of uveitis

in patients with inflammatory bowel disease when compared to other forms of SpA.⁽³⁶⁾ Likewise, the incidence of uveitis in SpA associated to reactive arthritis and psoriasis is lower when compared to ankylosing spondylitis.^(18,33)

Regarding therapy in uveitis management, topical corticosteroids play an important role in the acute phase of ocular manifestation, but its chronic use is associated to a greater chance of complications.⁽³⁷⁾ For many years, the therapies used for spondyloarthritis included the use of synthetic NSAIDs and DMARDs. At that time, a study with sulfasalasin seemed effective in relation to decreased recurrence of uveitis.⁽³⁸⁾ Regarding the use of methotrexate in the treatment of uveitis, some studies have demonstrated its efficacy in idiopathic uveitis or associated to other conditions⁽³⁹⁾, but in the population with spondyloarthritis there are no studies demonstrating the effectiveness of this drug, mainly due to its side effects.⁽³⁷⁾ In our study, there was no difference in the prescription of synthetic DMARD between patients with or without uveitis, confirming the fact that these should not be used as first-line therapy.

In patients with uveitis associated to various conditions there is an increased production of different proinflammatory cytokines in the vitreous secondary to the activation of T cells, and among them the tumor necrosis factor in special.⁽²⁹⁾ Studies conducted since 2004 show that that TNF block results in clinical improvement in uveitis in a number of non-infectious conditions such as Behcet's disease and sarcoidosis.⁽⁴⁰⁾ In spondyloarthritis, numerous studies confirm the good performance of anti-TNF in relation to the reduction of complications related to uveitis and in the prevention of recurrences.^(12,15) In our study, we observed that the presence of uveitis was associated to a higher frequency of the use of biological DMARD, in particular anti-TNF, when compared to the group of non-uveitis, and monoclonal antibodies such as adalimumab and infliximab were the most used. Several studies have shown that the latter two are presented as first-line therapy for the treatment of uveitis recurrence, in preference to the use of etanercept, a soluble TNF receptor which is less effective in AAU for reasons yet unknown.^(13,29)

Recently, we obtained the approval of other anti-TNF in spondylarthritis such as golimumab and certolizumab pegol, but no patient in this study used these medications. A Spanish study with certolizumab pegol demonstrated the efficacy and tolerability of this medication in patients with uveitis associated to spondyloarthritis.⁽⁴¹⁾ As golimumab has been shown to be effective in the refractoriness of uveitis episodes.⁽²⁹⁾ We also did not have patients in our study using secukinumab (IL-17 inhibitor) or ustekinumab (IL-23 inhibitor). Although further studies should be performed, the use of these drugs did not demonstrate a reduction in the recurrence of uveitis in patients with spondyloarthritis.⁽⁴²⁾

CONCLUSION

Considering the data presented, we can conclude that AAU is the main extra-articular manifestation of spondyloarthritis, and in many cases it is presented as the initial manifestation. In addition, it is associated to the presence of HLA-B27, and is more frequently found in males. Uveitis related to spondyloarthritis has a good prognosis with a low risk of long-term complication. Immunobiologicals, particularly those of the anti-TNF class, have recently emerged as a good treatment option, mainly in preventing the recurrence of uveitis.

REFERENCES

- Moll J, Haslock I, MacRae I, Wright V. Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies, and Behcet's syndrome. *Medicine (Baltimore)*. 1974;53(5):343-64.
- Taurog JD, Chhabra A, Colbert RA. Ankylosing Spondylitis and Axial Spondyloarthritis. *N Engl J Med*. 2016;374(26):2563-74.
- Braun J, Sieper J. Ankylosing spondylitis. *Lancet*. 2007;369(9570):1379-90.
- Webers C, Essers I, Ramiro S, Stolwijk C, Landewe R, Van Der Heijde D, et al. Gender-attributable differences in outcome of ankylosing spondylitis: Long-term results from the outcome in ankylosing spondylitis international study. *Rheumatol*. 2016;55(3):419-28.
- Landi M, Maldonado-Ficco H, Perez-Alamino R, Maldonado-Cocco J, Citera G, Arturi P, et al. Gender differences among patients with primary ankylosing spondylitis and spondylitis associated with psoriasis and inflammatory bowel disease in an iberoamerican spondyloarthritis cohort. *Medicine (Baltimore)*. 2016;95(51):441-76.
- Stolwijk C, Boonen A, van Tubergen A, Reveille J. Epidemiology of Spondyloarthritis. *Rheum Dis Clin North Am*. 2012;38(3):441-76.
- Stolwijk C, van Onna M, Boonen A, van Tubergen A. The global prevalence of spondyloarthritis: A systematic review and meta-regression analysis. *Arthritis Care Res*. 2016;68(9):1320-31.
- Sieper J, van der Heijde D, Landewe R, Brandt J, Burgos-Vagas R, Collantes-Estevez E, et al. New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of SpondyloArthritis international Society (ASAS). *Ann Rheum Dis*. 2009;68(6):784-8.
- Rudwaleit M, van der Heijde D, Khan MA, Braun J, Sieper J. How to diagnose axial spondyloarthritis early. *Ann Rheum Dis*. 2004;63(5):535-43.
- Report E. International ASAS consensus statement for the use of 2003;817-25.
- Van der Heijde D, Breban M, Halter D, DiVittorio G, Bratt J, Cantini F, et al. Maintenance of improvement in spinal mobility, physical function and quality of life in patients with ankylosing spondylitis after 5 years in a clinical trial of adalimumab. *Rheumatology (Oxford)*. 2015;54(7):1210-9.
- Maxwell LJ, Zochling J, Boonen A, Singh JA, Veras MMS, Tanjong Ghogomu E, et al. TNF-alpha inhibitors for ankylosing spondylitis. *Cochrane database Syst Rev*. 2015;4(4):CD005468.
- Sieper J, van der Heijde D, Dougados M, Brown LS, Lavie F, Pangan AL. Early response to adalimumab predicts long-term remission through 5 years of treatment in patients with ankylosing spondylitis. *Ann Rheum Dis*. 2012;71(5):700-6.
- Dougados M, Tsai W-C, Saaibi DL, Bonin R, Bukowski J, Pedersen R, et al. Evaluation of health outcomes with etanercept treatment in patients with early nonradiographic axial spondyloarthritis. *J Rheumatol*. 2015;42(10):1835-41.
- Ren L, Li J, Luo R, Tang R, Zhu S, Wan L. Efficacy of antitumor necrosis factor () agents on patients with ankylosing spondylitis. *Am J Med Sci*. 2013;346(6):455-61.
- Khan MA, Haroon M, Rosenbaum JT. Acute anterior uveitis and spondyloarthritis: more than meets the eye. *Curr Rheumatol Rep*. 2015;17(9):59.
- Rosenbaum JT. Uveitis in spondyloarthritis including psoriatic arthritis, ankylosing spondylitis, and inflammatory bowel disease. *Clin Rheumatol*. 2015;34(6):999-1002.
- Cantini F, Nannini C, Cassarà E, Kaloudi O, Niccoli L, Cassara E, et al. Uveitis in spondyloarthritis: an overview. *J Rheumatol Suppl*. 2015;93:27-9.
- Keck KM, Choi D, Savage LM, Rosenbaum JT. Insights into uveitis in association with spondyloarthritis from a large patient survey. *JCR J Clin Rheumatol*. 2014;20(3):141-5.
- Navarro-Compán V, Ramiro S, Landewé R, Dougados M, Miceli-Richard C, Richette P, et al. Disease activity is longitudinally related to sacroiliac inflammation on MRI in male patients with axial spondyloarthritis: 2-years of the DESIR cohort. *Ann Rheum Dis*. 2015;75(5):874-8.

21. Arends S, Maas F, Wink F, Efde M, Bootsma H, van der Veer E, et al. Male and female patients with axial spondyloarthritis experience disease activity, physical function and quality of life differently: results from the Groningen Leeuwarden Axial Spondyloarthritis Cohort. *Rheumatology*. 2015;54(7):1333–5.
22. Chung H, Machado P, van der Heijde D, D'Agostino M, Dougados M. HLA-B27 positive patients differ from HLA-B27 negative patients in clinical presentation and imaging: results from the DESIR cohort of patients with recent onset axial spondyloarthritis. *Ann Rheum Dis*. 2011;70(11):1930–6.
23. Stolwijk C, van Tubergen A, Castillo-Ortiz JD, Boonen A. Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: a systematic review and meta-analysis. *Ann Rheum Dis*. 2013;74(1):65–73.
24. Gouveia EB, Elmann D, Morales MS de A. Espondilite anquilosante e uveíte: Revisão. *Rev Bras Reumatol*. 2012;52(5):749–56.
25. Gameiro Filho AR, Albuquerque AF de, Martins DG dos S, Costa DS da. Epidemiological analysis of cases of uveitis in a tertiary Hospital. *Rev Bras Oftalmol*. 2017;76(4):181–5.
26. Braakenburg AMD, de Valk HW, de Boer J, Rothova A. Human leukocyte antigen-B27-Associated uveitis: long-term follow-up and gender differences. *Am J Ophthalmol*. 2008;145(3):472–9.
27. Mitulescu TC, Popescu C, Naie A, Prede eanu D, Popescu V, Alexandrescu C, et al. Acute anterior uveitis and other extra-articular manifestations of spondyloarthritis. *J Med Life*. 2015;8(3):319–25.
28. Xiong J, Chen J, Tu J, Ye W, Zhang Z, Liu Q, et al. Association of HLA-B27 status and gender with sacroiliitis in patients with ankylosing spondylitis. *Pak J Med Sci*. 2014;30(1):22–7.
29. Rosenbaum JT. New developments in uveitis associated with HLA B27. *Curr Opin Rheumatol*. 2017;29(4):298–303.
30. Loh AR, Acharya NR. Incidence rates and risk factors for ocular complications and vision loss in HLA-B27-associated uveitis. *Am J Ophthalmol*. 2010;150(4):534–42.
31. Pathanapitoon K, Dodds EM, Cunningham ET, Rothova A. Clinical spectrum of HLA-B27-associated ocular inflammation. *Ocul Immunol Inflamm*. 2017 ;25(4):569-76.
32. Muñoz-Fernández S, De Miguel E, Cobo-Ibáñez T, Madero R, Ferreira A, Hidalgo MV, et al. Enthesis inflammation in recurrent acute anterior uveitis without spondylarthritis. *Arthritis Rheum*. 2009;60(7):1985–90.
33. Sampaio Barros PD, Pereira IA, Hernández-Cuevas C, Berman A, Burgos-Vargas R, Gutierrez M, et al. An analysis of 372 patients with anterior uveitis in a large Ibero-American cohort: the RESPONDIA Group. *Clin Exp Rheumatol*. 2013;31(4):484–9.
34. Teixeira LP, Abrahão MM, Dália ER, Campos LM, Junior JJ, Da Fonseca VC. Study of the prevalence of uveitis in a tertiary ophthalmology hospital in Teresina, Piauí, Brazil. *Rev Bras Oftalmol*. 2016;75(3):174–80.
35. de Winter J, van Mens L, van der Heijde D, Landewé R, Baeten D. Prevalence of peripheral and extra-articular disease in ankylosing spondylitis versus non-radiographic axial spondyloarthritis: a meta-analysis. *Arthritis Res Ther*. 2016;18(1):1–11.
36. Cantini F, Niccoli L, Nannini C, Cassarà E, Kaloudi O, Rizzello F, et al. Case-control Study on dactylitis, enthesitis, and anterior uveitis in spondyloarthritis associated with inflammatory bowel diseases: role of coexistent psoriasis. *J Rheumatol*. 2017;44(9):1341–6.
37. Pasadhika S, Rosenbaum JT. Update on the use of systemic biologic agents in the treatment of noninfectious uveitis. *Biol Targets Ther*. 2014;8:67–81.
38. Muñoz-Fernández S, Hidalgo MV, Fernández-Melón J, Bonilla G, Ruiz-Sancho D, et al. Sulfasalazine reduces the number of flares of acute anterior uveitis over a one-year period. *J Rheumatol*. 2003;30(6):1277–9.
39. Oray M, Tu al-Tutkun . Treatment of juvenile idiopathic arthritis-associated uveitis. *Turk Oftalmoloji Derg*. 2016;46(2):77–82.
40. Vallet H, Riviere S, Sanna A, Deroux A, Moulis G, Addimanda O, et al. Efficacy of anti-TNF alpha in severe and/or refractory Behçet's disease: Multicenter study of 124 patients. *J Autoimmun*. 2015;62:67–74.
41. Llorenç V, Mesquida M, Sainz de la Maza M, Blanco R, Calvo V, Maíz O, et al. Certolizumab Pegol, a new Anti-TNF- in the armamentarium against ocular inflammation. *Ocul Immunol Inflamm*. 2014;24(2):167-72.
42. Dick AD, Tugal-Tutkun I, Foster S, Zierhut M, Melissa Liew SH, Bezlyak V, et al. Secukinumab in the treatment of noninfectious uveitis: Results of three randomized, controlled clinical trials. *Ophthalmology*. 2013;120(4):777–87.

Corresponding author:

Isabela Miyazaki Solano Vale
 Avenida Pedra Branca, 363 – Palhoça, Santa Catarina - SC -Brazil
 E-mail: miyazakisabela@gmail.com