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Original article

Profile of the use of disease modifying drugs in the Brazilian Registry of Spondyloarthritides

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ABSTRACT

Introduction: Few studies have evaluated the profile of use of disease modifying drugs (DMD) in Brazilian patients with spondyloarthritis (SpA).
Methods: A common research protocol was applied prospectively in 1505 patients classified as SpA by criteria of the European Spondyloarthropathies Study Group (ESSG), followed at 29 referral centers in Rheumatology in Brazil. Demographic and clinical variables were obtained and evaluated, by analyzing their correlation with the use of DMDs methotrexate (MTX) and sulfasalazine (SSZ).
Results: At least one DMD was used by 73.6 % of patients: MTX by 29.2 % and SSZ by 21.7%, while 22.7 % used both drugs. The use of MTX was significantly associated with peripheral involvement, and SSZ was associated with axial involvement, and the two drugs were more administered, separately or in combination, in the mixed involvement ($p < 0.001$). The use of a DMD was significantly associated with Caucasian ethnicity (MTX , $p = 0.014$), inflammatory back pain (SSZ, $p = 0.002$) , buttock pain (SSZ, $p = 0.030$), neck pain (MTX, $p = 0.042$), arthritis of the lower limbs (MTX, $p < 0.001$), arthritis of the upper limbs (MTX, $p < 0.001$), enthesitis ($p = 0.007$), dactylitis (MTX, $p < 0.001$), inflammatory bowel disease (SSZ, $p < 0.001$) and nail involvement (MTX, $p < 0.001$).
Conclusion: The use of at least one DMD was reported by more than 70% of patients in a large cohort of Brazilian patients with SpA, with MTX use more associated with peripheral involvement and the use of SSZ more associated with axial involvement.

Perfil do uso de drogas modificadoras de doença no registro brasileiro de espondiloartrites

Palavras-chave:
Espondiloartrites
Tratamento
Drogas modificadoras de doença
Metotrexato
Sulfasalazina

RESUMO

Introdução: Poucos estudos avaliaram o perfil do uso de drogas modificadoras de doença (DMD) em pacientes brasileiros com diagnóstico de espondiloartrite (EpA).
Métodos: Um protocolo comum de investigação foi prospectivamente aplicado em 1505 pacientes classificados como EpA pelos critérios do Grupo Europeu de Estudo das Espondiloartrites (ESSG), acompanhados em 29 centros de referência em Reumatologia no Brasil. Variáveis clínicas e demográficas foram obtidas e avaliadas, analisando-se suas correlações com o uso das DMD metotrexato (MTX) e sulfasalazina (SSZ).
Resultados: Pelo menos uma DMD foi utilizada por 73,6% dos pacientes, sendo MTX por 29,2% e SSZ por 21,7%, enquanto 22,7% utilizaram ambas as drogas. O uso do MTX foi significativamente associado ao acometimento periférico, e a SSZ foi associada ao comprometimento axial, sendo que as duas drogas foram mais utilizadas, isoladas ou combinadas, no comprometimento misto ($p < 0,001$). O uso de uma DMD esteve significativamente associado à etnia branca (MTX; $p = 0,014$), lombalgia inflamatória (SSZ; $p = 0,002$), dor em nádegas (SSZ; $p = 0,030$), cervicalgia (MTX; $p = 0,042$), artrite de membros inferiores (MTX; $p < 0,001$), artrite de membros superiores (MTX; $p < 0,001$), entesite ($p = 0,007$), dactilite (MTX; $p < 0,001$), doença inflamatória intestinal (SSZ; $p < 0,001$) e acometimento ungueal (MTX; $p < 0,001$).
Conclusão: O uso de pelo menos uma DMD foi referido por mais de 70% dos pacientes numa grande coorte brasileira de pacientes com EpA, sendo o uso do MTX mais associado ao acometimento periférico e o uso da SSZ mais associado ao acometimento axial.

Introduction

Spondyloarthritides are a group of chronic inflammatory diseases with similar clinical and genetic characteristics, which allows their analysis within the same group. Ankylosing spondylitis (AS) is a disease with predominantly axial clinical impairment, while psoriatic arthritis (PA), reactive arthritis, arthritis associated with inflammatory bowel disease and undifferentiated SpA often show an important peripheral involvement.[1] Recognizing this extension of the concept itself, SpAs were recently classified into axial[2] and peripheral[3]. The evaluation of Brazilian[4] and Latin American[5] patients with SpA reveals that, besides the characteristic axial involvement, often a significant number of patients with peripheral involvement are detected.

Studies evaluating the treatment of SpA, especially AS[6,7] and PA,[8,9] show that the use of disease-modifying drugs (DMD), such as methotrexate, sulfasalazine, and leflunomide, is related more to the involvement of the peripheral *versus* axial involvement.

This study analyzes the prescription of DMD for a large cohort of Brazilian patients with SpA.

Patients and methods

This is a prospective, observational, multicenter study with 1505 patients from 29 referral centers participating in the Registro Brasileiro de Espondiloartrites (RBE). All patients fulfilled the criteria of the European Group for the Study of Spondyloarthropathies (ESSG).[10] Data were collected from June 2006 to December 2009. The BRS participates in RESPONDIA (Registro Iberoamericano de Espondiloartrites) group, consisting of nine Latin American countries (Argentina, Brazil, Costa Rica, Chile, Ecuador, Mexico, Peru, Uruguay and Venezuela) and the two countries of the Iberian Peninsula (Spain and Portugal) .

The joint investigation protocol included demographic (gender, race, family history, HLA-B27), osteoarticular clinical (inflammatory back pain, buttock pain, neck pain, hip pain, lower extremity arthritis, arthritis of the lower limbs, enthesitis, dactylitis), extra-articular clinical (uveitis, inflammatory bowel disease [IBD], psoriasis, urethritis), and laboratory (erythrocyte sedimentation rate - ESR and C-reactive protein - CRP) variables.

Patients were evaluated for treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, DMD and biological agents. Regarding the use of DMD, methotrexate (MTX), sulfasalazine (SSZ) and leflunomide (LFN) were evaluated.

For the diagnosis of AS, New York criteria were used;[11] for psoriatic arthritis, the patients had to meet the criteria of Moll and Wright.[12] The diagnosis of reactive arthritis was considered if were present: asymmetric oligoarthritis of the lower limbs with enthesopathies and/or inflammatory lumbar pain arousing after enteric or urogenital infection,[13] and spondylitis/arthritis associated with inflammatory bowel disease, if the patient showed inflammatory axial features and/or peripheral joint involvement, associated with confirmed Crohn's disease or ulcerative colitis.

Statistical analysis. Categorical variables were compared using χ^2 and Fisher exact test, and continuous variables were compared using ANOVA. A value of $p < 0.05$ was considered significant, and $0.05 > p > 0.10$ was considered as statistical trend.

Results

Data analysis revealed that at least one DMD was used by 73.6% of patients; 51.9% reported the use of MTX - 29.2% as monotherapy and 22.7% with SSZ; and 44.4% used SSZ, of whom 21.7% as monotherapy. The use of leflunomide was reported by 0.2% of patients; for this reason, this agent was not included in the statistical analysis.

With respect to joint involvement, MTX was significantly associated with peripheral involvement and SSZ was associated with axial involvement, and the two drugs were used more often, as monotherapy or in combination, in the mixed involvement ($p < 0.001$) (Table 1).

The demographic variables showed that MTX was associated with Caucasian ethnicity ($p = 0.014$). Gender, family history and HLA-B27 were not associated with the use of any DMD (Table 2).

With respect to the clinical picture, MTX was significantly associated with cervical involvement ($p = 0.042$), arthritis of the lower limbs ($p < 0.001$), arthritis of the upper limbs ($p < 0.001$), cutaneous psoriasis ($p < 0.001$), dactylitis ($p < 0.001$) and nail involvement ($p < 0.001$). By the other hand, SSZ was associated with inflammatory back pain ($p = 0.002$), buttock pain ($p = 0.030$) and inflammatory bowel disease ($p < 0.001$), while the use of both drugs was associated with enthesites ($p = 0.007$). Coxofemoral pain, anterior uveitis and urethritis showed no association with the use of DMD (Table 3).

Discussion

This study confirms that the use of DMD is very common in Brazilian patients. In this multicenter study, which included patients from the five Brazilian regions (Southeast, South, Midwest, Northeast and North), the use of at least one DMD was reported by nearly three in four patients with SpA, with 51.7% to MTX and 44.4% to SSZ. The use of at least one DMD may be greatly associated with the significant number of patients with peripheral joint and mixed involvement observed in our cases.[4] A study evaluating 216 patients with AS in Tur-

Table 1 – Results of using DMD, according to the clinical picture.

	MTX(%)	SSZ (%)	MTX + SSZ (%)	p
Mixed	51.8	46.2	58.1	
Axial	24.4	43.0	24.3	< 0.001
Peripheral	19.2	4.9	8.3	
Enthesial	4.6	5.9	9.3	

DMD, disease modifying drug, MTX, methotrexate, SSZ, sulfasalazine.

Table 2 – Results of using DMD, according to epidemiological data.

		MTX (%)	SSZ (%)	MTX + SSZ (%)	p
Gender	– Male	68.6	74.0	75.4	0.161
	– Female	31.4	26.0	24.6	
Race	– Caucasian	70.2	65.1	61.0	0.014
	– Non Caucasian	29.8	34.9	39.0	
Family history		83.6	81.7	82.1	0.734
HLA-B27	– Positive	66.3	70.1	75.4	0.115
	– Negative	33.7	29.9	246	

DMD, disease modifying drug; MTX, methotrexate; SSZ, sulfasalazine.

Table 3 – Results of using DMD, according to the clinical data.

	MTX (%)	SSZ (%)	MTX + SSZ (%)	p
Inflammatory low back pain	60.8	70.9	72.7	0.002
Buttock pain	39.4	52.3	46.9	< 0.001
Neck pain	33.7	28.4	23.1	0.042
Coxofemoral pain	25.6	27.3	22.6	0.497
Arthritis of lower limb	58.1	42.5	54.5	< 0.001
Arthritis of upper limb	35.3	13.8	19.4	< 0.001
Enthesitis	51.5	47.1	56.0	0.007
Dactylitis	15.3	4.3	7.9	< 0.001
Uveitis	16.2	22.3	20.5	0.147
Cutaneous psoriasis	38.7	2.4	10.6	< 0.001
Nail	23.0	2.8	5.3	< 0.001
Inflammatory bowel disease	2.1	8.9	5.0	< 0.001
Urethritis	5.2	2.1	5.3	0.147

DMD, disease modifying drug; MTX, methotrexate; SSZ, sulfasalazine.

key revealed that 77.5% received SSZ and 15% MTX, and 9% received anti-TNF agents.[14]

The use of MTX has been studied in AS in the past two decades. Considering in general that its use is indicated for patients with predominantly axial involvement, the clinical response was not favorable;[15-17] the only two studies that demonstrated a better response to MTX were Latin American: one Brazilian[18] and one Mexican.[19] Also, the use of MTX for short period of time (16 weeks) might not be enough for the desired effect of the medication. On the other hand, MTX has been used for over 50 years in PA patients, with good results,[21-23] being the basal drug of first choice.

The present study confirmed this trend of MTX use in cases of peripheral involvement, associated or not with axial involvement. Statistical association with arthritis of the lower and upper limbs was noted. The association with Caucasians seems to be related to the presence of psoriasis and its sequels (dactylitis and nail involvement) as shown in the literature. [24,25]

Sulfasalazine is the most commonly used conventional DMD in AS.[6] Its use in AS comes from the 1980s, and its main action would be in cases of associated peripheral involvement.[26,27] The same action profile is observed in PA.[28-30] SSZ is also used in the case of reactive arthritis with gastrointestinal etiology[31] and in the arthritides associated with inflammatory bowel disease.[32,33] In contrast to what is traditionally observed in the literature, the use of SSZ in the present study was associated with axial involvement, particularly inflammatory low back pain and buttock pain, and with enteropathic arthritis.

However, although SSZ is significantly more used than MTX in patients with inflammatory bowel disease, it is noteworthy that less than 9% of patients with this type of impairment were using SSZ. The explanation for this use in patients with axial involvement lies in the fact that many rheumatology services in Brazil use empirically at least one DMD, preferably SSZ, in patients with AS, before prescribing biological agents, since we have an impressive number of patients with mixed (axial and peripheral) joint involvement. Regarding the entheseal involvement, quite frequent in our series,[34] is common practice the prescription of both MTX and SSZ, as monotherapy or in combination, for its treatment.

Conflicts of interest

The authors declare no conflicts of interest.

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