Systemic Immunomodulatory Therapy in Idiopathic Anterior Uveitis: 10-Year Profile

Análise do Perfil de Imunomodulação Sistémica em Doentes com Uveíte Anterior Idiopática ao Longo de 10 Anos

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ABSTRACT

INTRODUCTION: Anterior uveitis (AU) without underlying systemic disease sometimes requires immunomodulatory therapy (IMT) to control inflammation. Our primary purpose was to characterize the immunomodulatory therapy profile in patients with idiopathic AU (IAU) at our ophthalmology department.

METHODS: Data from all patients with AU under IMT evaluated in the past 10 years at the uveitis department of Hospital de S. João were reviewed. Data regarding demographics, type and duration of IMT, the pattern of disease remission and relapses were noted.

RESULTS: A total of 158 patients with AU under IMT were reviewed, from whom 30 patients with IAU were included and 128 patients with underlying systemic disease were excluded. The mean total follow-up time was 73.87±44.73 months [range 12-168]. Twenty-one patients (70%) presented bilateral involvement. The mean duration of treatment was 46.50±34.40 months and 21 patients (70%) were under IMT for at least 2 years. Methotrexate was the most widely used immunomodulator agent able to maintain disease remission (n=26, 86.7%) and the first attempt in IMT in 96.2% of the patients. Two patients (6.7%) needed the association of methotrexate and adalimumab to control the disease. Before treatment, patients presented a mean of 2.07±1.31 flare-ups per year, significantly decreasing to a mean of 0.60±0.67 relapses per year with the implementation of IMT (p<0.001). Twelve patients (40%) stopped treatment, in 5 cases (41.7%) a medical-based decision because of long-term remission of the disease, in 5 cases (41.7%) by patient initiative and in 2 cases (16.7%) because of medication side effects. Three (25%) of these 12 patients developed recurrence after a mean period of 10.67±6.43 months without IMT [range 6-18]. All patients who stopped IMT based on medical decision had been treated for a minimum of two years [range 2-5.8] without relapse of ocular inflammation.

CONCLUSION: Some patients with IAU need IMT to achieve the ultimate goal of durable remission. Methotrexate was the most widely used immunomodulatory drug for the treatment of IAU in our department. The medical decision to stop IMT based on a 2-year remission period appears to be a safe approach.

KEYWORDS: Immunomodulating Agents; Uveitis, Anterior/drug therapy.

RESUMO

INTRODUÇÃO: A uveíte anterior idiopática (UAI) requer por vezes tratamento com imunomodulação sistémica para controlo da doença. O nosso principal objetivo prende-se com a caracterização do perfil imunomodulação sistémica (IMS) em doentes com UAI no nosso departamento de oftalmologia.

MÉTODOS: Foram revistos os processos de todos os doentes com UA sob IMS avaliados nos últimos 10 anos pela secção de inflamação do Hospital de S. João, com análise de características demográficas, tipo e duração de IMS e padrão de remissão e recidiva da doença.

RESULTADOS: Foram avaliados 158 doentes com UA sob IMS, dos quais foram incluídos 30 doentes com UAI (após exclusão de 128 doentes com doença sistémica subjacente). O tempo médio total de seguimento foi de 73,87±44,73 meses [12-168]. Vinte e um doentes (70%) apresentaram envolvimento bilateral. A duração média do tratamento foi de 46,50±34,40 meses e 21 doentes (70%) estiveram sob IMS durante pelo menos 2 anos. O metotrexato foi o fármaco mais utilizado, capaz de manter a remissão da doença (n=26; 86,7%) e foi a primeira tentativa de IMS em 96,2% dos doentes. Dois doentes (6,7%) necessitaram da associação de metotrexato e adalimumab para controlo da doença. A IMS permitiu uma diminuição significativa do número médio de recidivas por ano (2,07±1,31 recidivas/ano para 0,60±0,67 recidivas/ano; p<0,001. Doze doentes (40%) interromperam o tratamento, em 5 casos (41,7%) uma decisão médica por remissão prolongada da doença, em 5 casos (41,7%) por iniciativa do paciente e em 2 casos (16,7%) por efeitos adversos da IMS. Três (25%) destes 12 doentes desenvolveram recorrência após um período médio de 10,67±6,43 meses sem TMI [6-18]. Todos os doentes que interromperam o tratamento com base na decisão médica foram tratados por um período mínimo de dois anos [2-5,8] sem recidiva da inflamação ocular.

CONCLUSÃO: Alguns doentes com UAI precisam de IMS para atingir uma remissão duradoura da doença. O metotrexato foi o fármaco imunomodulador mais utilizado no tratamento da UAI no nosso departamento. A decisão médica de interromper a IMS com base num período de remissão de 2 anos parece ser uma abordagem segura.

PALAVRAS-CHAVE: Imunomoduladores; Uveíte Anterior/tratamento farmacológico.

INTRODUCTION

Inflammatory ocular conditions are a significant cause of visual loss affecting young patients. Anterior uveitis (AU) is the most common form of intraocular inflammation, affecting the iris and the ciliary body, with varying incidence rates reported in the literature, similar in males and females, although more prevalent in females.[1,2] Generally, idiopathic anterior uveitis (IAU) accounts for most cases of AU, although cases of AU associated with underlying systemic disease are still significant.[3] The heterogenicity of this epidemiological data is probably related to the latter being more relevant in tertiary centers.[4] The pathophysiology behind IAU remains poorly understood.[5]

The mainstay of therapy for AU is topical corticosteroids, which are usually effective and well tolerated, although systemic therapy or complementary intra or periocular injections are sometimes necessary to fully control the disease manifestations.[6] Immunomodulatory drugs are initiated in refractory cases as an attempt to achieve disease remission or to minimize long-standing corticosteroids side effects.[7] Surgical interventions are necessary only if structural ocular complications develop (such as synechiae, secondary cataract and glaucoma).[8]

The ideal duration of immunomodulatory therapy (IMT) is still controversial. Foster *et al* suggests a minimum 2-year period under IMT as a good milestone, as long as there are no signs of inflammatory activity and no need for corticosteroids in all forms. After this period of remission, IMT can be slowly tapered off, making sure there are no relapses of ocular inflammation occur.[8] Treatment efficacy is critical to avoid the consequences of long-term ocular inflammation, associated with significant morbidity among the young active population, including permanent vision loss.[9] In most cases, AU prognosis is good assuming early detection and adequate treatment.[8] After all, clear therapeutic guidelines and protocols regarding the appropriate length of time of IMT for patients with idiopathic AU have not been developed. Since there is no underlying systemic disease, all decisions regarding IMT management fall to the ophthalmologist.[10]

Understanding the features of the patients who eventually require treatment with systemic immunomodulators in the course of their inflammatory disease will help us to better characterize diseases' natural history, establish the response level and duration of treatment we must expect and better define prognostic factors.

Our primary purpose was to characterize the immunomodulatory therapy profile in patients with idiopathic AU (IAU) under monitorization at our uveitis department in the past 10 years, to determine both efficacy and safety of the implemented treatment as well as relapse incidence.

METHODS

STUDY DESIGN, SETTING AND PARTICIPANTS

This is a retrospective, single-center, longitudinal study of patients with unilateral or bilateral idiopathic anterior uveitis, followed in the Ophthalmology Department of Centro Hospitalar Universitário São João (Porto, Portugal).

Data from all patients under systemic immunomodulatory therapy evaluated in the past 10 years at the uveitis department of Hospital de S. João were collected by chart review. Initial patient screening searched for patients under methotrexate, adalimumab, cyclosporine, azathioprine, infliximab and certolizumab, which provided a total of 509 medical processes. Afterward, all patients with evidence of systemic disease or patients with positive HLA-B27 haplotype were excluded, as well as patients without proper medical records. Infectious, postsurgical, and posttraumatic uveitis cases were also excluded. We further divided patients with intraocular inflammation by anatomical site involved and selected all cases of idiopathic anterior uveitis (IAU) to include in this study.

DATA COLLECTION

The following information was extracted for each study patient, based on the patient's electronic medical records and procedure reports: demographic data, AU initial episode's characterization (general details of the ophthalmological examination), type and duration of IMT, need for adjuvant corticosteroid therapy and pattern of disease remission and relapses were recorded. Intolerance or toxicity as well as the treatment's discontinuation were also documented.

STATISTICAL ANALYSIS

Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess whether each continuous variable followed a normal distribution. Normally distributed data is reported as mean ± standard deviation (SD) while non-normally distributed data is reported as median and interquartile range (IQR). Categorical variables are presented as absolute numbers and percentage. Parametric or non-parametric tests (student's T-Test or Mann-Whitney, respectively) were used for continuous variables comparison between groups, according to the normality of data. Categorical variables were compared using Chi-square or Fisher´s exact tests.

A p-value < 0.05 was considered statistically significant. Statistical analysis was done using the IBM SPSS® software (version 27.0, Chicago, IL).

RESULTS

We analyzed 158 patients with AU under immunomodulatory therapy, from whom 30 patients with idiopathic anterior uveitis were included and 128 patients with AU with evidence of underlying systemic disease were excluded.

DEMOGRAPHIC FEATURES AND AU CHARACTERIZATION

The mean total follow-up time of the patients in this sample was 73.87±44.73 months [range 12-168]. The mean patients' age was 33.57±20.07 years [range 5-67] and 20 patients (66.7%) were female. Six (20%) patients presented AU with macular edema, adequately documented by spectral domain-optical coherence tomography. Regarding initial features at the time of presentation, 6 patients (20%) had granulomatous AU (classified according to the presence of large and mutton-fat keratic precipitates on the corneal endothelium) and 7 patients (23.3%) had hypertensive AU (that resolved after adequate inflammation control, with the transitory need for IOP-lowering medications in 3 patients). Twenty-one patients (70%) presented bilateral involvement of the IAU (Table 1).

Table 1. Demographics and baseline anterior uveitis characterization.

Parameter	Total Subjects (n= 30)
Age, years	33.57 ± 30.07 [5-67]
Gender, male/female	10 (33.3) / 20 (66.7)
Total follow-up time, months	73.87 ± 44.73 [12-168]
P25	36
P50	66
P75	105
AU with macular edema	6 (20)
Granulomatous presentation	6 (20)
Hypertensive presentation	7 (23.3)
Unilateral / Bilateral	9 (30) / 21 (70)

Notes: data presented as mean ± standard deviation or frequency n (%), [range].

AU, anterior uveitis.

TREATMENT

The mean duration of treatment was 46.50±34.40 months [range 3-130] and 21 patients (70%) were under IMT for at least 2 years. Methotrexate was the most widely used immunomodulator agent able to maintain disease remission (n=26,

86.7%). It was the first attempt in immunomodulatory therapy in 96.2% of the patients. Fifteen patients (53.6%) were using oral methotrexate, and 13 patients (46.4%) were on the subcutaneous formulation due to gastrointestinal intolerance and/or improving bioavailability. Adalimumab (monthly 40 mg subcutaneous injection) was used in 1 patient, due to methotrexate intolerance. In 2 patients, ocular inflammation was only controlled with an association of methotrexate and adalimumab. Three patients (10%) needed additional intra/periocular corticosteroids, due to persistent macular edema despite IMT. This adjuvant approach was effective in all cases. Before IMT, patients presented a mean of 2.07±1.31 relapses per year, a number that significantly decreased to a mean of 0.60±0.67 with the implementation of effective IMT (p<0.001) (Table 2).

Table 2. Treatment and inflammation control. Comparison between the number of relapses per year before and after IMT.

Parameter	Total Subjects (n= 30)	
Immunomodulatory agent		
Methotrexate	26 (86.7)	
Adalimumab	1 (3.3)	
Methotrexate + Adalimumab	2 (6.7)	
Azathioprine	1 (3.3)	
Control after the first immunomodulator	25 (83.3)	
Control after the second immunomodulator	5 (16.7)	
Treatment duration, months	46.50 ± 34.41 [3-130]	
≥ 24	21 (70)	
≥ 36	17 (56.7)	
≥ 48	13 /43.3)	
Adjuvant oral corticosteroids	1 (3.3)	
Adjuvant intra/periocular corticosteroids	3 (10)	
Number of relapses/year before IMT	2.07 ± 1.31	p<0.001[a]
Number of relapses/year after IMT	0.6 ± 0.68	
Methotrexate formulation		
Oral	15 (53.6)	
Subcutaneous	13 (46.4)	
Methotrexate dosage in the oral group, mg/week		
P25	10	
P50	12.5	
P75	15	
Number of patients treated with monthly subcutaneous 40 mg adalimumab	3 (10)	

Notes: data presented as mean ± standard deviation or frequency n (%),[range].

[a] Independent t-test.

IMT, immunomodulatory therapy; P25, percentile 25; P50, percentile 50; P75, percentile 75.

TREATMENT DISCONTINUATION AND RELAPSE PROFILE

Twelve patients (40%) stopped treatment, in 5 cases (41.7%) as a medical-based decision because of long-term remission of the disease, in 5 cases (41.7%) because of a patient unconsented decision and in 2 cases (16.7%) because of side effects of the medication. Patients were monitored for a mean of 31±20.12 months after stopping treatment, during which 3 (25%) out of the 12 patients developed recurrence after a mean period of 10.67±6.43 months [range 6-18] without IMT (Table 3).

Two of these patients had been treated for less than one year. Eight out of the 9 patients (88%) who stopped treatment and did not relapse had been treated for more than 2 years, without any predominance regarding the type of systemic drug used. All patients who stopped IMT based on medical decision had been treated for a minimum of two years [range 2-5.8] and no relapse of ocular inflammation occurred among them.

Patients who relapsed were reinstated on the previous effective systemic drugs along with topical anti-inflammatory drugs, except the patient who developed side effects of the medication, that were successfully controlled with topical steroids only.

Table 3. Incidence of treatment discontinuation and relapse profile.

Parameter	Total Subjects (n= 30)
Treatment discontinuation	12 (40%)
Reason to stop	
Side effects	2 (16.7)
Medical decision	5 (41.7)
Patients' unconsented decision	5 (41.7)
Treatment duration according to stop motive	
Side effects	9 ± 3 [6-12]
Medical decision	46.40 ± 18.52 [24-70]
Patients' unconsented decision	34.86 ± 15.59 [12-94]
Follow-up time after stopping treatment, months	31 ± 20.12
Relapse after stopping treatment	3 (25%)
Time between stop and relapse	10.67 ± 6.43 [range 6-18]

Notes: data presented as mean ± standard deviation or frequency n (%), [range].

DISCUSSION

This study represents an attempt to review the most relevant aspects concerning systemic immunomodulatory therapy in idiopathic anterior uveitis. This common inflammatory entity, when uncontrolled or inadequately managed, may become chronic and have a serious impact on visual function. Clear therapeutic guidelines and protocols regarding the appropriate length of time of IMT for patients with idiopathic AU have not been developed.

Idiopathic anterior uveitis is typically well controlled

with topical treatment, with only a minority of patients requiring IMT.[11] At our uveitis department, the prevalence of AU associated with underlying systemic disease needing IMT was significantly higher when compared to idiopathic AU, which is in line with the prevalence rates reported in other studies in the literature.[2] Our clinic runs in a tertiary central hospital, with a high volume of patients with ocular inflammation in the context of systemic diseases, as our hospital is a reference center for rheumatologists and autoimmune diseases experts.[4,12]

Our study presented a mean follow-up period of patients with IAU of around 6 years. This is a very significant length of follow-up, allowing us to understand whether the implementation of appropriate treatment effectively controls the disease in the long-term, thus preventing the occurrence of repetitive episodes of intraocular inflammation that ultimately would lead to serious complications and permanent visual disability.[13] IAU affected predominantly young female patients, which is in line with other publications.[13,14] Our study agrees with other studies in the literature concerning the heterogeneity of the most common clinical signs at AU presentation episode (unilateral *vs* bilateral, granulomatous inflammation and hypertensive response).[15]

Since there is not a known underlying systemic process to target, treatment is directed to symptomatic relief and prevention of complications with non-specific anti-inflammatory therapies such as steroids and immunosuppressive agents.[16] Methotrexate was the most widely used systemic immunomodulatory drug for the treatment of IAU in our department, both in its oral or subcutaneous formulation. Several studies agree with this first-line therapy choice in patients with anterior uveitis, and in our study, it was indeed the first attempt in immunomodulatory therapy in 96.2% of the patients.[17] Gangaputra *et al* suggests a good effect of methotrexate for the management of inflammatory activity and for achieving corticosteroid-sparing objectives, although many months may be required for therapeutic success.[18] Adalimumab (subcutaneous injection of 40 mg every two weeks) was necessary when there was methotrexate intolerance or when ocular inflammation was not adequately controlled with methotrexate monotherapy.

Periocular corticosteroid injection was needed in 3 patients due to macula edema persistence despite systemic IMT, an intervention that effectively treated this inflammatory complication in all of them. Sen *et al* evaluated the benefits and complications of periocular corticosteroid injections in patients with ocular inflammatory disorders, concluding they were effective in improving reduced visual acuity attributed to macular edema, with cataract and ocular hypertension occurring in only a minority of cases.[6] None of our patients developed such complications.

Regarding tolerance, only 2 out of 30 patients in this sample stopped treatment (specifically, oral methotrexate) because of significant side effects, which represents an overall favorable safety profile. All patients who stopped IMT because of side effects of the medication had been treated for less than 1 year. Patients under IMT also got frequent laboratory evaluation, to promptly detect and address toxicity (by switching to the subcutaneous formulation or a different drug if necessary). This practical approach agrees with the guidelines and consensus about immunosuppressive therapy management.[19] All patients under methotrexate in our sample received appropriate folic acid supplementation.

In our study, 90% of patients were treated for more than one year and 70% were treated for more than two years. IMT was associated with a statistically significant reduction in the number of relapses per year, defined as the increase in the inflammatory activity after a period of remission (development of pain, photophobia, and red eye; the presence of ciliary injection, anterior chamber cells or flare or presence of keratic precipitates).

The medical decision to safely stop immunomodulatory treatment based on a 2-year remission period appears to be a safe approach, without increasing the incidence of recurrence. In the study of Foster *et al*, a minimum 2-year period under IMT was also identified as a safe recommendation, keeping in mind that the presence of signs of active disease is preponderant in the decision to stop IMT.[8] Eight out of the 9 patients (88%) who stopped treatment and did not relapse had been treated for more than 2 years, without any predominance regarding type of systemic drug used.

Regarding the 3 patients (25%) with relapse of the AU after treatment discontinuation, 2 of these had been treated for less than 1 year. In the study of Sobrin *et al*, several predictors associated with medication-free remission of anterior uveitis were identified, which included longer duration of uveitis, younger age, bilateral involvement, prior cataract surgery, presence of keratic precipitates and synechiae and the existence of underlying systemic diagnoses.[20] In our cohort, none of the patients had an underlying systemic diagnosis and the 3 patients who relapsed were on average 45 years old, had the AU diagnosis for a mean period of 5 years and 2 of them had previous cataract surgery.

The mean time for recurrence after stop was 11 months, ranging from 6 to 18 months, and this result must be outlined in a mean period of surveillance of 31 months after IMT stop. This implies a long follow-up period for patients with IAU even after they have stopped systemic immunomodulatory therapy. Clinical guidelines are necessary to clarify and uniformize the most appropriate length of this follow-up.[10]

Our study limitations include its small sample size and single-center design. Nonetheless, as a tertiary hospital, we were able to analyze a cohort of patients with idiopathic anterior uveitis with a significative length of follow-up, which is an advantage regarding the long-term evolution and follow-up of these patients. Further studies are warranted to compare idiopathic anterior uveitis, AU associated with underlying systemic disease and AU that could be fully controlled with only topical treatment, thus not requiring systemic IMT. This kind of revision would possibly highlight specific characteristics of each group, thus allowing for the establishment of management protocols in the future.

CONCLUSION

To conclude, several patients with IAU need IMT to achieve the ultimate goal of durable remission. Methotrexate was the most widely used systemic immunomodulatory drug for the treatment of IAU in our department. The medical decision to safely stop immunomodulatory treatment based on a 2-year remission period appears to be a safe approach, without increasing the incidence of recurrence.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

LF, MIS, CP, COF, STC and JRA: Preparing the material.

AMF, RVM and JRA: Data collection and analysis, first draft of the manuscript.

All the authors contributed to the conception of the study, read and approved the final manuscript.

LF, MIS, CP, COF, STC e JRA: A preparação do material.

AMF, RVM e JRA: A recolha e análise de dados, primeira versão do manuscrito.

Todos os autores contribuíram para a conceção do estudo, leram e aprovaram o manuscrito final.

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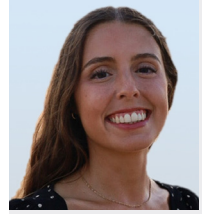

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