Clinical science

Methotrexate versus conventional disease-modifying antirheumatic drugs in the treatment of non-anterior sarcoidosis-associated uveitis

Mathilde Leclercq ,[1,2] Pascal Sève,[3] Lucie Biard,[4] Mathieu Vautier,[2] Georgina Maalouf,[2] Gaëlle Leroux,[2] Fanny Domont,[2] Adélaïde Toutée,[5] Christine Fardeau ,[5] Thomas Sales de Gauzy,[5] Sara Touhami,[5] Laurent Kodjikian ,[6] Patrice Cacoub,[2] Bahram Bodaghi,[5] David Saadoun,[2] Anne-Claire Desbois[2]

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For numbered affiliations see end of article.

Correspondence to
Dr Mathilde Leclercq, CHU de Rouen, Rouen, France; mathilde.leclercq@chu-rouen.fr

BB and DS contributed equally.

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ABSTRACT

Aims To compare the safety and efficacy of methotrexate (MTX), mycophenolate mofetil (MMF) and azathioprine (AZA) in non-anterior sarcoidosis-associated uveitis.

Methods Retrospective study including non-anterior sarcoidosis-associated uveitis according to the revised International Workshop on Ocular Sarcoidosis criteria. The primary outcome was defined as the median time to relapse or occurrence of serious adverse events leading to treatment discontinuation.

Results 58 patients with non-anterior sarcoidosis-associated uveitis (MTX (n=33), MMF (n=16) and AZA (n=9)) were included. The time to treatment failure (ie, primary outcome) after adjustment for corticosteroids dose and the presence of vasculitis was significantly higher with MTX (median time of 34.5 months with MTX (IQR: 11.8 –not reached) vs 8.4 months (3.1–22.9) with MMF and 16.8 months (8.0–90.1) with AZA (p=0.020)). The risk of relapse at 12 months was more than twice lower in MTX as compared with MMF (p=0.046). Low visual acuity at the last visit was significantly lower with MTX (4% vs 9% in MMF vs 57% in AZA group (p=0.008)). Regarding all 75 lines of treatment (MTX (n=39), MMF (n=24) and AZA (n=12)), MTX was more effective than MMF and AZA to obtain treatment response at 3 months (OR 10.85; 95% CI 1.13 to 104.6; p=0.039). Significant corticosteroid-sparing effect at 12 months (p=0.035) was only observed under MTX. Serious adverse events were observed in 6/39 (15%), 5/24 (21%) and 2/12 (17%) with MTX, MMF and AZA, respectively.

Conclusion In non-anterior sarcoidosis-associated uveitis, MTX seems to be more efficient compared with AZA and MMF and with an acceptable safety profile.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Methotrexate, mycophenolate mofetil and azathioprine have shown their efficacy in the treatment of non-anterior sarcoidosis-associated uveitis. However, no studies have compared these immunosuppressive drugs.

WHAT THIS STUDY ADDS

⇒ The occurrence of the primary outcome (relapse and/or serious adverse events) was significantly lower with methotrexate as compared with the other groups (p=0.020).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Methotrexate should be used as first-line immunosuppressive drug in non-anterior sarcoidosis-associated uveitis.

INTRODUCTION

Sarcoidosis is a multisystem disease of unknown aetiology, characterised by epithelioid non-necrotising granulomas.[1] Ocular involvement is the most frequent manifestation of lung symptoms.[2] Uveitis is the most common ocular manifestation, affecting 20%–30% of patients with sarcoidosis.[2] Moreover, uveitis is the first manifestation of sarcoidosis for 21%–78% of patients.[3 4] Anterior uveitis is the most frequently encountered condition (40%–71%),[5] followed by posterior uveitis (10%–40%) and panuveitis (10%–30%).[6]

The treatment strategy in sarcoidosis-associated uveitis is similar to the treatment of non-infectious uveitis of any aetiology. In patients with corticodependency, severe uveitis or comorbidities, immunosuppressive drugs are necessary.[2] Approximately, 20% of patients with sarcoidosis-associated uveitis need immunosuppressive drugs, such as methotrexate (MTX), mycophenolate mofetil (MMF) or azathioprine (AZA).[2 4] Recently, the International Workshop on Ocular Sarcoidosis (IWOS) updated recommendations for the diagnosis and therapeutic management of uveitis during sarcoidosis.[7] No studies have compared the efficacy of these immunosuppressive drugs during sarcoidosis-associated uveitis. Gangaputra *et al*[8] and Rathinam *et al*[9] have compared the efficacy of MTX and MMF in uveitis of all aetiologies, with different outcomes.

The aim of our study was to compare the efficacy and safety of MTX, MMF and AZA in the treatment of non-anterior sarcoidosis-associated uveitis.

MATERIALS AND METHODS

Patients

This was a retrospective observational study conducted in the Internal Medicine and Ophthalmology departments of Pitié-Salpêtrière Hospital, Paris and Hospice Civil, Lyon, between 2000 and 2019. Sarcoidosis-associated uveitis was defined according to the revised IWOS criteria[10] as follows: definite ocular sarcoidosis (ie, compatible uveitis picture with epithelioid non-necrotising granulomas on biopsy), presumed ocular sarcoidosis (ie, compatible uveitis picture with bilateral hilar lymphadenopathy on chest X-ray or CT) and probable ocular sarcoidosis (ie, three specific intraocular signs and two specific systemic investigations in the absence of biopsy and bilateral hilar lymphadenopathy). Only patients with non-anterior uveitis treated with MTX, MMF and AZA as the first immunosuppressive drug, were included. Patients treated with local corticosteroids or systemic corticosteroids without immunosuppressive drugs or with biological agents (ie, anti-TNF-α or tocilizumab) as the first immunosuppressants were excluded.

The choice of first-line immunosuppressive drug (MTX, MMF and AZA) was left to the discretion of the clinician. First-line immunosuppressive drugs were specially studied. Each treatment line involving MTX, MMF or AZA was considered for each patient. Changes in immunosuppressive drugs were secondary to relapse or occurrence of serious adverse events leading to treatment discontinuation. Patients were censored if treatment discontinuation was due to other reasons than those previously mentioned.

The MTX dose ranged between 15 and 25 mg/week, depending on the patient's weight, the MMF dose ranged between 2 and 3 g/day and the AZA dose ranged between 100 and 175 mg/day, depending on the patient's weight. The dose was gradually increased over a period of 2–4 weeks until reaching the target dose. For MTX, the oral or subcutaneous route was left to the discretion of the clinician. The median doses reported in the results section represent the doses at which treatment efficacy was achieved.

Data collection

Collected data included demographic characteristics (age, sex and date of diagnosis), uveitis characteristics (anatomic localisation according to the Standardisation of Uveitis Nomenclature (SUN),[11] course of visual acuity (logMAR), evolution of anterior chamber cells according to SUN classification,[11] evolution of vitreous haze grade according to Nussenblatt classification,[12] the presence of retinal vasculitis based on fluorescein angiography, the presence of inflammatory choroidal lesions based on indocyanine green angiography, the presence of macular oedema based on fluorescein angiography and central foveal thickness measured with optical coherence tomography (Cirrus HD-OCT Carl Zeiss Meditec, Dublin, California, USA and Spectralis, Heidelberg Instruments, Heidelberg, Germany)), systemic manifestations of sarcoidosis, median serum ACE level, treatment characteristics (corticosteroid dose, adverse events). Ophthalmological data were collected at the time of immunosuppressive drug introduction, at 3 months, at 12 months and at the end of follow-up. For bilateral uveitis, the most affected eye was considered for analysis.

Study endpoints

The primary outcome was defined as the median time to relapse or the occurrence of serious adverse events leading to treatment discontinuation. Relapse was defined as an increase of macular thickness and/or the occurrence of new retinal vasculitis lesions and/or the occurrence of new inflammatory choroidal lesions and/or an increase of vitreous haze grade in at least one eye. For the evaluation of the primary end point, only the first line of immunosuppressive treatment was considered.

Secondary outcomes included complete and partial response at 3 months and 12 months for first-line therapy and for all treatment lines, risk of low visual acuity for first-line therapy and for all treatment lines and adverse events. Low visual acuity was defined as a visual acuity in at least one eye of ≥1 logMAR (logarithm of the minimum angle of resolution). Each treatment line was considered per patient for univariate and multivariate analysis. A line of treatment was defined as the sequence from the initiation of a new therapeutic strategy to the next one or last follow-up. We assumed treatment lines as independent.

Complete response was defined as a complete resolution of macular oedema and/or retinal vasculitis lesions and/or inflammatory choroidal lesions, without intraocular inflammation (anterior chamber cells[11] and vitreous haze[12] ≤ 0.5+). Partial response was defined as an improvement of macular oedema and/or retinal vasculitis lesions, without complete resolution, and/or uncontrolled intraocular inflammation (anterior chamber cells[11] and vitreous haze[12] ≥0.5+). Patients with multiple inflammatory lesions, such as macular oedema or retinal vasculitis lesions or inflammatory choroidal lesions, who experienced complete resolution of one parameter but persistent lesions for other parameters without aggravation, were also considered partial responders. The remaining patients were considered as non-responders.

Statistics

Data on categorical variables were summarised as number and per cent and compared using Fisher's exact test. Data on continuous variables were summarised as the median and IQR and were compared using Wilcoxon test or Kruskal-Wallis tests. The distribution of the time to first relapse or adverse event requiring treatment discontinuation (primary outcome) was estimated using Kaplan-Meier method and compared according to treatments with adjustment on corticosteroid dose and presence of retinal vasculitis lesions, using a likelihood ratio test in a Cox regression model. For the evaluation of secondary outcomes, all treatment lines were used for univariate and multivariable analysis, including a random effect on patients. Statistical tests were two sided at the 5% significance level. Statistical analyses were performed by using R Studio V.4.0.1.

RESULTS

First-line therapy

Clinical and ophthalmological characteristics

58 patients were included, of which 33 (57%) patients received MTX, 16 (28%) patients received MMF and 9 (15%) patients received AZA (table 1). There was no significant difference in uveitis characteristics regarding inclusion centres. The median duration (IQR) of uveitis before the use of immunosuppressive drugs was 5 months (0–15) in the MTX group and 3 months in the MMF (0–7) and AZA (0–4) groups. The median dose (IQR) of effective treatment was, respectively, 20 mg/week (15–20) for MTX, 2 g/day (2–2) for MMF and 150 mg/day (100–150) for AZA. Most of the patients were treated with concomitant systemic corticosteroid (95%) and no patient was recently treated with intravitreal implant of dexamethasone.

Uveitis was the first symptom of sarcoidosis for 83% of patients. Regarding systemic manifestation of sarcoidosis, 93%

Table 1 Patients' characteristics at the first-line therapy

	Total (n=58)	Methotrexate (n=33)	Mycophenolate mofetil (n=16)	Azathioprine (n=9)	P value
Median age (years)	43 (33, 59)	56 (37, 68)	44 (34, 67)	28 (24, 37)	0.013
Male sex	30 (52)	14 (42)	11 (69)	5 (56)	0.22
Geographic ancestry					0.30
Caucasian	35 (76)	21 (72)	10 (83)	4 (67)	
North Africa	3 (7)	1 (3)	1 (8)	1 (17)	
Sub-Saharan Africa	6 (13)	6 (21)	0 (0)	0 (0)	
Asia	1 (2)	0 (0)	1 (8)	0 (0)	
NA	12	5	4	3	
Uveitis characteristics					
Bilateral	49 (84)	28 (88)	14 (88)	7 (88)	1
Location					
Intermediate	4 (7)	4 (12)	0 (0)	0 (0)	0.34
Posterior	14 (24)	6 (19)	6 (38)	2 (25)	0.35
Panuveitis	38 (66)	22 (69)	10 (62)	6 (75)	0.85
Granulomatosus	18 (50)	14 (56)	3 (43)	1 (25)	0.60
NA		8	9	5	
IOP elevation	8 (15)	6 (20)	1 (6)	1 (12)	0.59
NA		3	1	0	
Median visual acuity (logMAR)	0.35 (0.1, 0.7)	0.30 (0.1, 0.5)	0.26 (0.0, 0.5)	0.50 (0.25, 1.30)	0.29
Anterior chamber cell (Tyndall≥1+)	16 (30)	7 (23)	5 (31)	4 (50)	0.55
NA		3	1	0	
Vitreous haze grade (Nussenblatt≥1+)	20 (37)	9 (30)	8 (50)	3 (38)	0.028
NA		3	0	1	
Papillary oedema	17 (31)	8 (26)	6 (38)	3 (38)	0.65
NA		2	0	1	
Retinal vasculitis	21 (36)	10 (33)	10 (62)	1 (14)	0.049
Cystoid macular oedema	29 (55)	18 (58)	8 (53)	3 (43)	0.86
NA		2	1	2	
Duration of uveitis before immunosuppressive drug (months)	4 (0;13)	5 (0;15)	3 (0.7)	3 (0;4)	0.36
Sarcoidosis characteristics					0.015
Definite ocular sarcoidosis	22 (38)	17 (52)	3 (19)	2 (22)	
Presumed ocular sarcoidosis	22 (38)	13 (39)	5 (31)	4 (44)	
Probable ocular sarcodosis	14 (24)	3 (9)	8 (50)	3 (33)	
Uveitis revealing sarcoidosis	48 (83)	25 (76)	15 (94)	8 (89)	0.83
Systemic manifestations					
Pulmonary	25 (60)	24 (73)	8 (50)	3 (33)	0.061
Neurological	2 (3)	2 (6)	0 (0)	0 (0)	1
Cardiac	2 (3)	1 (3)	1 (6)	0 (0)	1
Median ACE level (IU)	78 (32, 123)	65 (42, 119)	67 (32, 94)	102 (84, 124)	0.20
Concomitant treatment with corticosteroid	55 (95)	31 (94)	15 (94)	9 (100)	
Median dose of immunosuppressive drugs	N.A	20 (15, 20)	2 (2, 2)	150 (100, 150)	

Data are presented as median (IQR) or number (percentage).
ACE, angiotensin-converting enzym; IU, international unit; LogMAR, logarithm of the minimum angle of resolution; NA, not available; OP, intra-ocular pressure.

of patients had pulmonary involvement before the diagnosis of uveitis, whereas neurological and cardiac symptoms occurred during follow-up in 50% (1 patient treated with MTX) and 100% (2 patients including one with cardiac flare before immunosuppressant and one after MMF treatment) of cases, respectively. A definite or presumed sarcoidosis was diagnosed for 91%, 50% and 66% of patients treated with MTX, MMF and AZA, respectively.

Patients treated with AZA were significantly younger (p=0.013). Regarding the uveitis characteristics, there was no significant difference between the three groups for uveitis localisation, median initial visual acuity, papillary oedema. However, the three groups were not comparable for the presence of vitritis and retinal vasculitis, which were more frequent in the MMF group (50% of patients with vitreous haze ≥1+ and 62% of patients with retinal vasculitis). Comparisons in this study were, therefore, adjusted for the presence of retinal vasculitis. The frequency of macular oedema was similar in the three groups.

Primary outcome (occurrence of relapse and/or serious adverse events)

The occurrence of the primary outcome (relapse and/or serious adverse events) was significantly lower with MTX as compared

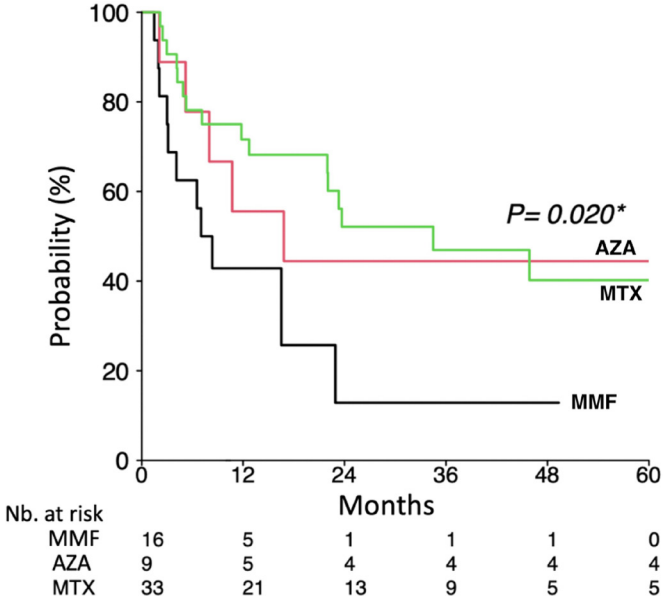

Figure 1 Event-free survival (relapse and/or serious adverse events) after first-line therapy (p value adjusted according to the baseline dose of corticosteroids and the presence of retinal vasculitis). AZA, azathioprine; MMF, mycophenolate mofetil; MTX, methotrexate; Nb. at risk, number at risk. *Significant results.

with the other groups (p=0.020): median time to relapse or serious adverse events of 34.5 months in the MTX group (IQR: 11.8 –not reached), 8.4 months in the MMF group (IQR: 3.1–22.9) and 16.8 months in the AZA group (IQR: 8.0–90.1) (figure 1). The comparison between the different groups was adjusted according to the baseline dose of corticosteroids and the presence of retinal vasculitis.

At least one relapse and/or serious adverse events occurred in 17 (52%) patients in the MTX group, 12 (75%) patients in the MMF group and 8 (89%) patients in the AZA group. The cumulative incidence of relapse (95% CI) at 12 months was 17% (6% to 32%) in the MTX group, 44% (12% to 74%) in the AZA group and 45% (19% to 68%) in the MMF group (p=0.14). MTX was significantly superior to MMF to prevent relapse at 12 months (HR 0.41, 95% CI 0.17 to 0.98, p=0.046). The cumulative incidence of serious adverse events at 12 months was 13% (64–27) in the MTX group, 0% (0–0) in the AZA group and 6% (<1–26) in the MMF group (p=0.64). Finally, the cumulative incidence of relapse requiring a switch to another immunosuppressant or biological agent at 12 months was 7% (1–20) in the MTX group, 33% (7–64) in the AZA group and 32% (11–56) in the MMF group (p=0.26) (HR 0.36; 95% CI 0.10 to 1.25; in MTX group, p=0.11). The details of the clinical course of first-line therapy are presented in online supplemental figure 1.

Treatment response at 3 and 12 months

At 3 months, a complete or partial response was achieved in 94% of patients in the MTX group, 64% in the MMF group and 88% in the AZA group. MTX treatment showed a trend towards superiority in terms of response rate at 3 months (OR 9.71; 95% CI 0.92 to 103; p=0.059). At 12 months, a complete or partial response was achieved in 60% of patients in the MTX group, 27% in the MMF group and 43% in the AZA group, with no significant difference in MTX (OR 4; 95% CI 0.74 to 21.5; p=0.11) (table 2).

Low visual acuity

MTX was significantly associated with a preservation of visual function at the last visit of the first line of treatment (a low visual acuity of 4% vs 9% in the MMF group vs 57% in the AZA group (p=0.008)).

Side effects

For first-line therapy with MTX, serious adverse events were fatal SARS CoV2 infection, injection-site reaction (two patients), elevation of the liver enzyme and abdominal pain. For first-line therapy with MMF, serious adverse events were herpes zona ophthalmicus, prostate cancer and abdominal pain. For first-line therapy with AZA, serious adverse event was elevation of the liver enzyme.

All treatment lines

Clinical and ophthalmological characteristics

Considering the 75 lines of treatment (39 lines of MTX, 24 lines of MMF and 12 lines of AZA), there was no significant difference between the three groups for uveitis characteristics (online supplemental table 1). The first-line therapy has been previously described. The second-line therapy included MTX (n=6), MMF (n=5) and AZA (n=3). The third-line therapy included MMF (n=3). The details of the clinical course of second-line and third-line therapy are presented in online supplemental figure 2 and online supplemental figure 3.

Treatment response at 3 and 12 months

At 3 months, a complete or partial response was achieved in 95% of patients in the MTX group, 59% in the MMF group and 90% in the AZA group. Treatment with MTX was significantly associated with an increased response rate at 3 months (OR 10.85; 95% CI 1.13 to 104.6; p=0.039). At 12 months, a complete or partial response was achieved in 61% of patients

Table 2 Complete and partial response at 3 months and 12 months

	Methotrexate	Mycophenolate mofetil	Azathioprine
Complete and partial response at 3 months to first-line therapy	9.71 (0.92–103) p=0.059	1	4 (0.35–45.4) p=0.26
Complete and partial response at 12 months to first-line therapy	4 (0.74–21.5) p=0.11	1	2 (0.27–14.8) p=0.50
Complete and partial response at 3 months to all treatment lines	10.85* (1.13–104.6) p=0.039	1	4.07 (0.39–42.51) p=0.24
Complete and partial response at 12 months to all treatment lines	8.21 (0.89–75.37) p=0.063	1	5.96 (0.55–63.99) p=0.13

Factors associated with complete and partial response at 3 and 12 months of treatment are presented as OR and CI.
*Significant results.

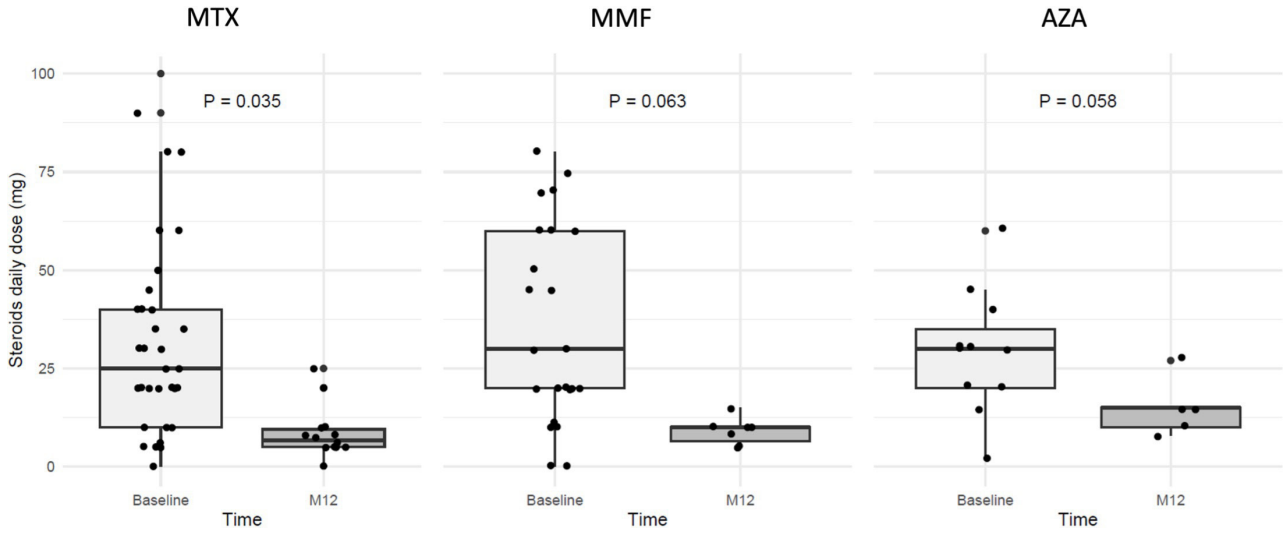

Figure 2 Corticosteroid-sparing effect at 12 months for the different treatments. AZA, azathioprine; M12, 12 months; MMF, mycophenolate mofetil; MTX, methotrexate.

in the MTX group, 25% in the MMF group and 62% in the AZA group. Treatment with MTX tended to be associated with an increased response rate (OR 8.21; 95% CI 0.89 to 75.37; p=0.063) (table 2).

For partial responders, macular oedema showed poor improvement while most patients experienced correction of retinal vasculitis. At 3 months, only 14% of patients achieved complete resolution of macular oedema, whereas 56% had resolution of retinal vasculitis. At 3 months, among partial responders, 64% of patients and 16% of patients exhibited macular oedema or retinal vasculitis, respectively.

Low visual acuity

MTX was significantly associated with a preservation of visual function at the last visit of all lines of treatments (low visual acuity of 5% vs 8% in the MMF group and 33% in the AZA group (p=0.027)).

Corticosteroid-sparing effect

At 12 months, considering all treatment lines, MTX was the only treatment associated with a significant systemic corticosteroid-sparing effect: the median (IQR) daily dose of prednisone decreased from 22 mg (10–40) at treatment initiation to 7 mg (5–10) after 12 months of treatment (p=0.035) (figure 2). For MMF, the median (IQR) daily dose of prednisone decreased from 30 mg (20–60) at treatment initiation to 10 mg (6–10) after 12 months of treatment (p=0.063). Finally, for AZA, the median (IQR) daily dose of prednisone decreased from 30 mg (29–35) at treatment initiation to 15 mg (10–15) after 12 months of treatment (p=0.058).

Side effects

Adverse events occurred in 15 (20%) therapeutic lines and serious adverse events requiring treatment discontinuation were observed in 13 (17%) therapeutic lines. Six patients (15%) out of 39 therapeutic lines presented a serious adverse event in the MTX group vs 5/24 (21%) in the MMF group and 2/12 (17%) in the AZA group (table 3). Most of the serious adverse events were infections (n=2), elevation of liver enzyme (n=3) and cancer (n=3). Two patients died during the study: one in the MTX group due to SARS-CoV2 infection and one in the MMF group secondary to progressive cardiac sarcoidosis.

DISCUSSION

In this retrospective study, we aimed to explore the efficacy and safety of MTX, MMF and AZA in the treatment of non-anterior sarcoidosis-associated uveitis. The main conclusions drawn by this study are that patients with non-anterior sarcoidosis-associated

Table 3 Adverse events occurring during treatment

	Total (n=75)	Methotrexate (n=39)	Mycophenolate mofetil (n=24)	Azathioprine (n=12)
Any adverse events	15 (20)	7 (18)	6 (25)	2 (17)
Serious adverse events	13 (17)	6 (15)	5 (21)	2 (17)
Infection	2 (3)			
SARS CoV2 infection	1 (1.3)	1 (2.6)		
Herpes zona ophthalmicus	1 (1.3)		1 (4)	
Cancer	3 (4)			
Prostate cancer	1 (1.3)		1 (4)	
Gastric cancer	1 (1.3)		1 (4)	
Breast cancer	1 (1.3)	1 (2.6)		
Injection-site reaction	2 (3)	2 (5)		
Abdominal pain	2 (3)	1 (2.6)	1 (4)	
Elevation of the liver enzyme	3 (4)	1 (2.6)		2 (17)
Non-serious adverse events	2 (3)	1 (2.6)	1 (4)	0 (0)
Infections				
Bronchitis				
Herpes infections	1 (1.3)		1 (4)	
Abdominal pain	1 (1.3)	1 (2.6)		

Data are presented as median (IQR) or number (percentage).

uveitis treated with MTX as first-line therapy had lower rates of treatment failure (defined by occurrence of relapse and/or serious adverse events) and of low visual acuity as compared with MMF and AZA. The risk of relapse at 12 months was more than twice lower in MTX as compared with MMF. The results considering all treatment lines are consistent and suggested that MTX had a better efficacy to control ocular inflammation and to achieve corticosteroid sparing. Adverse events were similar and consistent with the known safety profile of all these immunosuppressive drugs.

The effectiveness of MTX, MMF and AZA was previously suggested in sarcoidosis-associated uveitis.[13] However, to our knowledge, there is no comparative study on these treatments in sarcoidosis-associated uveitis. In a large retrospective study, Baughman *et al*[14] included 365 patients with sarcoidosis-associated uveitis treated with MTX. Only 26 patients (7%) had a failure with MTX and 3.8% had to stop treatment for toxicity. In this study, AZA had a similar efficacy but was less tolerated (19.1% stopped the treatment for toxicity). The effectiveness of MTX is known and well established in sarcoidosis.[15] In neurosarcoidosis, a significantly lower risk of relapse was observed with MTX, in comparison with MMF or AZA.[16] Others reported a higher rate of relapse with MMF compared with MTX in neurosarcoidosis (p=0.058), as well as a significantly shorter time to relapse with MMF (p=0.049).[15]

In a recent meta-analysis, MTX and MMF efficacy was compared in uveitis of all aetiologies.[17] The authors observed a comparable effect between MTX and MMF for treatment success at 6 months and for adverse events. A superiority of MTX was found for posterior and panuveitis at 6 months of treatment. Time to treatment success was shorter with MMF. In a retrospective study including 107 patients, the retention time of immunosuppressive drugs was significantly longer with MTX compared with AZA or MMF.[18] These results were consistent with our study in which a longer median time to treatment discontinuation (for relapse or adverse events) was observed with MTX. Rathinam *et al*[9] compared the efficacy of MTX and MMF in a randomised controlled trial including 216 patients with non-anterior non-infectious uveitis. At 6 months, there was no significant difference between the two groups in treatment success. However, MTX was more efficient in two subgroups: (1) subgroup of panuveitis and posterior uveitis (p=0.02) and (2) subgroup excluding patients from India (p=0.08). In our study, most of the patients (65%) had panuveitis, which may explain the superiority of MTX that we observed. In two retrospective studies,[8 19] authors showed a faster efficacy of MMF. In Gangaputra's study,[8] this difference disappeared after 9 months of treatment. In our secondary outcomes, we did not find a superiority of MMF at 3 months, which could be explained by a low dose of MTX in Gangaputra's study (12.5 mg/week vs 20 mg/week in our study). The importance of MTX dose has been previously suggested.[20]

In our study, we found that first-line immunosuppressive drug with MTX preserved significantly visual acuity, compared with MMF and AZA. In the SITE (Systemic Immunosuppressive Therapy for Eye Diseases) study,[21–23] the visual prognosis was not specifically investigated. A prospective study,[9] which included only 7% of sarcoidosis, found no statistically significant difference in visual acuity between MTX and MMF at 6 months. This may suggest a specific benefit of MTX in sarcoidosis-associated uveitis, but further observational studies are needed to conclude.

Concerning all treatment lines, a decrease in corticosteroid dose was obtained for all treatments, with a statistically higher corticosteroid-sparing effect with MTX after 12 months of treatment. A corticosteroid-sparing effect of MTX, MMF and AZA was previously shown in the SITE studies.[21–23] In Gangaputra *et al*'s study[8] MMF had a statistically significant overall higher rate of corticosteroid-sparing success as compared with MTX. This highlights the need for future studies focusing on corticosteroid sparing as primary endpoint to better address this question.

We acknowledge some limitations in this study. Due to the retrospective nature of this study, MTX dosages in mg/kg were not available. However, MTX dosage is rarely expressed in mg/kg, even in prospective trials such as Rathinam.[9] We chose to include definite and presumed ocular sarcoidosis but also probable ocular sarcoidosis, leading to potential misdiagnosis. However, we used the new IWOS criteria and most of our patients (76%) had definite or presumed ocular sarcoidosis. We chose to use a composite endpoint, based on occurrence of relapse or serious adverse events. This choice, although including two distinct parameters, was based on a pragmatic approach in clinical practice and intended to identify the most effective treatment with the best safety. Patients in the MMF group had a more severe profile (more retinal vasculitis lesions) but a similar rate of macular oedema. Thus, we adjusted the statistical analysis according to the presence of retinal vasculitis. We did not use a standardised protocol for corticosteroid tapering in our study. To account for this limitation, results for the primary endpoint were adjusted on corticosteroid dose. Interestingly, the dose of corticosteroids was lower in the MTX group compared with the MMF and AZA groups at 12 months of treatment, suggesting that the efficacy observed was related to MTX rather than corticosteroid therapy.

In conclusion, we provide here new data comparing the efficacy and safety of different DMARDs in the treatment of sarcoidosis-associated uveitis. MTX seems to be more effective to prevent relapse and low visual acuity, in non-anterior sarcoidosis-associated uveitis, as compared with MMF and AZA. Further prospective studies are needed to confirm these results.

Author affiliations
[1]Department of Internal Medicine, CHU Rouen, F-76000 Rouen, France
[2]Department of Internal Medicine and Clinical Immunology, Centre National de Références Maladies Autoimmunes et Systémiques Rares, Centre National de Références Maladies Autoinflammatoires Rares et Amylose Inflammatoire and INSERM, UMR S 959, Immunology- Immunopathology-Immunotherapy, Sorbonne Universités, AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Paris, France
[3]Department of Internal Medicine, Hopital de la Croix-Rousse, Lyon, France
[4]Department of Biostatistics and Medical Information, CRESS UMR 1153, INSERM, ECSTRRA Team, Saint-Louis University Hospital, AP-HP, University of Paris, Paris, France
[5]Department of Ophthalmology, DHU ViewRestore, Pitié Salpêtrière Hospital, Sorbonne Université, Paris, France
[6]Department of Ophthalmology and Faculté de Médecine Lyon-Sud, Croix Rousse University Hospital and Faculté de Médecine Lyon-Sud, Université Claude Bernard-Lyon 1, Lyon, France

Contributors Research design: PS, LK, PC, BB, DS and ACD. Data acquisition and/or research execution: ML, MV, GL, FD, AT, CF and TSdG. Data analysis and/or interpretation: ML, LB, GM and ST. Manuscript preparation: ML, PS, DS and ACD. Guarantors: ML and ACD.

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ORCID iDs
Mathilde Leclercq http://orcid.org/0000-0001-6262-1740
Christine Fardeau http://orcid.org/0000-0003-1935-2711
Laurent Kodjikian http://orcid.org/0000-0002-3908-6716

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