

Original article

UVEITIS MANAGEMENT : A MULTIDISCIPLINARY APPROACH TO ASSESS SYSTEMIC INVOLVEMENT AND SIDE EFFECTS OF TREATMENTS

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ABSTRACT

Objective

Non-infectious uveitis is often associated with systemic diseases severe enough to require corticosteroids (CS) and immunosuppressive drugs, which have potential serious side effects.

Methods

28 patients with non-infectious uveitis were referred by the ophthalmologist.

Results

A systemic disease was found in 17/28 patients (60%) : sarcoidosis in 11, spondylarthropathy in 3, Behcet's disease in 2, Crohn's disease in 1 patient. Eighteen patients received CS, 21 patients received immunosuppressive drugs. Most side effects were due to CS treatment : Cushing's syndrome in 12, cataract in 11, glucose intolerance in 3, gastric ulcer in 1, hypertension in

1, osteoporosis in 17, avascular bone necrosis in 3 patients. Prophylaxis or treatment of corticosteroids induced osteoporosis consists in calcium, 500 mg/day and vitamin D 400 IU in most of them with in addition hormone replacement therapy (n = 8) or bisphosphonates (n = 13)

Conclusion

Sixty percent of patients with severe uveitis had a systemic disease. CS were the most deleterious drugs in spite of bi- or tri-therapy with CS sparing immunosuppressive drugs.

INTRODUCTION

Uveitis includes inflammation of the uveal tract (iris, ciliary body and choroid) and of the retina. Up to 40 % of patients with uveitis have a systemic diseases, mainly an autoimmune disease (1). In non-infectious uveitis, appropriate treatment often requires the use of moderate to high doses of systemic CS and other immunosuppressive drugs for weeks or years to reduce the inflammatory process and to prevent vision loss (2). These drugs are known for their potential toxicity complicating the management of the ocular and of the underlying disease. A close collaboration between the ophthalmologist, the internist and/or the rheumatologist would be helpful to establish the diagnosis and for the monitoring of the patient. We report our clinical experience as a multidisciplinary team involved in the management of systemic diseases and of the complications of treatment, especially those involving bone.

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PATIENTS AND METHODS

The present retrospective series includes 28 patients with a clinical diagnosis of non-infectious active uveitis requiring in most cases a systemic immunosuppressive treatment due to the severity of the disease. The reason for medical advice and care was ocular symptoms. The patients were referred by the ophthalmologist to the internist and/or the rheumatologist for medical follow up, identification and management of side effects of treatments.

The uveitis was classified according to the International Uveitis Study Group Recommendations (3), based on the anatomic site of inflammation. Anterior uveitis was

defined as an inflammation involving mainly the anterior segment. Intermediate uveitis as an inflammation of the vitreous, peripheral retina, pars plana and ciliary body. Posterior uveitis involved mainly the part of the eye posterior to the lens including the choroid and the retina. Panuveitis involved 2 or more segments of the eye. The course of the ocular inflammation was further classified according to the duration of the disease, laterality and the granulomatous aspect of the inflammatory process. Our patients had chronic and bilateral ocular inflammation.

The patients underwent an ophthalmologic evaluation by the same ophthalmologist, a complete general medical history and physical examination by the internist and an articular and bone examination by the rheuma-

Table 1 : Clinical characteristics of the patients at referral

Ocular lesions	F/M	Granulomatous	Final Diagnosis	Corticosteroids presently in the past	Immunosuppressive drugs	Osteoporosis
Anterior uveitis, n=4	F	N	Sarcoidosis	Y	MTX	Y
	M	N	ASP	N	Local	N
	F	Y	Sarcoidosis	Y	-	N
	F	N	Crohn	Y	MTX	N
Intermediate, n=2	F	N	Sarcoidosis	Y	-	N
	F	N	Idiopathic uveitis	N	Y Cyclosporin , MTX	Y, AVN
Posterior n=13	F	N	Serpiginous	Y	Aza , cyclosporin	Y
	M	N	Birdshot	Y	Aza, cyclosporin	Y
	M	N	Birdshot	Y	Cyclosporin	Y
	F	N	Serpiginous	Y		Y
	F	N	Serpiginous	Y	Cyclosporin	Y
	M	N	Birdshot	N	Y Aza, cyclosporin	N
	F	N	Serpiginous	N	Y -	Y
	M	N	Birdshot	Y	Aza, cyclosporin	Y
	F	N	Birdshot	Y	Cyclo	N
	F	N	Behcet	N	Aza, cyclosporin, MTX	N
	M	N	Behcet	Y	Cyclosporin	N, AVN
	F	N	Sarcoidosis	Y	Aza	Y
	F	N	Serpiginous	Y	Aza, Cyclosporin, MTX	Y
Panuveitis, n=9	M	Y	Sarcoidosis	N	Y MTX	N
	M	N	ASP	Y	MTX	Y
	F	Y	Sarcoidosis	N	Y Aza, MTX	N
	F	Y	Sarcoidosis	Y	-	Y
	F	N	ASP	N	Y MTX, cyclosporin	Y, AVN
	F	Y	Sarcoidosis	N	Y Aza	Y
	F	Y	Sarcoidosis	N	Y MTX	Y
	F	Y	Sarcoidosis	Y	Aza, cyclosporin	Y
	M	Y	Sarcoidosis	Y	-	N
Total, 28	19/9	8 (28%)	17 (60%)	18	8 21	17

ASP : Ankylosing Spondylitis; Y : Yes; N : No; MTX : methotrexate; Aza : azathioprine; AVN : avascular bone necrosis

tologist. Systemic treatment was initiated by the ophthalmologist according to the ocular inflammation and then modified if necessary according to systemic or bone involvement. A patient with avascular bone necrosis would not receive corticosteroids or the lowest dose possible. Prophylaxis of osteoporosis was applied to all patients with corticosteroids and consisted in calcium 500 mg at least with vitamin D 440 UI/day except in patients with sarcoidosis in whom vitamin D was not advised. Postmenopausal women received in addition hormone replacement therapy when acceptable. Treatment of osteoporosis consisted in bisphosphonates administered orally or intravenously.

Laboratory tests performed in all patients were : hemogram, erythrocyte sedimentation rate, C-reactive protein, creatinine, liver tests, antinuclear antibodies (on Hep2 cells), rheumatoid factor (RIA), immune complexes (C1q and rheumatoid factor fixation). Bone densitometry of the lumbar spine from L2 to L4 (BMDL) and of the total hip (BMDH) was performed using DXA (Hologic QDR 1000, Waltham, Ma). Results were expressed in g/cm² (bone density), T score (referred to the mean of sex-matched young healthy adults). Osteoporosis was defined according the WHO definition (4) : a T score \leq -2.5 is osteoporosis, a T score between -2.5 and 1 is osteopenia.

Diagnostic criteria were applied for spondylarthropathies (5) Behcet 's disease (6) Sarcoidosis was diagnosed on the basis of biopsy proven non caseating granuloma or a combination of X-rays evidence of hilar adenopathy, alveolar lymphocytosis with CD4/CD8 lymphocyte count >3 , abnormal gallium scan, elevated angiotensin converting enzyme dosage. A systemic illness was defined as a disease affecting organ systems in addition to the eye (7).

RESULTS

Twenty-eight patients, 19 women and 9 men, mean age 55 y (range : 21-79 y) were evaluated. The median disease duration from the onset of eye disease until the present examination was 7 y (range :1-18y). The time elapsed from the beginning of the ocular symptoms and the referral to our ophthalmologist was 0 to 14 y and the delay until referral by our ophthalmologist to the internist and/or the rheumatologist was 0 to 4 y.

As shown in table 1, anterior uveitis was present in 4 patients, intermediate uveitis in 2, posterior uveitis in 13, panuveitis in 9. Granulomatous lesions were ob-

served in anterior, intermediate and panuveitis but not in posterior uveitis. A systemic disease was found in 17/28 patients (60 %) : sarcoidosis in 11, ankylosing spondylitis (ASP) in 3, Behcet 's disease in 2, Crohn 's disease in 1 patient. The presence of a systemic disease was found in 4/4 patients (100%) with anterior uveitis (; 2 sarcoidosis, 1 ASP and 1 Crohn 's disease, in 1/2 (50 %) with intermediate uveitis (1 with sarcoidosis, the other with idiopathic uveitis) in 9/9 (100%) with panuveitis (7 sarcoidosis, 2 ASP) and only, in 3/13 patients (23%) with posterior uveitis (Behcet 's disease in 2 and sarcoidosis in 1). In the latter group, the disease restricted to the eye was identified as Birdshot (n= 5) or serpiginous uveitis (n=5). The lungs, the skin, the joints and the muscles were the most frequently affected parts. Interestingly, some patients with a disease localized to the eye complained of polyarthralgia and/or myalgia that could not be attributed to another disease such as osteoarthritis or fibromyalgia.

Twenty-six patients were treated by different combinations of oral treatments : CS alone (n=5), CS in association with at least one immunosuppressive drug (n=13) or immunosuppressive drugs alone (n=8). Eighteen patients were treated by CS at the time of the study and 8 patients were former CS users. Thus 26/28 (93 %) patients received CS during the course of their disease. The median duration of CS treatment was 4 y (range : <1-17y) and the median dose of methylprednisolone was 12 (8-32) mg/day. One patient was free of treatment at the time of the study and one patient received local treatment.

Nine patients received 1 immunosuppressive drug, 10 patients received 2 immunosuppressive drugs and 2 received 3 immunosuppressive drugs. Patients receiving at least 2 immunosuppressive drugs had posterior uveitis (n= 6/9), panuveitis (n=3/9) or intermediate uveitis (n=1/2).

Biological parameters showed a low-grade inflammation (median, range) : ESR 14 (1-46) mm/h, CRP 10 (1-34) mg/l, NI <5 mg/l. No patient had renal insufficiency. Immune parameters were abnormal in a minority of patients : ANA were present in 4 patients, RF in 3 patients. The 3 patients with ASP had an HLA B27 antigen.

Side effects of treatment were mostly due to CS. Cushing 's syndrome was present in 12 patients (43 %), glucose intolerance in 3 (11%) and cataract in 11 (39 %). HTA in 1 (3.5 %) and endoscopically proven gastric ulcers in 1 (3.5 %). Osteoporosis defined as a BMDL T

score lower than -2.5 or the presence of a fragility fracture, was present in 17/28 patients (60 %), 3 of them having vertebral fractures. BMDLT score (mean \pm SD, n=28) was -2.6 ± 1.4 , BMDH T score (n=22) was -1.8 ± 0.9 (figure 1). Avascular bone necrosis was observed in 3 patients, 2 of the hip and 1 of the knee. Moderate renal or hepatic tests alterations were observed in 3 patients that resolved after lowering the dose of the immunosuppressive drugs. In addition, one patient had haemolysis due to azathioprine and three women had hirsutism attributed to cyclosporin A rather than to CS because it disappeared when the dose of cyclosporin A was lowered.

All patients treated with CS received prophylactic calcium salts (500 mg/day calcium element) and 400 IU vitamin D supplementation except patients with sarcoidosis who received calcium only. Bisphosphonates was administered to 13 patients : 1 with etidronate, 5 with alendronate, 7 with intravenous pamidronate. Eight women received hormone replacement therapy, 3 of them in addition to bisphosphonates. The treatment with bisphosphonates, either orally or intravenously, was well tolerated and was not associated with a relapse or exacerbation of the disease.

DISCUSSION

In the present series from a referral centre for uveitis, a systemic disease was diagnosed in 60 % of the

patients. Patients referred by the ophthalmologist were those with a strong presumption or evidence of a systemic disease and those with inflammatory diseases restricted to the eye requiring aggressive therapeutic regimens. The diagnosis was usually suggested by the ophthalmologist, expert in immune diseases who sought the advice of the internist or the rheumatologist for further confirmation (or infirmation). The systemic involvement was thus more important than that reported in the literature. Rosenbaum (1) and Brezin (8) found 40 to 50 % systemic involvement whereas other series had even a lower prevalence ranging from 19 to 32 % (1, 9-11). Patients with visual loss due to uveitis presented an inflammatory rheumatic disease in 22 % (9). However, series are difficult to compare because of biases due to the referral patterns, often including infectious or neoplastic diseases.

Anterior, intermediate and panuveitis were often associated with systemic diseases while inflammation restricted to the eye was most likely found in patients with posterior uveitis. These findings were in agreement with data from the literature after excluding infectious causes (1, 10). The most frequent systemic diseases were spondylarthropathy, juvenile rheumatoid arthritis, sarcoidosis, and Behcet's disease. The presence of granulomatous lesion is often considered as the hallmark of sarcoidosis, tuberculosis, brucellosis and herpes. In our series, granulomatous lesions were restricted to patients with sarcoidosis, the other etiologies of infectious origin being excluded.

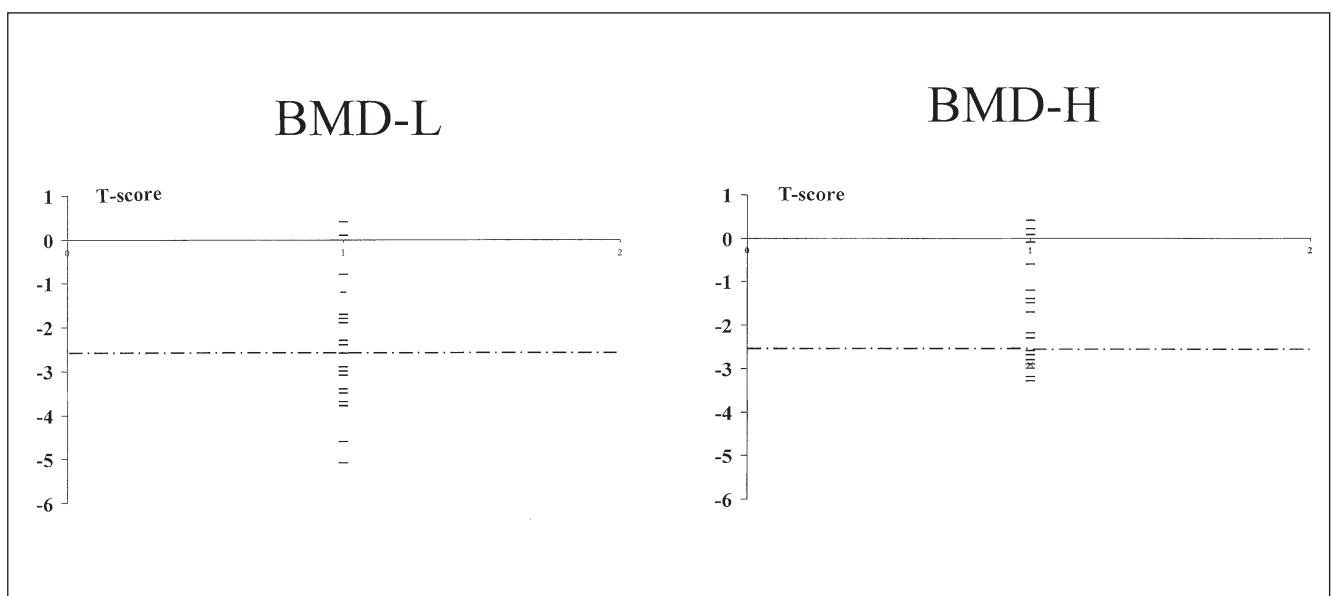


Figure 1 : Bone mineral density of the lumbar spine (BMDL, n=28) and of the hip (BMDH, n=22) expressed as T score for individual patients.

The choice of the diagnostic procedures was based on an approach, which was focused and tailored to the particular patient as recommended by several authors (1, 7, 10). Biological tests were often disappointing, revealing few abnormalities especially when inflammatory parameters were concerned. The fact that patients had been treated with CS for months or years at the time of referral to our Clinic could be one explanation. In addition, patients with Birdshot choroidoretinopathy and serpiginous uveitis have usually no systemic inflammation (13). Similarly, immune parameters were of little interest in the present series where Rheumatoid Arthritis, Systemic Lupus Erythematosus or Sjögren's disease were not observed.

The severity of uveitis was attested by the treatments. Most patients had received CS for years, and 75 % were treated by at least one immunosuppressive drug (14, 15). CS were responsible for most side effects. The use of CS-sparing immunosuppressive drugs in most patients was however not sufficient or was introduced too late in the therapeutic regimen to prevent the deleterious effects of CS. Cataract, a well-known complication of CS, was of particular importance in these patients with ocular inflammation. They develop this complication more rapidly and with a higher incidence than other patients (16). Bone complications such as osteoporosis and avascular bone necrosis were present in 75 % of the patients far exceeding the incidence of 20 % usually reported (17). Osteoporosis was evidenced by DXA and/or fragility fractures. BMDL was lower than BMDH, a finding in agreement with the sensitivity of trabecular bone to the effects of CS (18). BMDL mean T score fit the WHO diagnosis for osteoporosis. It is recommended that prophylactic measures and bone densitometry should be performed when a therapeutic regimen with CS is initiated since bone loss occurs during the first 6 to 12 months of treatment (17, 18). In spite of these recommendations recently revised, most physicians do not apply them. In the United Kingdom, 75 % of consultant ophthalmologists used CS at doses greater than 5 mg/day for at least 3 months and 75 % of them gave no advice on osteoporosis prevention (19). Even in our series, the patients were referred with some delay and more than 50 % had osteoporosis when bone densitometry was performed. The revised version of the American College of Rheumatology guidelines for corticosteroids osteoporosis were to treat all patients who initiate a corticosteroid treatment for at least 3 months whatever the bone densitometry results (20). The proposed treatment was calcium, vitamin D, and an oral bisphosphonate at least in

postmenopausal women and in men. For patients who were on treatment, the attitude will depend on the bone densitometry results. Those with osteoporosis or osteopenia should receive calcium, vitamin D, HRT for postmenopausal women and an oral bisphosphonate. Those with normal bone densitometry should be rechecked regularly.

Calcium supplements, hormone replacement therapy (in postmenopausal women) and/or bisphosphonates were administered in osteoporotic patients after referral as recommended (20). The treatment was well tolerated and no patient presented an exacerbation of the disease. Intravenous amino-bisphosphonates (pamidronate and risedronate) have been associated with the development of acute uveitis or iritis in patients with Paget's disease (21, 22). The incidence of acute uveitis in the whole population of patients receiving IV pamidronate was however low (1/1000). The sensitivity of patients with ocular diseases to this side effect is not known (23) but this complication should be seriously considered.

The importance of side effects due to CS prompted the use of immunosuppressive agents as CS sparing drugs. Providing that the treatment is adequately monitored, immunosuppressive agents have indeed low and reversible toxicity (11, 20). Methotrexate and cyclosporine A alone or in combination, together with low doses of CS are reported to be effective in steroid-resistant uveitis or in the presence of severe side effects attributed to CS (24, 25). However, as far as osteoporosis is concerned, cyclosporine A is involved in accelerated bone loss (26) minimizing then its sparing effect.

In conclusion, the appropriate management of uveitis requires the participation of physicians involved in a multidisciplinary team. CS was associated with most side effects, particularly cataract and osteoporosis. Prophylactic measures should be instituted early after the beginning of the treatment in patients requiring long term CS treatment whatever their bone status. Bone density measurements evaluation should be recommended in all patients on chronic CS treatment.

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