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ORIGINAL ARTICLE

Do systemic steroids increase the risk of ocular complication in uveitis patients? Focus on a Italian referral center

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Abstract

Introduction To describe the ocular inflammatory and iatrogenic complications in a cohort of uveitic patients treated in an Italian referral centre.

Material and methods Retrospective non-comparative case series. Medical history and clinical findings of all consecutive patients referred to the uveitis center of Pisa University from January 2015 to January 2017 were reviewed. Only patients with at least three follow-up visits in our center were included in our series.

Results Three hundred and eighty-nine patients were visited in our center during study period; only 142 patients (90 men and 52 female) satisfied the inclusion criteria. Mean age at presentation was 41 ± 14 years. The most common ocular feature was anterior uveitis (46%) and was mainly unilateral. A specific etiological diagnosis was established in 61% of patients. At presentation, 71.43% of patients were on medical therapy for rheumatic disease; 42.86% of patients used systemic steroids Cataract and ocular hypertension were the most common ocular complications during the study period but were not statistically related to systemic steroid treatment.

Conclusions Systemic steroids treatment in uveitis patients does not seem to increase the risk of iatrogenic complications such as cataract and glaucoma. In our series, increasing age appears to be the main risk factor for cataract and glaucoma development.

Key points
- *Cataract, ocular hypertension, and glaucoma are the most common iatrogenic complications.*
- *Systemic steroids can be safely used in uveitis patients.*

Keywords Cataract · Glaucoma · Steroids · Uveitis

Introduction

Uveitis represents a heterogeneous group of eye diseases affecting the uvea and other eye's structures from the anterior to the posterior pole. Uveitis present a general incidence of 17–52/100.000 person-year with a prevalence of 38–284/100.000 people [1–7] and usually show a higher frequency in younger patients [8]. They are responsible of 5–10% of legal blindness in the industrialized countries and therefore represent an important sanitary issue [9]. Even if a large number of uveitis shows an underlying disease up to 40% of uveitis are idiopathic and may therefore present a challenging workup [9–13].

Uveitis, when not properly managed, may also hesitate in severe eye complications such as cystoid macular edema [14], epiretinal membranes [15], retinal detachment [7], neovascular membranes [16], floaters, and vitreous hemorrhage. Beside the aforementioned complications, glaucoma [7, 17–20] and cataract [21–24] represent the two most common iatrogenic complications of uveitis and are believed to be strictly connected with systemic steroid treatment [25–27].

The introduction of new delivery system [27–30] together with the introduction of immunosuppressive drugs and biologic agents seem to slowly reduce the incidence of iatrogenic and inflammatory complications [31–33].

Our referral center at the University of Pisa takes part of a multidisciplinary management of these patients in cooperation

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with the rheumatologic unit. The majority of the patients of this cohort was referred by the rheumatologic unit and already presented a diagnosis of systemic disease and a previous long history of steroid treatment.

The aim of the present study is to collect and describe the inflammatory and iatrogenic complications of our cohort of patients, who have been treated with systemic steroids and followed in the last 2 years in an Italian multidisciplinary uveitis clinic of a rheumatologic referral center.

Methods

The study included all consecutive patients with uveitis examined at the multidisciplinary uveitis clinic (afferent to the Rheumatology Unit of Department of Internal Medicine and the Ophthalmology Unit of the Neurosciences Department) of the University of Pisa from January 2015 to January 2017. Three hundred eighty-nine patients were visited during the abovementioned period, but only patients with at least three follow-up visits were included in the study; therefore, 142 patients fulfilled the inclusion criteria and took part to the analysis.

Data regarding sex, ages at the onset, nationality, source of referral, clinical features, ocular involvement, and presence of signs and symptoms of systemic diseases were collected in an electronic database. The classification of uveitis was made according to the International Uveitis Study Group (IUSG) criteria [7, 9]. All patients had a comprehensive rheumatologic and internist evaluation. The diagnosis of autoimmune systemic disease was performed according to the related international criteria currently used in clinical practice. The diagnosis of infectious uveitis was performed by mean of clinical examination and serology; moreover, ocular fluid tests were used to detect parasite's DNA by polymerase chain reaction in case of clinical diagnosis of ocular toxoplasmosis. Moreover, all patients had a comprehensive ophthalmological evaluation, including ocular clinical history, Snellen visual acuity, slit-lamp examination, applanation tonometry, and dilated fundus examination; visual field, fluorescein-angiography, and optical coherence tomography were performed when required.

The percentage of inflammatory and iatrogenic complications was collected. Systemic steroids' total dosage has been registered in order to evaluate possible correlations with eye complications such as cataract and/or glaucoma.

Additionally, all patients underwent the standard protocol of serological examinations for uveitis, including routine blood test (hematocrit, white blood cell count and differential, platelets count, urea and electrolytes assessment, blood glucose, and glycosylated hemoglobin), acute phase reactants, human leucocyte antigen (HLA) typing, serum fluorescent treponemal antibody absorption detection, main viral and bacterial screening, serum angiotensin-converting enzyme, serum lysozyme, tuberculin reaction tests, and non-organ specific auto antibodies profile (antinuclear antibodies, anti-ENA antibodies profile, antiphospholipid antibodies, rheumatoid factor). Finally, when there was a strong suspicion of a systemic autoimmune disease associated, (i.e., sarcoidosis, HLA-B27-associated spondyloarthropathies, Behçet's disease, malignancies) all the serological and radiological examinations expected according to criteria for each disease were also performed in order to assess the diagnosis.

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

Statistical analysis

All results are expressed in means ± standard deviation (SD). The Kolmogorov-Smirnov test has been used to assess normality of data. Chi-square test, t-test and Analysis of Variance (ANOVA) were used to evaluate the differences among the subgroups. P value <0.05 was considered statistically significant. All calculations were done using StatView program ver. 5.0.

Results

One hundred and forty-two patients (M/F 90/52) were studied; all but ten were from Italian origin, and their mean age was 41 ± 14 years (min15-max 83). For 77 patients, uveitis represented the first episode of ocular impairment, while for 65, uveitis had a relapsing feature (> 1 < 5 overall episodes: 43 patients, > 5 overall episodes 22). Demographic profile of the cohort studied is summarized in Table 1. Sixty-five percent of

Table 1 Demographic profile

Number of patients	142
M/F	90/52
Mean ± SD age (min-max) (years)	41 ± 14 (15–83)
Mean ± SD age at disease onset (min-max) (years)	38 ± 13 (12–83)
Mean ± SD follow-up duration (min-max) (months)	40 ± 9 (9–60)
First episode of ocular impairment/ relapsing uveitis	77/65
Geographical origin	Italy 132 Morocco 4 Albania 2 France 1 UK 1 Senegal 1 India 1

patients referred by ophthalmologists, 32% patients attending directly our rheumatology unit, and 3% referred by general practitioners.

The most common ocular feature was represented by anterior uveitis (48%) and was mainly unilateral followed by posterior uveitis (28%), in all but 5 cases, unilateral, then panuveitis (16%) and intermediate uveitis (8%) (Fig. 1). For 86 of 142 (61%) patients with uveitis, a specific etiological diagnosis was established, while 56 (39%) of patients were found to have an idiopathic uveitis. The most common anatomical localization of idiopathic uveitis resulted the anterior segment, that was involved in 33/56 cases (Table 2). Considering patients with a defined diagnosis, the distribution of specific diagnosis according to the anatomical location is shown in Fig. 2. Fuchs' heterochromic iridocyclitis represented the most common cause of anterior uveitis, reported in 15 patients. In the contest of posterior uveitis, the most common diagnosis was represented by Behçet's disease (BD), reported in 16 patients. Moreover, we observed two cases of Masquerade neoplastic syndrome in two men affected by lung and colon cancer respectively. BD (six patients) and infectious uveitis (toxoplasmosis 3, tuberculosis 2, cytomegalovirus 1, HIV 1) represented the unique etiologies of panuveitis. We did not observe any difference in terms of demographic profile according to anatomical lesion and etiology, while only the relapsing feature of uveitis was significant associated with a young age at the onset ($p < 0.001$).

Best corrected visual acuity (BCVA) was 0.7 ± 0.3 in the right eye and 0.8 ± 0.2 in the left eye; 9.52% of patients had a BCVA between 1/10 and 1/20, the 4% had a BCVA of 1/20, the 3.4% had a BCVA of 1/200 and blindness was observed in 1.3% of patients. Mean intra-ocular pressure (IOP) was within normal limits in both eyes (14.53 ± 2.3 mmHg in the right eye and 13.72 ± 3.5 mmHg in left eye). Other ocular findings are summarized in Table 3.

At first visit, 71.43% of patients were already on medical therapy; 42.86% of patients used systemic steroids for rheumatic disease, local therapy was ongoing in 39.46% of patients; 65.51% applied local steroids and 68.96% used antiglaucoma agents. The mean dose of steroids for each patient at first visit was 3908.96 mg; this result may be influenced by a lack of medical history. 13.6% of patients using steroid was also treated with antimetabolites (35%), ciclosporin (30%), biologic agents (30%), or alkylating agents (5%). At the last, follow-up visits half of patients receiving systemic steroids (54.54%) were in polytherapy: the 42.85% with anti-metabolites, the 45.24% with cyclosporine, the 40.47% with biologic agents, and 2.4% with cyclophosphamide. Local therapy was carried out by 59.86% of the patients, of these 100% used steroids eye drops and 62.5% used antiglaucoma agents.

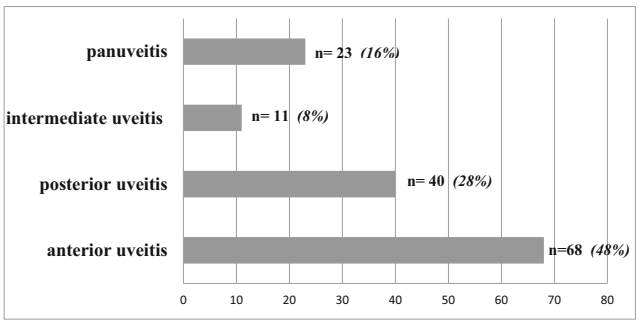

Fig. 1 Prevalence of uveitis according to anatomical location

Table 2 Distribution of diagnosis

	Idiopathic uveitis (%)	Specific diagnosis (%)
Anterior uveitis (68)	33 (49)	35 (51)
Posterior uveitis (40)	8 (20)	32 (80)
Intermediate uveitis [11]	5 (45)	6 (54)
Panuveitis [22]	10 (44)	13 (56)
Total (142)	56 (39)	86 (61)

Systemic therapy increase of 11% (X 2[1] = 11.63 $p < 0.001$) during follow-up time; particularly there was an increase of steroids total dosage from 3908.96 mg of the first visit to 6125.82 mg of the last follow-up (paired t test t (76) = − 6.019 $p < 0.0001$).

An increase of all the other systemic, steroid sparing, and treatments was also noted: antimetabolites increase of 7% ($X^2(1) = 9.03$, $p = 0.002$), immunomodulators increased of 6% (X 2[1] = 5.04 $p = 0.03$), and biologic agents increased of 6.8% (X 2[1] = 10.00 $p = 0.002$). Topical and peribulbar treatment showed a similar trend, topical therapies in fact increased of 20% ($X^2(1) = 26.28$ $p < 0.0001$) while peribulbar increased of 4.7% (X 2[1] = 5.44 $p = 0.04$).

Recurrences were observed in 70% of cases in patients treated with systemic steroids. Looking at inflammatory complications, it's possible to identify an increase in the percentage of synechiae (from 16.3 to 24.49%) and vitreomacular traction (from 4.08 to 9.52%), and there was an increase in opacities not allowing fundus observation. Cystoid macular edema did not vary during the follow-up time, and the number of intravitreal injections was greater in those patients that were not treated with systemic steroids.

Iatrogenic complications such as cataract (with a statistically significant increase of 22% as revealed by the McNemar test: $X^2(1) = 24.38$ $p < 0.0001$) and laser iridotomy (statically significant increase of 5% X 2[1] = 9.00 $p = 0.004$) increased from the first to the last visit whether glaucoma did not statistically increase between the two measurement (X 2[1] = 2.00 $p = 0.157$). Laser iridotomy is a standard procedure in patients with seclusion pupillae and pupillary block to avoid an increase of IOP.

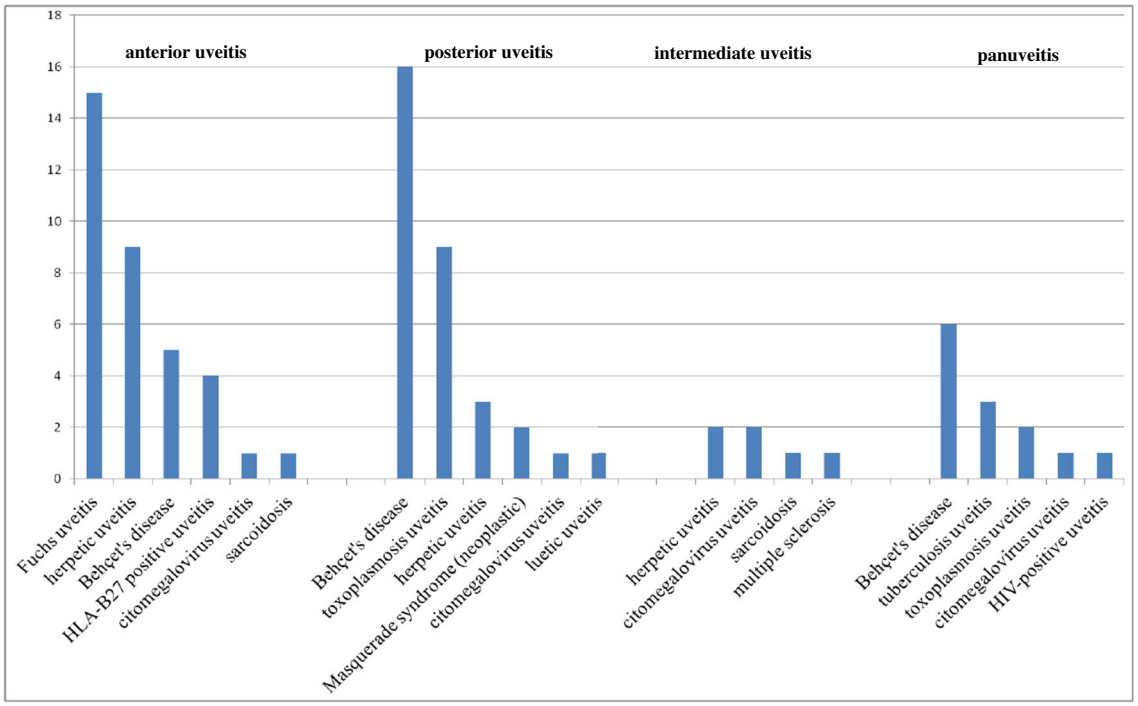

Fig. 2 Distribution of specific diagnosis according to the anatomical location

Complications occurred in the 54.54% of patients treated with systemic steroids. Main inflammatory complications were anterior synechiae (3.89%), posterior synechiae (18.18%), vitreomacular traction (12.33%), vitritis (7.14%), and cystoid macular edema (5.19%).

Patients treated with systemic steroids also developed cataract (37.66%), ocular hypertension (25.97%), and glaucoma (10.39%); some of them also underwent to laser iridotomy (14.28%), cataract surgery (27.27%), and glaucoma surgery (trabeculectomy) (3.89%). Patients who underwent intravitreal injections were 7.79% (66.66% were treated with intravitreal dexamethasone), and in the 3,89% of cases, both eyes were injected.

In order to investigate whether the dosage of systemic steroids could be associated with the probability to develop medical disorders, we perform a logistic regression analysis. The analysis reveals no association between the dose of steroids and the odds of development of medical disorders (glaucoma χ^2 (1) = 0.51, $p = 0.47$; cataract $\chi^2(1) = 0.06$, $p = 0.79$; hypertension $\chi^2(1) = 0.82$, $p = 0.36$) Table 4.

Moreover, a logistic regression was performed to investigate the effects of age and type of treatment on the likelihood

Table 3 Ocular findings at first and at last visit from the anterior segment to posterior pole

Ocular finding	Percentage of patients at first visits	Percentage of patients at last visit
Synechiae	16.3	24.49
Iridotomy	4.76	11.56
Unilateral cataract	8.2	10.9
Bilateral cataract	13.6	19.7
Unilateral pseudophakia	12.9	12.9
Bilateral pseudophakia	12.24	12.24
Normal fundus	47.31	38.76
Signs of previous vitreous inflammation	38.22	47.6
Optic nerve excavation	12.58	12.70
Vitreitis	6.46	6.8
Retinal angiosclerosis	3.4	3.66
Vitreo-macular tractions	4.08	9.52
Opacities not allowing fundus observation	4.8	68

Table 4 Logistic regression of steroid dosage on the odds of development of medical disorders

Variables	B	SE B	Wald χ^2	*p* value	OR	95% CI OR
Cataract						
Dose	0.00	0.00	0.06	0.79	1.00	[1.00, 1.00]
Glaucoma						
Dose	0.00	0.00	0.51	0.47	1.00	[1.00, 1.00]
Hypertension						
Dose	0.00	0.00	0.82	0.366	1.00	[1.00, 1.00]

95% CI OR confidence interval; *OR* odds ratio

to develop cataract in the two subgroups. The logistic regression model was statistically significant, $\chi^2(2) = 12.55$, $p < 0.0001$. The model explained 15% (Nagelkerke R^2) of the variance in cataract and correctly classified 66% of cases. The analysis showed no correlation between cataract development and systemic therapy applied but revealed increasing age as the main risk factor for cataract development (OR = 1.041 95% CI 1.018–1.064). We performed the same analysis for the others medical disorders. We did not find any difference in the risk of developing glaucoma ($\chi^2(2) = 3.65$, $p = 0.06$) or ocular hypertension ($\chi^2(2) = 2.99$, $p = 0.08$). Results of logistic regression analysis are tabulated in Table 5.

Comparing ocular surgery outcome, the logistic regression revealed only a significant effect of age both in cataract surgery ($\chi^2(2) = 6.52$, $p = 0.01$) and trabeculectomy ($\chi^2(2) = 3.85$, $p = 0.05$); as expected, increasing age (cataract surgery OR = 1.03 95% CI 1.007–1.055; trabeculectomy OR = 1.05 95% CI 1.000–1.099) was associated with an increased likelihood of undergoing a surgery (Table 5).

Recurrences seemed to be higher (75% of the total cases) in steroid-treatment subgroup ($X^2(1) = 14.65$, $p < 0.0001$) with an odds ratio of 4.24.

Table 5 Multiple logistic regression analysis showing the effect of age and treatment (systemic steroid) on medical disorders and ocular surgery

Variables	B	SE B	Wald χ^2	*p* value	OR	95% CI OR
Cataract						
Age	*0.04*	*0.01*	*12.55*	*0.000*	*1.04*	*[1.01, 1.06]*
Treatment	− 0.05	0.39	0.01	0.892	0.94	[0.44, 2.03]
Glaucoma						
Age	0.03	0.01	3.65	0.056	1.03	[0.99, 1.06]
Treatment	− 0.09	0.56	0.02	0.872	0.91	[0.30, 2.75]
Hypertension						
Age	0.02	0.01	2.99	0.084	1.02	[0.99, 1.04]
Treatment	− 0.29	0.40	0.53	0.465	0.74	[0.33, 1.64]
Cataract surgery						
Age	*0.39*	*0.01*	*6.52*	*0.011*	*1.03*	*[1.00, 1.05]*
Treatment	0.37	0.42	0.76	0.382	1.45	[0.63, 3.32]
Trabeculectomy						
Age	*0.04*	*0.02*	*3.85*	*0.049*	*1.04*	*[1.00, 1.09]*
Treatment	− 0.48	0.78	0.37	0.539	0.61	[0.13, 2.88]

Significant comparisons are highlighted in italics. 95% CI OR confidence interval; *OR* odds ratio

Discussion

The present work was aimed at exploring inflammatory and iatrogenic complications of our cohort of patients with uveitis, who have been treated with systemic steroids and followed in the last 2 years in an Italian multidisciplinary uveitis clinic.

Cataract and glaucoma development in our cohort is related more with increasing age than with systemic steroid treatment. In terms of systemic therapy, our analysis shows that the need for systemic therapy increases with disease duration (71% of subjects in treatment at first visit vs 83% of subjects in treatment at last visit). Systemic steroids still represent the most frequent treatment for uveitis and can be associated with other drugs such as biological agents (17% of cases), immunomodulators (15.64% of cases), or antimetabolites (12.24% of cases). Periocular therapy is quite frequent (8.84% of cases) as intravitreal injections while topical therapy with corticosteroid eye drops is performed by almost all patients affected by uveitis.

From our cohort of patients emerged that inflammatory complications such as synechiae, cystoid macular edema, and vitreomacular traction increase with disease duration but are not statistically influenced by systemic steroids. In our cohort, this increase of inflammatory complications lead to an increased number of laser iridotomies and intravitreal injections.

The number of recurrences appeared higher in patient treated with systemic steroids. This detail may be connected to the fact that patients requiring systemic steroid therapy usually present more active diseases that progressively become less responsive to systemic therapy.

Some scientific studies described a direct correlation between topical and systemic corticosteroid therapy and cataract and/or glaucoma incidence [25–27]. In our study, the mean age of the cohort at first visit was 44 ± 14 years, and our analysis showed no correlation between cataract development and systemic therapy applied. Our analysis in fact revealed increasing age as the main risk factor for cataract development. Cataract incidence was not related to systemic steroid usage and was dose independent. Increasing age was associated to a higher rate of cataract incidence and need for surgery. Similarly, to cataract also glaucoma and ocular hypertension were not related to systemic steroid usage; also, Neri et al. in 2004 reported that the incidence of glaucoma increased with time and was similar among the different types of uveitis [34]. These observations suggest that systemic steroid therapy may

not be related to iatrogenic complications of uveitis such as cataract and glaucoma and may therefore be safely used in this kind of patients. Interestingly, considering local therapy, all patients receive eye drops with steroids during follow-up time, and the percentage of patients treated with glaucoma medications reduced from 65.51 to 62.5%. Moreover, our results may be partially explained by the fact that in our cohort, the most common ocular feature was represented by anterior uveitis (46%), and anterior uveitis when properly diagnosed and adequately treated often solved without sequalae.

In terms of epidemiological findings, our results are perfectly in line with previous published papers [1–13, 35].

The main limitation of this study resides in its retrospective nature that may have partially affected the reliability of acquired data. Uveitis represents a group of complex pathology that requires frequent therapy adjustments and that frequently become chronic. In this situation, it's not always possible to collect the complete documentation of the ocular disease from its first appearance, and this could represent a bias for statistical analysis. Another limitation resides in the heterogeneity of patient population and the wide age range. Subjects considered in this study presented ocular inflammation as the one and only factor in common. Causes of uveitis, intensity of the disease, and previous systemic therapies are different and may have affected data analysis even if adequate statistical corrections have been made.

In conclusion, our results support the prompt use of systemic steroid in treating uveitis patients. Inflammatory complications were not steroids dependent; cataract development and its surgical removal together with trabeculectomy increased with age and were not related to medical treatment. Therefore, an early diagnosis and an appropriate treatment of each etiological form of uveitis will prevent sight threatening complications.

Further studies are needed to adequately investigate the complex relationship between systemic corticosteroids and ocular complications.

Compliance with ethical standards

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study

Disclosures None.

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