• Clinical Research •

Impact of systemic steroids combined with immunosuppressive treatment on glaucomatous features in patients with systemic lupus erythematosus

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Abstract

● **AIM:** To evaluate the incidence of increased intraocular pressure (IOP) and glaucomatous changes in systemic lupus erythematosus (SLE) patients in comparison with systemic steroids and immunosuppressive treatment.

● **METHODS:** Sixty-two women with SLE were divided into two groups: treated (*n*=47, 94 eyes) and not treated (*n*=15, 30 eyes) with systemic glucocorticosteroids (GC; GC-free). Twenty-one individuals in GC group were treated with immunosuppressive agents (immunomodulating and biologic). The visual acuity and IOP with ocular pulsatile amplitude (OPA) measurements, as well as scanning laser polarimetry (GDx) with nerve fiber index (NFI) measurement, spectral domain optical coherence tomography (SD-OCT) of the optic disk with retinal nerve fiber layer (RNFL) analysis and the macular region with ganglion cell analysis (GCA) were performed.

● **RESULTS:** Mean IOP values in group with combined GC and immunosuppressive therapy was 15.8±2.56 mm Hg and was significantly lower than in individuals with exclusive GC treatment (17.63±4.38 mm Hg, *P*=0.043). Contrary, no differences in mean IOP values between GC-free group and individuals treated with combined GC and immunosuppressive therapy were detected (*P*=0.563). Similarly, mean IOP in GC was 17.14±3.94 mm Hg and in GC-free patients was equal to 16.67±3.45 mm Hg (*P*=0.671). According to treatment regimen no statistical differences in optic disk SD-OCT for RNFL thickness, RNFL symmetry, cupping volume and the C/D ratio were observed. Similarly, no statistical differences for the mean and minimal ganglion cell layer (GCL) thickness measured in macular SD-OCT or NFI in GDx were detected.

● **CONCLUSION:** Combined immunosuppressive and systemic GC therapy in SLE patients may lower the risk of iatrogenic ocular hypertension. No relationship between treatment regimen and glaucomatous damage of optic nerve fibers in analyzed groups with SLE is detected.

● **KEYWORDS:** immunosuppression; ocular hypertension; steroid induced glaucoma; steroid therapy; systemic lupus erythematosus

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease caused by autoantibodies and complement fixing immune complexes, associated with an abnormally activated immune system. This disease can affect various organs, among which the eyeball can be involved in about 34.6%, as a result of both lupus-induced and iatrogenic events. It is known that SLE may affect almost any structure of the eye and the commonly known ocular manifestations include keratoconjunctivitis sicca, scleritis, retinal vascular disease and neuro-ophthalmic diseases[1-2]. The common use of glucocorticosteroids (GC), taking advantage of their anti-inflammatory and immunosuppressive effects to treat SLE, shows potential ocular side effects in the form of posterior subcapsular cataract (6.4%-38.7%), increased risk of local infection, ocular hypertension as well as steroid-induced

Table 1 The demographic characteristics of the SLE groups and the results of basic ophthalmic examinations depending on systemically administered steroids

Parameters	GC groups	GC-free groups	*P*
No. of examined patients	*n*=47 (94 eyes)	*n*=15 (30 eyes)	
Age (y)	40.62±13.02	44.2±12.9	0.357
Time of SLE duration (y)	8.97±7.74	2.48±7.72	0.000
Age at the diagnosis (y)	31.46±14.46	41.8±14.47	0.015
No. of medicines used	2.17±0.86	0.73±0.88	0.000
Medicines used	CQ (*n*=17), HCQ (*n*=16), immunomodulating (*n*=17), biologic (*n*=4)	CQ (*n*=3), HCQ (*n*=8)	
Family history of glaucoma	*n*=8 (16 eyes, 17.02%)	*n*=1 (2 eyes, 6.67%)	0.240
BCVA	0.96±0.17	1.01±0.17	0.358
IOP (mm Hg)	17.14±3.94	16.67±3.45	0.671
OPA	3.16±1.24	2.81±1.23	0.379

SLE: Systemic lupus erythematosus; GC: Patients receiving systemic steroids; CQ: Chloroquine; HCQ: Hydroxychloroquine; GC-free: Patients not receiving systemic steroids; BCVA: Best corrected visual acuity; IOP: Intraocular pressure; OPA: Ocular pulsatile amplitude.

iatrogenic glaucoma (SIG) or neovascular glaucoma in the course of severe SLE retinopathy (3%). Ophthalmological adverse effects can be very disabling, leading to visual field loss and even blindness[1-2].

For over 30 years, there has been observed a relation between GC and ocular hypertension as well as secondary or primary open angle glaucoma (POAG) but the influence of a long-term use of steroids combined with immunosuppressive agents on glaucoma in SLE remains unclear. Therefore, we decided to investigate this subject more thoroughly. This paper addresses the role immunosuppressive therapy may play in altering intraocular pressure (IOP) in SLE patients. Moreover, the relationship between the administered therapy in early glaucomatous signs established in optical coherence tomography (OCT) of the optic disk, as well as the macular region, scanning laser polarimetry (GDx) and perimetry. The aim of the study was to determine the association between already applied SLE treatment schemes with early glaucomatous lesions or IOP values in the studied group.

SUBJECTS AND METHODS

Ethical Approval The study was approved by the Local Ethics Committees and was performed in accordance with the Declaration of Helsinki. The written informed consent was provided by all individuals.

Subjects This study was designed as a clinical, original case-control study of an observation type. The study involved randomly selected 62 women (124 eyes) with SLE diagnosed in line with the recommendations of the American College of Rheumatology[3]. All the patients with SLE treated at the Outpatient Rheumatology Clinic received invitations to ophthalmological examinations. The studied group comprised individuals who attended the examinations and did not meet the exclusion criteria for the study. The authors of this paper did not modify nor model the risk factors for post-steroid glaucoma, which include systemic GC therapy and immunosuppressive treatment. Moreover, all SLE patients were treated according to the recommendations of the European League Against Rheumatism (EULAR)[4].

The patients were divided into groups based on GC administered systemically: 47 patients (94 eyes) who received systemic oral and/or intravenous GC therapy (GC group) and 15 individuals (30 eyes) not treated with systemic GC (GC-free group). The GC doses of prednisolone and methylprednisolone amounted to 16.55±5.97 mg/d. The mean GC treatment time was 7.89±0.52y. According to the fact that GC-induced changes might appear asymmetrically the decision of inclusion of both eyes of each individual in the analysis was made. The mean age was 40.62±13.02y without significant differences in both groups. The women receiving GC suffered from the disease significantly longer and SLE was diagnosed at a younger age than in the GC-free group (P<0.05). The number of administered immunosuppressive and immunomodulating agents (methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, cyclosporine A) was significantly higher in the group receiving GC (P<0.05). This group also received biologic treatment (belimumab) significantly more often than the GC-free group. The demographic characteristics of the studied group were presented in Table 1. The exclusion criteria for the analysis were: glaucoma diagnosed prior to SLE (*n*=3), diabetes, high degenerative myopia, chronic ophthalmic diseases unrelated to increased IOP, previous eyeball surgeries excluding uncomplicated phacoemulsification or history

of eye injuries. The presence of eye fundus changes (n=2, postinflammatory scars) and changes in perimetry unrelated to increased IOP were also exclusion criteria for the analysis (n=2, suspicion of an intracranial pathologies).

Eye Examination The following ophthalmic examinations were performed: best corrected visual acuity (BCVA) and IOP with ocular pulsatile amplitude (OPA) measurements with the use of Snellen's chart and dynamic contour tonometry (PASCAL, SMT Swiss Microtechnology AG), respectively. Spectral domain optical coherence tomography (SD-OCT, Cirrus HD 5000 Carl Zeiss, Germany) of the optic disc was conducted after dilation of the pupils. The optic nerve head (ONH) and RNFL OU analysis with Optic Disk Cube 200×200 formula was performed. The evaluated parameters included: the thickness of the retinal nerve fiber layer (RNFL), the symmetry of RNFL between eyes, the volume of the central cup and the ratio of the central cup diameter to the surface of the optic nerve (C/D ratio). Additionally, measurements of the RNFL thickness in nasal, temporal, inferior, and superior parts of the optic disc were evaluated. The Ganglion Cell Analysis Protocol was used in the OCT test of the macular region what assessed automatically the average and minimal total thickness of the ganglion cell layer and the inner plexiform layer (GCL+IPL). GDx was also used (GDx VCC: 5.5.1, Carl Zeiss, Germany), to measure the thickness of the nerve fibers around the optic nerve disc and the retinal nerve fiber index (NFI) was assessed. The analysis was based on the Nerve Fiber Analysis formula. Static and kinetic perimetry were performed in all patients in order to rule out deficiencies or narrowing of the peripheral visual field. Considering the fact, that functional changes in perimetry seem to appear later than morphological lesions in OCT or GDx, perimetry parameters have not been analyzed and served exclusively to exclude lesions unrelated to increased IOP. Due to the possible asymmetry in occurrence of changes in the posterior pole, a decision was made to include into the study ophthalmic examinations of both eyes for each patient. OCT images with signal strength less than 6 were considered as poor quality and were not used for further evaluation. Glaucoma in first degree relatives occurred in 8 patients from the GC group and in 1 patient from the GC-free group. Due to the lack of a representative quantity, the relationship for this parameter has not been analyzed.

Statistical Analysis The statistical analysis for parameter variables was performed with the use of the Student's t test and for the non-parameter variables with the Mann-Whitney U test. The calculations were made using the Statistica 13.3 (Statsoft, Tulsa, OK, USA) software. The values of P<0.05 were deemed statistically significant.

RESULTS

The mean time of GC therapy in GC group was 7.89±0.52y. Detailed analysis of basic ophthalmological examinations according to GC treatment were presented in Table 1. No statistical differences in BCVA, IOP or OPA between GC and GC-free groups were detected. Since increased IOP values are the best known factor in both glaucoma and SIG the detailed analysis of IOP according to the treatment regimen in SLE patients was performed. Consequently, IOP values over 21 mm Hg were observed in 3 eyes (3.19%; 2 patients) in GC group and 5 eyes (16.67%; 3 patients) in GC-free group. Only one of the individuals from GC group had received topical IOP decreasing therapy (timolol twice a day) due to increased IOP values diagnosed during SLE therapy and the rest were newly discovered. In GC-free group none of the examined patients received any IOP decreasing therapy. Interestingly, the mean IOP value in GC group treated with immunosuppressive agents was 15.8±2.56 mm Hg and was significantly lower than in individuals with exclusive GC administration (17.63±4.38 mm Hg, P=0.043). Moreover, no significant differences in mean IOP values between GC-free group and individuals treated with combined GC and immunosuppressive therapy were observed (P=0.563).

The mean GCL+IPL thickness in the GC group reached 84.07±8.41 μm while in the GC-free group 81.77±8.49 μm (P=0.425). The minimum thickness of the GCL+IPL complex noted in the first group was 80.53±12.59 μm and 75.04±12.54 μm in the second group (P=0.146). The complex thickness of ganglion cells in the following sectors in each eye separately were also assessed: superior, inferior, temporal superior, temporal inferior, nasal superior, and nasal inferior. No significant differences in particular sectors were found in the studied groups (Table 2).

In the optic disc OCT, the thickness of the RNFL in patients treated with GC was 92.85±12.14 μm. In GC-free SLE patients this value was equal to 94±12.27 μm (P=0.705). Analysis of this and other parameters of the optic disc in SLE patients depending on the administration of GC were presented in Table 3.

No statistical significance was found while comparing the optic nerve parameters in the OCT examination depending on GC administration in SLE individuals (Table 4). Similarly, no statistically significant differences for the NFI parameter in GDx were shown between groups (GC group: 15.95±7.66 μm; GC-free group: 18.31±7.74 μm, P=0.517).

Similarly, no significant differences in OCT or NFI values in the subjects with combined GC and immunosuppressive therapy in comparison with GC exclusive or GC-free groups were observed.

DISCUSSION

The data in literature show that the response of the eye to steroid therapy is genetically determined with 18%-36% of the population belonging to the group of GC-sensitive

Table 2 Thickness of the ganglion cell complex and the inner plexiform layer depending on steroids administered systemically in SLE patients with division into macular sectors μm

Analyzed macular region	GC group	GC-free group	*P*
Nasal superior	85±9.03	88.13±8.91	0.336
Nasal inferior	82.98±9.12	85.8±8.94	0.349
Inferior	79.49±10.62	83.2±10.74	0.183
Temporal inferior	80.57±9.94	81.4±10.1	0.987
Temporal superior	79.59±9.43	80.8±9.53	0.799
Superior	82.38±9.39	84.4±9.33	0.485

SLE: Systemic lupus erythematosus; GC: Patients receiving systemic steroids; GC-free: Patients not receiving systemic steroids.

Table 3 Thickness of RNFL and selected parameters of the optic disc in SLE patients depending on receiving systemic glucocorticosteroid therapy

Parameters	GC group	GC-free group	*P*
RNFL (μm)	92.85±12.14	94±12.27	0.705
RNFL symmetry (%)	78.6±21.47	72.8±21.83	0.143
Optic disc surface (mm^2)	1.92±0.37	1.84±0.37	0.439
Vertical C/D ratio	0.38±0.19	0.38±0.19	0.786
Cupping volume (mm^3)	0.1±0.12	0.125±0.12	0.954

SLE: Systemic lupus erythematosus; GC: Patients receiving systemic steroids; GC-free: Patients not receiving systemic steroids; RNFL: Retinal nerve fiber layers; C/D: Cup to disc ratio.

Table 4 Thickness of RNFL depending on the administration of systemic glucocorticosteroids in SLE patients in OCT examination μm

RNFL thickness	GC group	GC-free group	*P*
Nasal	71.64±12.9	69.2±12.93	0.528
Inferior	124.02±25.5	125.53±26.01	0.889
Temporal	67.45±12.48	71.47±12.49	0.281
Superior	107.91±22.83	110.4±23.33	0.961

SLE: Systemic lupus erythematosus; OCT: Optical coherence tomography; GC: Patients receiving systemic steroids; GC-free: Patients not receiving systemic steroids; RNFL: Retinal nerve fiber layer.

individuals[5]. This means that in predisposed individuals, administration of topical GC in the form of eye drops with dexamethasone for 4-6wk, leads to an increase in IOP by over 15 mm Hg in 5% of individuals while in 30% of persons an increase by 6-15 mm Hg can be expected[2,6-7]. Two thirds of the population belong to the group of the so called “insensitive to GC”, what means that after a local steroid therapy an increase in IOP does not exceed 5 mm Hg, according to Armaly’s classification[7]. SLE patients as individuals successfully treated with GC are usually in the group of GC sensitive population.

The influence of GC on IOP is strictly related to the dose, treatment duration and the route of administration. SIG has been reported in all GC administration routes, including intravenous, oral, topical as skin ointment or eye drops, intravitreal and inhalatory. Moreover, steroid-induced increase of IOP is usually transient, reversing after cessation of GC but only if used for less than a year[8]. Elevated IOP may be permanent if GC are continued for over 17mo, which results inaltered GC metabolism and an increased aqueous humor outflow resistance in the trabecular meshwork (TM) with the following changes: thickening of trabecular beams, decrease of intratrabecular spaces, increased deposition of extracellular material in the juxtacanalicular tissue (juxtacanalicular region)[6,8-10]. Moreover, receptor complex, nuclear transcription factors, a change in the PGF2a and PGE2 metabolism, as well as the *GLC1A/MYOC* gene are the risk factors for both POAG and SIG in SLE patients[6,11]. Although a steroid induced increase of IOP may be reversible, the subsequent optic nerve damage is permanent.

A chronic use of topical GC in the form of eye drops leads to IOP elevation within a few weeks whereas after intravitreal steroid injection, incorrect IOP values can be noted right after completion of this procedure. In the literature, the IOP increase in 11%-32% of eyes lasting 2mo after intravitreal dexamethasone injection was described. However, some authors describe lower rate in a low risk group of patients[12]. In the case of systemic administration of the drug it is assumed that this effect will be achieved after a few years of therapy[1,7,9,13]. The literature describes the tendency of IOP increase which correlates with an increase of the dose and treatment duration. However, correlation of higher mean IOP values with dose or treatment duration was not observed in the GC group. By contrast, in the examined GC group a lower incidence of ocular hypertension was observed than in GC-free group and as described in the literature in the general population. These observations have been supported with imaging results (Tables 2-4). Another factor, described as significant for IOP rise in GC therapy, is the particle structure. GC with lipophilic structure, *e.g.*, acetates, are characterized by a greater influence on the development of SIG as compared to hydrophilic phosphates, due to a higher corneal permeability[13]. Other risk factors for SIG include both ocular hypertension and POAG in patients receiving GC as well as POAG in first degree relatives of these individuals. Two peaks of SIG incidence have been reported: in children and elderly populations. In children, the response to GC was found to be more expressed. This results in IOP increase by over 21 mm Hg in 71.2% of patients who receive eye drops with dexamethasone 4 times a day and 59.2% if used twice a day. Moreover, high myopia predisposes the patient to a higher incidence of POAG as well as to secondary glaucoma. Systemic diseases, such as type 1 diabetes, rheumatoid arthritis or connective tissue diseases especially in the male sex may also increase the risk of SIG[2,6,13]. It has been suggested

that POAG is more common in patients exposed to 7.5 mg daily doses of prednisone-equivalent for over 1y[1]. In the studied group of patients, the drug doses were higher but that correlation was not observed.

Despite a long time of GC treatment and high doses of GC in the examined group neither an increase of IOP nor features of neuropathy in SD-OCT or GDx were observed. The abovementioned observations motivated the authors to look for an explanation for the absence of SIG in the studied SLE patients.

According to some authors, glaucoma in SLE may be accompanied either by severe SLE complications, which involve neovascular processes in severe lupus-retinopathy or it may be associated with long-term use of GC[9]. Due to the presence of the glucocorticoid receptor (GRs) in the TM and persistent elevation of cortisol level, SIG is especially associated with biochemical changes in the morphology of the TM cells. Characteristic features include an increased deposition of extracellular material in the trabecular beams and in the juxtacanalicular tissue (cribriform region) with a decrease of intratrabecular spaces, thickening of trabecular beams and an activation of the TM cells. Increased deposition of extracellular matrix composed of glycosaminoglycans, fibronectin and elastin is a result of its increased synthesis and reduced degradation. The function of the TM is inhibited with a decreased proliferation, migration and phagocytosis what results in accumulation of debris in both, intratrabecular spaces and the uvea[8,14].

The literature also describes gene expression of specific cellular components in the glycosaminoglycan composition with decreased hyaluronic acid and an increased deposition of chondroitin sulfate and glycosaminoglycogenase resistant material. It cannot be excluded, that the key mechanism of hypertension are the changes leading to altered cytoskeleton architecture due to cross-linked actin networks present in the TM tissue. All the processes mentioned above result in an increased outflow resistance of aqueous humor. Also, GC may cause morphological changes in the TM cells *via* the GRs, which belongs to a super family of highly conserved proteins including receptors for mineralocorticosteroids, androgens, estrogens, thyroid hormone, retinoic acid, progestins and vitamin D[11,15]. Since these receptors bind to and modulate specific gene promoters they have also been termed ligand-dependent transcriptions factors. The interaction of GC with the receptor is complex. Specific mechanisms involve the translocation of the activated GRs to the nucleus and GC response elements (GREs), sGREs, and nGREs as well as coactivators to elicit gene expression. Nuclear transcription factors associated with the GRE complex, *GLC1A* gene locus and the expression of myocilin in the TM cells may also be involved in the hypothesis of SIG[10-11]. Mutations of *MYOC* are observed in 2%-4% of POAG patients. The *MYOC* promotor transcription is manipulated by 4-hydroxy estradiol, which is a metabolic product of 17βestradiol in TM. The CYP1B1 enzyme has an impact on 17βestradiol metabolism and its level. The mutation of *CYP1B1* and the production of an enzyme with a decreased activity can lead to an increased level of 17βestradiol in TM cells. Consequently, the upregulation of myocillin expression may be found. A higher prevalence of POAG in postmenopausal women may confirm the thesis of *CYP1B1* involvement in the etiology of glaucoma[16]. Despite a long-term use of systemic GC in the analyzed group, ocular hypertension and SIG were not confirmed in performed tests (Tables 2-4).

One of the hypotheses explaining the decreased incidence of ocular hypertension or lack of SIG in the GC group, is the expression pattern of GRs as a subject of major regulatory variation. The negative effect of GC on GRs expression may represent a short-loop feedback mechanism which protects tissues from excessive GC levels. The other factor is hypersensitivity within the TM and the lack of ability to self-regulate the levels of GRs[15]. The other hypothesis is an increased expression of the *GLC1A* gene in the TM, which is responsible for myocilin synthesis. *MYOC* is a subunit of β3 integrin which induces the activation of calcineurin and the nuclear factor of activated T-cells (NFAT). This gene is present in 4% of patients with POAG and determinates a late onset of the disease. The basis of glaucoma related to *MYOC* is impaired secretion of myocilin from the cell, its accumulation and endoplasmatic reticulum stress. This process leads to an altered TM cell function. The influence of TM cells stretching and IOP elevation on induction of the *GLC1A* expression is also suspected[6,8]. An *in vitro* study showed a 30-fold increase of *GLC1A* expression after one day of treatment with topical dexamethasone, which lasted for up to 12d from the cessation of eye drops. Faralli *et al*[6] proved that cyclosporine A, as a suppressor of calcineurin phosphatase activity, significantly decreases the rise of IOP after dexamethasone implementation. Addition of 10 μmol/L of cyclosporine A reduced cell response by 71%, compared to dexamethasone. The same observation concerned the selective calcineurin inhibitor (INCA-6) which prevents calcineurin from binding to NFAT. Hence, calcineurin and the *NFAT1c* pathway are suspected as responsible for *MYOC* upregulation and a dexamethasone-induced IOP increase. This thesis is supported by the fact that GC combined with GRs cause the release of heat shock proteins. This activates calcineurin in a calcium independent mechanism. According to our knowledge, this is the first study to reveal IOP differences due to immunosuppressive therapy in SLE patients. However, further investigation of this field may be crucial for the treatment and prevention of SIG. Moreover, the exact mechanism of "glaucoma gene" currently remains unknown[6,8].

Difficulty of finding a larger group of patients not treated with GC was a limitation of our study, which resulted from the fact that a GC therapy at the first flare of SLE treatment according to the EULAR recommendations[4]. Nevertheless, the differences in IOP values in subjects treated with GC combined with immunomodulating agents in comparison with GC only occurred to reach satisfactory significance level.

Even though the results of this study ruled out SIG in the analyzed group, a long term use of systemic GC should remain an alert to ophthalmologists and rheumatologists. Regular ophthalmological examinations are needed for early diagnosis and treatment of post-GC complications such as intraocular hypertension or secondary glaucoma, which could improve the prognosis of vision[2]. Although glaucoma in SLE is relatively uncommon, a variety of its forms and a long asymptomatic course may lead to serious complications including vision loss and therefore, it ought not to be neglected. In the studied group of women suffering from SLE, systemic GC were not associated with a rise of IOP and early glaucomatous lesions. It is worth to highlight that this is the first study to present a significant impact of immunosuppressive agents on IOP values in patients treated with systemic GC. However, further investigation of immunosuppressive agents, including calcineurin inhibitors as well as an immunomodulating therapy role in the incidence of both ocular hypertension and SIG in SLE patients is needed.

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