Original Article

Anti-inflammatory effect of cortistatin in rat endotoxin-induced uveitis model

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Purpose: To evaluate the anti-inflammatory effect of cortistatin (CST) in endotoxin-induced uveitis (EIU) model and to compare the results with corticosteroid treatment. **Methods:** A total of 35 healthy Wistar albino rats were randomly divided into five groups. EIU was induced by a single subcutaneous injection of lipopolysaccharide (LPS). Group I received intraperitoneal (ip) normal saline (NS), Group II received ip 150 µg LPS plus NS, Group III received ip 150 µg LPS plus 250 µg/kg CST, Group IV received ip 150 µg LPS plus 1mg/kg dexamethasone, and Group V received ip 250 µg/kg CST only. The aqueous humor was collected 24 h after injection and the infiltrating cells were determined. Moreover, histopathological and immunohistochemical examinations were also performed. **Results:** The clinical score and infiltrated cell count were reduced in Groups III and IV compared with Group II ($P < 0.001$). The pathological findings of Groups III and IV were significantly reduced compared with Group II ($P < 0.001$). These findings were similar between Groups III and IV ($P = 1.000$). Tumor necrosis factor-alpha (TNF-α) and interleukin 1 beta (IL-1β) immunoreactivity in the ciliary body of Group III and Group IV were significantly reduced compared with Group II ($P < 0.001$). TNF-α and IL-1β immunoreactivity in the ciliary body of Group III and Group IV were similar compared with Group I and Group V (range of P values was 0.539–0.958). **Conclusion:** CST administration as a therapeutic agent might ameliorate the severity of intraocular inflammation in uveitis patients. In conclusion, effect of CST and dexamethasone in EIU model was comparable.

Key words: Cortistatin, endotoxin-induced uveitis, interleukin-1, tumor necrosis factor-alpha

Uveitis is an intraocular inflammatory disease, which affects different parts of the eye and has different clinical manifestations, depending on the location and severity of inflammation.[1] Uveitis can affect individuals of all ages, genders, and races and accounts for 10–15% of all blindness cases.[2]

The animal models are necessary to better understand the pathophysiology of uveitis and also to provide the development of new treatment protocols against this disease in humans. The endotoxin-induced uveitis (EIU) model mimics many of the immunopathogenic mechanisms associated with human uveitis and was originally utilized as a model of anterior uveitis.[3,4] In the treatment of non-infectious uveitis, corticosteroids are used in the acute period and immunosuppressive agents are used to prevent recurrence in the chronic period. These agents suppress the immune system and have serious side effects. Therefore, treatment-resistant cases can lead physicians to seek new treatment methods.[5]

Cortistatin (CST) is a recently discovered neuropeptide and is structurally similar to somatostatin (SST). Many pharmacological and functional properties of CST resembles that of SST, including the reduction of neuronal activity and the suppression of growth hormone, prolactin, and insulin secretion.[6] On the contrary, CST also differs from SST in many ways, including the promotion of slow-wave sleep cycle, reduction of locomotor activity, and inhibition of cell proliferation.[6,7] Inflammatory response and immune stimulation triggers the production of CST by macrophages and T-cells, supporting the physiological role of CST in the immune system.[8] In rat, mouse and human tissues, CST is found in 14 (CST-14) or 17 (CST-17) amino acid-containing forms. Among them, CST-14 exhibits properties as a potent anti-inflammatory peptide. It is responsible for inhibiting Th1 cells proliferation and release of proinflammatory cytokines [interleukin (IL)-1, IL-6, IL-12 and interferon (IFN)-gamma] while increasing the anti-inflammatory signals (IL-10).[9]

In the current study, our aim was to evaluate the anti-inflammatory effects of CST on ciliary body, which is a part of uvea in EIU model. At the same time, we planned to compare the results with corticosteroid treatments, which have been used frequently and have been proven to be effective in uveitis patients.

Methods

This study was carried out in accordance with the ARVO Statement for Use of Animals in Ophthalmic and Vision

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Research guidelines. Experimental Animal Studies Ethics Committee of Fırat University approved the study protocols of the present study (2018/103). In the current study, 8-10 weeks old male Wistar albino rats obtained from Fırat University experimental animal research center were used. All animals were maintained under 12 h light/12 h dark cycle, with food and water were provided ad libitum.

Induction of EIU was performed through single subcutaneous injection of lipopolysaccharide (LPS) (150 µg) obtained from Salmonella typhimurium (Sigma Chemical, St. Louis, USA). LPS was dissolved in 0.1 ml sterile saline as previously described.[4] A total of 35 healthy rats were randomly divided into five groups (seven rats in each group). Group I received intraperitoneal (ip) normal saline [NS, (0.9% NaCl)], Group II received ip 150 µg LPS plus NS, Group III received ip 150 µg LPS plus ip 250 µg/kg CST (Phoenix Pharmaceuticals Inc. Belmont, CA, USA), Group IV received ip 150 µg LPS plus ip 1 mg/kg dexamethasone and Group V received only ip 250 µg/kg CST.

CST and dexamethasone treatment were administered at 2 h following LPS injection. All animals were examined for clinical scoring of inflammation with slit lamp biomicroscopy 24 h following injection which was considered the most prominent in EIU model.[3] The clinical scoring in EIU was assigned to each eye based on a grading scale as previously described.[10] The animals were sacrificed by intracardiac high dose anesthesia following clinical examination. Right eyes were enucleated for histopathological and immunohistochemical examination. Left eyes were used to collect aqueous humor (AqH) for infiltrated cell count. The removed right eyes were fixed in 10% formaldehyde solution for 12 h. After the fixation, the tissues were dehydrated through a series of graded ethanol concentrations. Then, the tissues were cleared in xylol and embedded in paraffin wax. The tissue blocks were sectioned at a thickness of 5 µm to perform immunohistochemical and histopathological staining. In each tissue, randomly selected six sections from each group were examined microscopically.

Infiltrated cell count in aqueous humor
The cell counting in AqH was performed as previously described.[11] The AqH was collected by puncturing the anterior chamber of the eye with a 30-gauge needle. Equal amounts of the AqH and trypan blue solution (Sigma-Aldrich, USA) were mixed and a drop from the cell suspension was applied onto a hemocytometer for cell counting. Under the light microscope, cell numbers per square (equivalent to 0.1 µL) was determined manually. In order to perform the correction from the previous dilution, mean numbers of cells for each sample counted from five different microscopic fields were multiplied by two.

Histopathology
Tissue samples of all groups were stained by using standard hematoxylin & eosin (H&E) method. For histopathological examination, anterior chamber tissues, including the iris, ciliary body, ciliary process, and corneal endothelium, were scored for the severity of inflammation as previously described.[12] Grade 0: normal tissue, Grade I: dilated iris vessels and thickened iris stroma, Grade II: infiltration of inflammatory cells into the stroma of the iris and/or ciliary body, Grade III: heavy infiltration of inflammatory cells within the iris stroma and ciliary body, Grade IV: heavy infiltration of inflammatory cells within the iris stroma and ciliary body and inflammatory cell deposits on the corneal endothelium.

Immunohistochemistry
TNF-α and IL-1β were detected in the rat eye tissue with EIU by immunohistochemical staining using rabbit polyclonal antibodies (TNF-α;bs-2081R, IL-1β;bs-6319R, Bioss, USA) and the streptavidin–biotin peroxidase technique. The procedure was performed under the same conditions for all sections as previously described.[13]

Immunohistochemical evaluations were performed using the extensity of the staining. The distribution (0.1: <25%, 0.4: 26%–50%, 0.6: 51%–75%, 0.9: 76%–100%) and intensity (0: no staining; +0.5: very little staining; +1: little staining; +2: medium staining; +3: very strong staining) of immune reactivity was used to obtain a histoscore (Histoscore = distribution × intensity).[14]

The SPSS statistical software package version 25.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. The data were reported as mean ± standard deviations for each data set. A statistical significance was considered if $P < 0.05$. The statistical analyses of the data were performed using one-way analysis of variance test, Kruskal–Wallis test and post hoc analyses (Tukey test and pairwise comparisons using Bonferroni correction, respectively).

Results

Clinical scores of intraocular inflammation
According to the clinical examination, clinical scores of Groups I, II, III, IV, and V were 0.0, 3.24 ± 0.49, 1.04 ± 0.81, 0.70 ± 92, and 0.0, respectively [Fig. 1]. Clinical scores of Group III and Group IV were significantly reduced compared with Group II ($P < 0.001$). There was no difference between the clinical scores of Group III and Group IV ($P = 0.975$).

Infiltrated cell count in aqueous humor
Infiltrated cell count of Groups I, II, III, IV, and V were 0.52 ± 0.57 × 10^4/mL, 28.76 ± 5.67 × 10^4/mL, 12.81 ± 2.21 × 10^4/mL, 11.22 ± 1.82 × 10^4/mL, and 1.54 ± 0.57 × 10^4/mL, respectively. In Group II, the number of infiltrated cells was significantly increased than the other groups ($P < 0.001$). The number of infiltrated cells of Group III and Grade IV were significantly reduced compared with Group II ($P < 0.001$). There was no difference between the infiltrated cell count of Group III and Group IV ($P = 0.906$).

Histopathology
The ciliary body of Group I did not show any cellular infiltration [Fig. 1A]. Except for Group II, there was no remarkable microscopic changes in the uvea. 24 h following the injection of LPS, the histological analysis indicated moderate to severe lymphohistiocytic anterior uveitis characterized by increased surface area of iris leaflets and ciliary body due to edema, mild to moderate congestion and inflammatory infiltrate [Fig. 1B].

The pathological findings of Group III and Group IV were significantly reduced compared with Group II ($P < 0.001$, for both) [Fig. 1C and D]. When Group III and Group IV were compared with Group I and Group V, the results were similar ($P = 0.080$ for Group I and Group III, $P = 0.262$ for Group I and Group IV, $P = 0.080$ for Group V and Group III, $P = 0.262$ for Group V and Group IV). Likewise, the results between Group III and IV were similar ($P = 0.952$). Structural appearance of Group V was also similar to Group I ($P = 1.000$) [Fig. 1E].
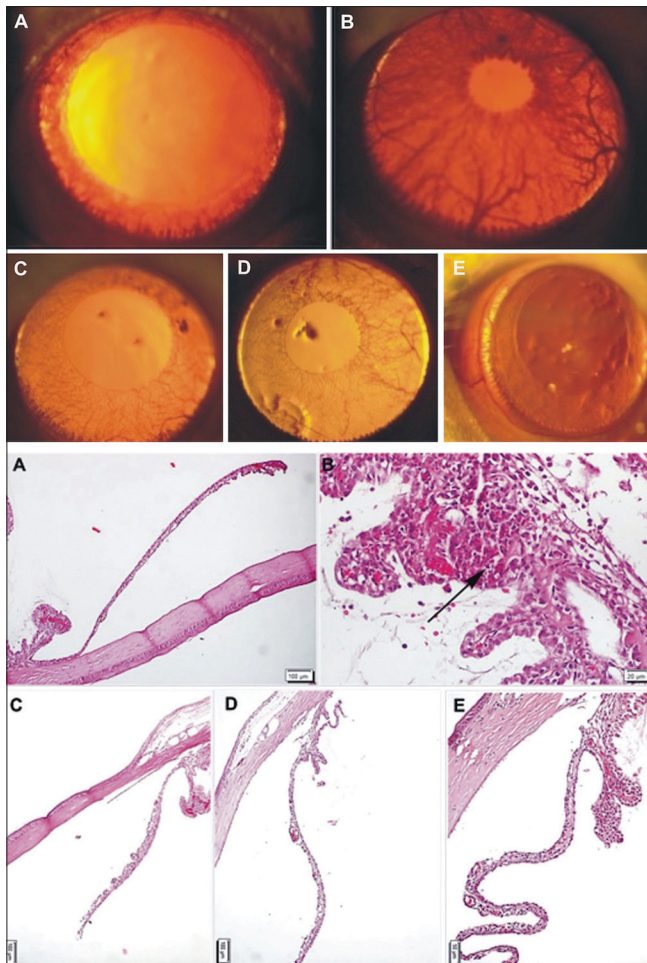
Figure 1: Anterior segment images; normal in Group I (A), intense vasodilatation in the vessels of the iris and conjunctiva, miosis and anterior segment reaction in Group II (B), decreased hyperemia and vasodilatation in the conjunctiva and iris of Group III (C) and IV (D), and normal in Group V (E) and histopathological images; normal in Group I (A), intense inflammatory cell infiltration (arrow), edema, vasodilatation, and hyperemia in the ciliary body of Group II (B), decreased hyperemia and inflammation in the ciliary body of Group III (C) and IV (D), and normal in Group V (E)

Immunohistochemistry

TNF-α immunoreactivities were 0.05 ± 0.06, 1.42 ± 0.48, 0.26 ± 0.10, 0.22 ± 0.12, and 0.12 ± 0.03, respectively [Fig. 2]. TNF-α immunoreactivity in the ciliary body of Group I displayed light intensity [Fig.3a]. TNF-α expression increased considerably in Group II [Fig. 3b] compared to Group I ($P < 0.001$). However, TNF-α immunoreactivity in the ciliary body of group III [Fig. 3c] and Group IV [Fig. 3d] decreased significantly compared to Group II ($P < 0.001$, respectively). TNF-α immunoreactivity in the ciliary body of Group III and Group IV was similar to that of Group I and Group V ($P = 0.741$ for Group I and Group III, $P = 0.820$ for Group I and Group IV, $P = 0.887$ for Group V and Group III, $P = 0.938$ for Group V and Group IV). Likewise, TNF-α immunoreactivity in the ciliary body was also similar between the Group III and Group IV ($P = 1.000$). Similar results were obtained for ciliary body TNF-α immunoreactivity between the Group V and the Group I [$P = 0.998$; Fig. 3e].

IL-1β immunoreactivity were 0.05 ± 0.07, 1.26 ± 0.41, 0.27 ± 0.15, 0.21 ± 0.14, and 0.09 ± 0.02, respectively [Fig. 2]. IL-1β
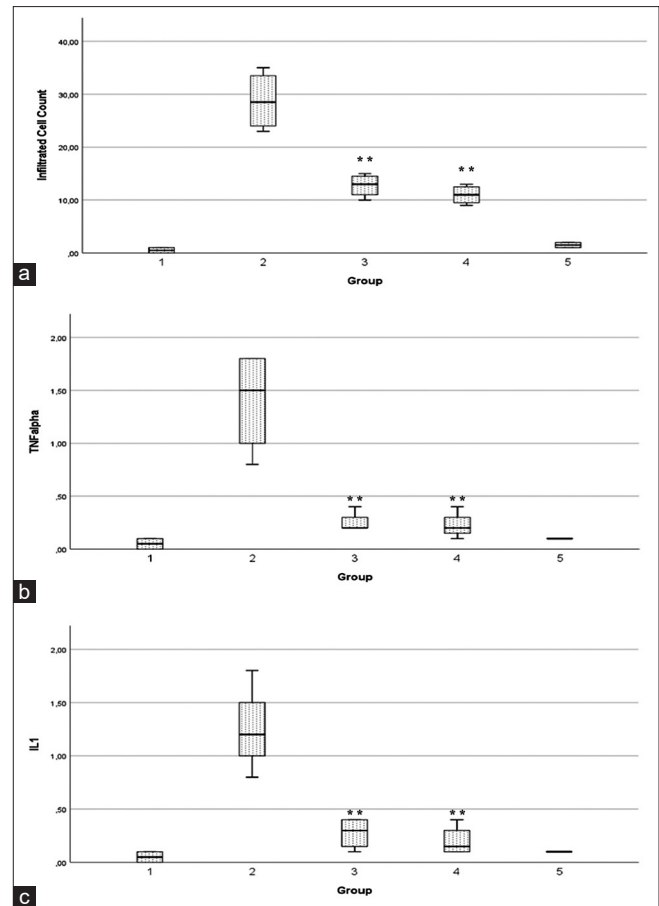

Figure 2: Boxplot representations of the studied parameters. (a) Infiltrated cell count in all groups, (b) TNF-α immunoreactivity examination in all groups, (c) IL-1β immunoreactivity examination in all groups (*$P < 0.05$ and **$P < 0.01$ significantly different from Group II)

immunoreactivity in the ciliary body of Group I also displayed minimal intensity [Fig. 4a]. In Group II, IL-1β immunoreactivity increased markedly [Fig. 4b] compared to Group I ($P < 0.001$). However, IL-1β immunoreactivity of Group III [Fig. 4c] and IV [Fig. 4d] decreased significantly compared to Group II ($P < 0.001$ for both). IL-1β immunoreactivity in the ciliary body of Group III and Group IV were similar to that of Group I and Group V ($P = 0.559$ for Group I and Group III, $P = 0.842$ for Group I and Group IV, $P = 0.756$ for Group V and Group III, $P = 0.958$ for Group V and Group IV). Similar results were also observed between Group III and IV ($P = 0.985$). Likewise, IL-1β immunoreactivity of Group V was found to be similar to the Group I [$P = 0.987$; Fig. 4e].

Discussion

In the current study, we investigated the effects of systemic administration of CST on EIU using rat models. CST treatment ameliorated histopathologic changes as well as TNF-α and IL-1β immunoreactivity, where the present results were comparable to dexamethasone treatment in the ciliary body. Moreover, infiltrated cell count, histopathological and immunohistochemical scores were also similar between CST and dexamethasone treated groups.

Immunohistological examination of experimental uveitis model demonstrated that the predominant cell type in the
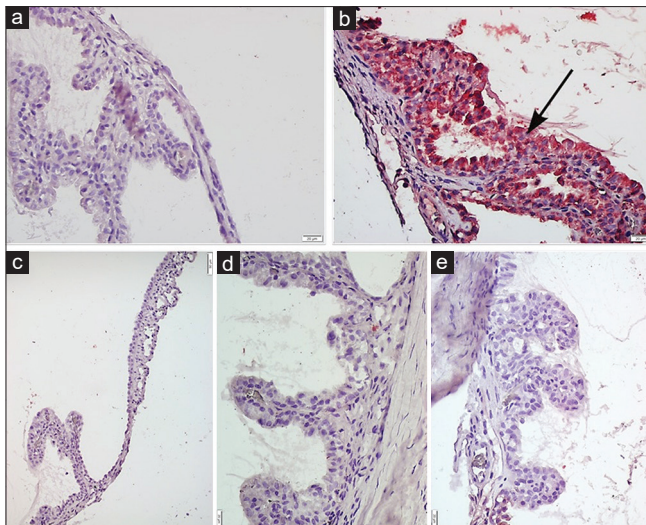
Figure 3: TNF-α expression in the ciliary body of all groups. TNF-α expression in the control ciliary body demonstrated light intensity in Group I (a). TNF-α expression (arrow) is very prominent in Group II (b). Decreased TNF-α expression in the ciliary body of Group III (c) and IV (d). TNF-α expression in the ciliary body demonstrated light intensity in Group V (e)

Figure 4: IL-1β immunoreactivity in the ciliary body of all groups. IL-1β expression in the control ciliary body demonstrated light intensity in Group I (a). IL-1β immunoreactivity (arrow) is highly pronounced in Group II (b). Decreased IL-1β expression (arrow) in the ciliary body of Group III (c) and IV (d). IL-1β expression in the ciliary body demonstrated light intensity in Group V (e).

early period is T cells. However, other actors of inflammation, such as macrophages migration to the area, have also been observed. In addition to T cells, proinflammatory cytokines, such as TNF-α, IL-1, IL-6, and IL-8 were abundantly detected in the inflammatory area.[15] During the first step of the immune response, two important cytokines such as TNF-α and IL-1 are secreted. In the cases of uveitis, high levels of TNF-α promote disruption of the blood-retinal barrier and increase vascular permeability, leading to edema.[16] IL-1 represents another pleiotropic proinflammatory cytokine and predominantly secreted by activated macrophages, B lymphocytes, and endothelial cells. The effect of IL-1 is similar to TNF-α and is thought to play a key role in the development of uveitis.[17]

Recently, some neuropeptides and hormones, such as vasoactive intestinal peptide, adrenomedullin, urocortin, ghrelin, alpha-melanocyte stimulating hormone, and CST have been reported to play significant roles throughout the inflammatory events.[18] Numerous immune cells in human body, including lymphocytes, monocytes, macrophages and dendritic cells, have been demonstrated to have CST.[19] Some studies reported that the levels of CST are correlated with the differentiation and activation state of immune cells.[8,20] These findings suggests that CST may have important regulatory functions in the pathogenesis of inflammatory diseases. Previous studies demonstrated that CST exerts general anti-inflammatory actions. For instance, CST inhibited the production of a wide panel of inflammatory cytokines (TNF-α, IL-1, IL-6, and IL-12), chemokines and nitric oxide by macrophages when they are activated with bacterial endotoxins.[21,22] Moreover, macrophage associated production of the anti-inflammatory cytokine IL-10 have been shown to be stimulated by CST.[21,22] In addition to its effect in innate immunity, CST is also able to modulate the adaptive immune response, mainly by regulating the activation and differentiation of T lymphocytes.[23] The results of the current study demonstrated a decreased TNF-α and IL-1 immunoreactivity following CST treatment, where the results were comparable to that of dexamethasone treatment.
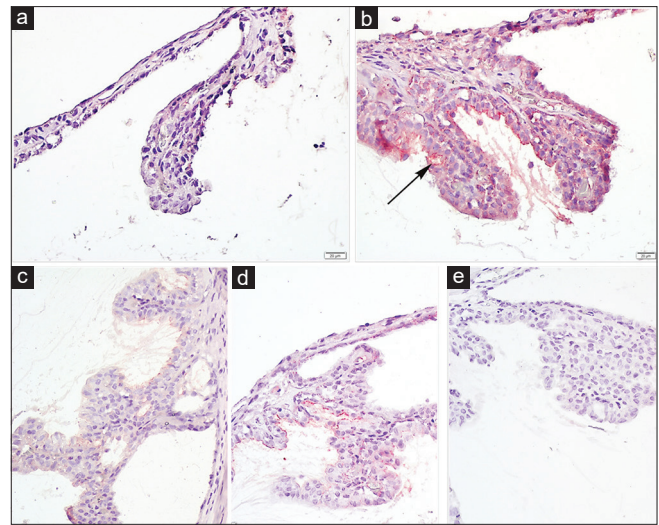
Septic shock associated histopathological signs, including inflammatory cell infiltration and disseminated coagulation in various vital organs, were prevented by CST.[24] In previous studies, it was shown that a single injection of CST at the onset of inflammatory bowel disease ameliorated the clinical and histopathological severity.[21] Moreover, initial treatment with CST has also been reported to prevent recurrence of the disease.[21] The therapeutic effects were associated with down-regulation of various inflammatory mediators in colonic mucosa and with impairment in Th1-driven autoimmune responses in colon.[21] In psoriasis patients with reduced serum CST levels, keratinocyte proliferation was inhibited following the use of CST as a therapeutic agent.[25] A recent study reported that the systemic injection of CST ameliorated both chronic and relapsing-remitting experimental autoimmune encephalomyelitis in mice, which clinically and histopathologically resembles two forms of human multiple sclerosis. Treatment with CST after the onset of disease reduced the presence of inflammatory infiltrates in the cervical and lumbar segments of spinal cord and, hence, decreased the subsequent demyelination.[26] These effects were accompanied by a decrease in the presence of Th1 and Th17 in the central nervous system.[26] Moreover, CST was able to reduce the production of inflammatory mediators.[26] To our knowledge, this is the first study to investigate the anti-inflammatory effect of CST in EIU model. In the present study, an effective dose of CST in previously published studies was chosen as a single injection treatment.[21,27] The results showed that the anti-inflammatory effects of CST were comparable to that of dexamethasone in the EIU model. CST treatment significantly ameliorated histopathological changes (inflammatory cell infiltration, edema, vasodilatation, and hyperemia) as well as TNF-α and IL-1β immunoreactivity in the ciliary body. In the present study, ip injection of CST did not cause any detectable side effect in animals. In addition, in the study of Chen *et al*., serum CST, fasting plasma glucose (FPG), insulin and hemoglobinA1c (HbA1c) levels as well as blood lipid profiles were evaluated in newly diagnosed diabetic patients.

In their study, they found significantly decreased serum CST levels. Moreover, they also reported a negative correlation between serum CST and FPG as well as HbA1c and insulin.[28] On the contrary, one of the most important side effects of corticosteroids is hyperglycemia. We thought that this could be an important advantage of CST over steroids.

There were several limitations in the current study. Effects of CST treatment were investigated only on the ciliary body using the EIU model. In addition, dose response relationship, pharmacokinetic and functional analyses were not evaluated. Therefore, future studies are required to determine the optimal dosing protocol. Although, short-term effects were quite promising, future studies should be performed to confirm the long-term effects.

Conclusion

In conclusion, the results of the present study demonstrated that CST administration as a therapeutic agent might ameliorate the severity of intraocular inflammation in rat EIU model. Moreover, the effects obtained by CST treatment using EIU models were comparable to the effects following dexamethasone administration.

Disclosure statement

The authors alone are responsible for the content and writing of the paper.

Conflicts of interest

There are no conflicts of interest.

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