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Original Article

The Impact of Etanercept, Cyclosporine A, Triamcinolone Acetonide on Interleukin-23 in Experimental Autoimmune Uveitis

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Abstract

Background: We aimed to investigate the effect of etanercept, Cyclosporine A (CsA) and Triamcinolone Acetonide (TA) on Interleukin-23 (IL-23) in the Experimental Autoimmune Uveitis (EAU) model.

Materials and methods: Thirty-five guinea pigs were divided into five groups consisting seven animals in each: Group 1 (control group), Group 2 (sham group), Group 3 (etanercept group) and Group 4 (CsA group) and Group 5 (TA group). The experiments in Group 1 were not given any treatment. The single eyes of all experiments in the groups except Group 1 administered intravitreally 1mg/ml concanavalin A to induce the EAU. On the 14th day, after clinical confirmation of uveitis, the eyes of the animals in Group 2, 3 and 5 received single dose intravitreally of 0.1ml saline, 2 mg/0.1 ml etanercept and 4 mg/0.1 ml TA, respectively. The animals in Group 4 were given intravitreally 100 µg/0.1 ml CsA weekly. At the end of the 6th week following the drug administrations, the eyes, including also controls, were excised. Vitreous IL-23 levels were measured by ELISA and evaluated.

Results: The mean IL-23 level in Group 2 was found to be higher than that of Group 1 ($p<0.05$). There was no statistically significant difference in the IL-23 levels among the treatment groups (Group 3, 4 and 5) ($p>0.05$).

Conclusion: This study suggests that intravitreal etanercept, CsA and TA do not affect the levels of IL-23 in EAU model.

Keywords

Cyclosporine A; Etanercept; Experimental autoimmune uveitis; Triamcinolone acetonide; IL-23

Introduction

Uveitis is the inflammatory disease of the uvea. Although it may be caused by autoimmune diseases, infections, or trauma, approximately half of the cases with uveitis are idiopathic. It often courses with attacks and remissions and can be complicated with permanent ocular damage and visual loss. Although the exact pathogenic mechanism of uveitis is not known, it is clearly demonstrated that pro-inflammatory cytokines such as Interleukin (IL)-1, IL-6, and Tumor Necrosis Factor-alpha (TNF-α) play the important role in uveitis [1,2]. Thus, the various anti-TNF agents in the treatment of uveitis have been currently researched.

Etanercept that inhibits the action of both TNFα and TNFβ is a fusion protein consisting the extracellular ligand-binding portion of human TNF receptor p75 and the Fc portion of human IgG1. It has been used in the treatment of autoimmune diseases such as Rheumatoid Arthritis (RA) and ankylosing spondylitis [3-5]. It has been demonstrated that systemically or intravitreal etanercept is efficacious in the treatment in both the patients with chronic uveitis and Experimental Autoimmune Uveitis (EAU) [6-9].

Interleukin-23 is a member of the IL-12-related cytokine family. It was firstly described by Kastelein et al., [10]. IL-23 plays the role in the activation and proliferation and stabilization of Th17 which differentiated before. IL-23 increases the lymphocyte proliferation, promotes the production of IFN-γ [11-18]. In the Behcet's patients with active uveitis, IL-23, IL-17 and IFN-γ levels were found to be significantly higher [19]. IL-23 is responsible for the survival and amplification of Th17 cells as well as the production of IL-22 and IL-21 [20]. It was observed that the receptor gene expression of IL-23 has also been shown to increase in Inflammatory Bowel Diseases (IBD), RA, psoriasis and Graves' ophthalmopathy [21-23]. Additionally, Chen et al., [14] showed that administration of anti-IL-23p19 mAb in Experimental Autoimmune Encephalomyelitis (EAE), decreased central nervous system expression and the serum level of IL-17. Thus, it is considered that Th17 development is dependent on the presence of both IL-23 and IL-6. IL-23 may function at a late stage of the differentiation of Th17 cell following initial induction by other pro-inflammatory cytokines [16-18]. It was demonstrated that the rats deficient in IL-23 were completely resistant to EAE [24,25]. Toussirot et al., demonstrated that the IL-23/Th17 axis plays a key role in the development of chronic inflammatory and autoimmune-mediated diseases [17]. It was reported by Luger et al., [26] that systemic neutralization of IL-23 prevented the development of EAU.

We considered that etanercept will be able to affect the vitreous IL-23 levels and conducted this study. In this study, we aimed to investigate the effect of etanercept on IL-23, and to compare its effect with those of CsA and TA in EAU.

Materials and Methods

This study was carried out in the single eye of each experiment, with approval from the institutional ethics committee of Fırat University. All procedures were performed with strict adherence to the guidelines for animal care and experimentation prepared by the Association for Research in Vision and Ophthalmology and Guidelines for the Housing of Rats in Scientific Institutions.

The study included 35 male albino guinea pigs, of mean weight 400 g. The experiments were housed in special wire-bottomed cages at room temperature on a 12-hour light-dark cycle in the experimental research center at Fırat University along the study. They were fed with standard guinea pig chow but were given only water 12 hours before surgery.

The experiments were randomly allocated to five groups, with seven rats in each group: Group 1 (control group) was composed of the animals which were not operated on and did not receive any treatment. Group 2 (sham group) was composed of the animals in which induction of EAU was performed and which received single dose intravitreally 0.1ml saline. Group 3 (etanercept group) was composed of the animals in which induction of EAU was performed and which received intravitreally single dose 2 mg/0.1 ml etanercept (Enbrel, Wyeth Pharmaceuticals, Philadelphia, PA, USA). Group 4 (cyclosporine A-CsA-group) was composed of the animals in which induction of EAU was performed and which received intravitreally 100 μg/0.1 ml cyclosporin A (Sandimmune 50 mg/ml ampoule, Novartis Pharma AG, Basel, Switzerland) weekly. Group 5 (triamcinolone acetonide-TA-group) was composed of the animals in which induction of EAU was performed and which received intravitreally single dose 4 mg/0.1 ml triamcinolone acetonide (Kenacort A 40 mg/ml ampoule, Bristol-Myers Squibb Co., Princeton, NJ, USA).

At the end of the 6th week following the drug administrations, the enucleation of eyes was performed following induction of analgesia and anesthesia.

Induction of EAU

The animals in the groups except the control group were injected intravitreally with concanavalin A (Sigma Chemical Co, St Louis, MO) 1 mg/mL in the right eye only. Drug administration was started when uveitis-like inflammation developed 2 weeks later. Topical antibiotic drops were instilled into eyes.

Anesthetic and surgical technique

A combination of ketamine hydrochloride 50 mg/kg (Ketalar®, Eczacıbaşı, Turkey) and xylazine hydrochloride 5 mg/kg (Rompun®, Bayer, Turkey) was intramuscularly injected to induce anesthesia and analgesia.

After induction of anesthesia and analgesia, 1 mg/0.1 mL concanavalin A was injected using a 30-gauge needle into the right eye only, except in the animals in the control group. At the end of the second week, slit-lamp biomicroscopy revealed flare in the anterior chamber, moderate cell numbers, fibrin behind the lens, and moderate cataract. After the development of uveitis was confirmed clinically, the sham and treatment groups were given intravitreal injections at the end of the second week. At the end of 6th week, the eyes of the experiments were enucleated. Vitreous samples were obtained by aspiration using a 27-gauge needle and sent to immunology laboratory for the measurement of vitreous IL-23 levels.

Immunological evaluation of vitreous IL-23 levels

IL-23 levels in vitreous samples of the experiments were measured by mouse IL-23 (p19/p40) kit (eBioscience, San Diego, CA) using the solid phase sandwich Enzyme-Linked Immunosorbent Assay (ELISA). The detection limit for this assay was 1.0 pg/ml. The assays were performed according to the manufacturers' instructions. Results are expressed in picogram per milliliter as a mean ± standard deviation.

Histopathologically confirmation of EAU

The histopathological findings including heavy infiltration of inflammatory cells, edema, congestion of the retina and uvea and proliferation in the ciliary epithelium after intravitreal injection of concanavalin A were interpreted as evidence of induction of uveitis.

Statistical analyses

The means (±standard deviations) of the data obtained were calculated. The statistical analysis was carried out using the Statistical Package for Social Sciences version 13 (SPSS Inc, Chicago, IL). Analysis of variance was carried out for multiple comparisons using the Kruskal-Wallis test and the Mann-Whitney U test was used for dual comparisons between groups. A P value less 0.05 was accepted as being statistically significant.

Results

The mean vitreous IL-23 levels were found as 2.75±0.22, 3.49±0.34, 3.83±0.10, 3.53±0.17 and 3.73±0.25 pg/ml, respectively. The mean vitreous IL-23 levels in the sham and treatment groups were significantly higher than control ($p<0.01$). There was no significant difference among sham and treatment groups in terms with IL-23 levels ($p>0.05$). When compared with control group, IL-23 levels were observed to be higher in each treatment group ($p<0.001$) (Table 1 and figure 1).

Additionally, the comparison of edema, tissue congestion, Mononuclear Cell (MNC) and Polymorphonuclear Leukocyte (PNL) infiltration in the study groups was given in table 1.

Discussion

Uveitis, the inflammatory disease of the uvea is responsible for 10% of legal blindness [1]. Although, there is currently no effective treatment for the uveitis, glucocorticosteroids and some immunosuppressive agents have been widely used in the treatment of disease [2]. Although many cytokines contributed to uveitis, the minority of them play significant roles. TNF-α stimulates mononuclear phagocytes as well as other cell types that produce IL-1, IL-6 and chemokines, and induces the migration of PNL [1,27-29]. Recent studies have shown that a new T helper subset that produces IL-17 (Th17) is also involved in the development of EAU [25-30]. The animal models have been demonstrated that the number of T-helper types 17 cell (Th17) increased in the active uveitis and scleritis while it reduced after treatment [31-33].

IL-23, a member of the IL-12 family of cytokines, is a heterodimeric cytokine composed of the p40, shared with IL-12, and p19, a subunit that belongs to the IL-6 superfamily of cytokines [10-13]. IL-23 is synthesized by activated macrophages and the dendritic cells with the stimulation of immune triggers such as bacterial products, viral infection and pro-inflammatory cytokines or CD40 signaling and regulate TH17 function and proliferation [16-21]. Additionally, IL-23 induces CD8+ memory T cells to proliferate and produce IL-17 [12,34-39].

IL-23 binds to a heterodimeric receptor composed of IL-12Rβ1 and IL-23R. Th17 cells are enriched for expression of IL23R [16-21]. IL-23 plays an important role in chronic inflammatory responses and the pathogenesis of some autoimmune inflammatory disorders [12,16,34-39]. It has been demonstrated in recent studies that IL-23-deficient (IL-23p19−/−) mice are resistant to EAE, IBD and EAU [21,22]. IL-23 also affects the innate immune system, inducing the production of pro-inflammatory cytokines [10,21]. Recent studies demonstrated that blood levels of IL-23, IL-17 and IFN-γ simultaneously increased in intraocular inflammation in Behcet's disease [19,34].

In the mice formed IL-23 gene disorder, it has been observed that the formation of EAE, arthritis, and IBD was not composed [24]. IL-23 increases the synthesis of IL-17 IL-17F, IL-6 and TNF-α from activated T cells [10,25]. It has been considered that IL-23 that increases the levels of cytokines such as TNF-α, IL-6, IL-17 and IFN-γ is the orchestrating conductor of the inflammatory cascade [35,36].

In the patients with IBD, it was demonstrated that IL-23 stimulated the expression of Th17 cells and the synthesis of IL-17 [40]. It has been suggested that IL-23 might play in role in the development of uveitis in Vogt-Koyanagi-Harada disease via the stimulation of IL-17-producing CD4+ T cells [11]. Caspi et al., reported that IL-23 and a Th17 effector response affected by IL-23 are needed for the development of uveitis [41]. In recent studies, it has been observed that mice given IL-12/IL-23 inhibitor did not develop IL-23 response and the increase of IL-17 [42]. In our study, it was found that IL-23 level elevated in uveitis created eyes (sham group).

Etanercept is a soluble fusion protein produced by recombinant DNA of the extracellular ligand-binding portion of human TNF receptor p75 and the Fc portion of human IgG1. This agent inhibits the action of both TNF-α and TNF-β, important pro-inflammatory cytokines [5-11]. Etanercept is a large molecule with a molecular weight of 150 kDa. It binds to TNF-α and decreases its effect in disorders involving excess inflammation in humans and animals, including autoimmune diseases such as ankylosing spondylitis, juvenile RA, psoriasis, psoriatic arthritis, RA, and potentially,

	Control	Sham	Etanercept	Cyclosporine A	Triamcinolone
IL-23 (pg/ml)	2.75± 0.22*	3.49±0.34	3.83±0.10	3.53±0.17	3.73±0.25
Congestion	0.43± 0.53*	1.86±0.69	1.57±0.53	1.71±0.75	1.43±0.78
MNC Infiltration	0.43± 0.53*	2.43±0.78	1.00±0.00*	1.14±0.38*	1.43±0.53*
PNL Infiltration	0.71±0.48*	1.14± 0.37	0.86±0.37	2.29±0.95*	1.00± 0.00
Edema	0.86± 0.37*	1.86±0.37	2.00±0.57	1.00±0.00*	1.29±0.48*

Table 1: The mean levels of IL-23, mean values of congestion, MNC and PNL infiltration and edema in the study groups.

IL: Interleukin; MNC: Mononuclear Cell; PNL: Polymorphonuclear Leukocyte

Compared to the sham group: *p<0.05

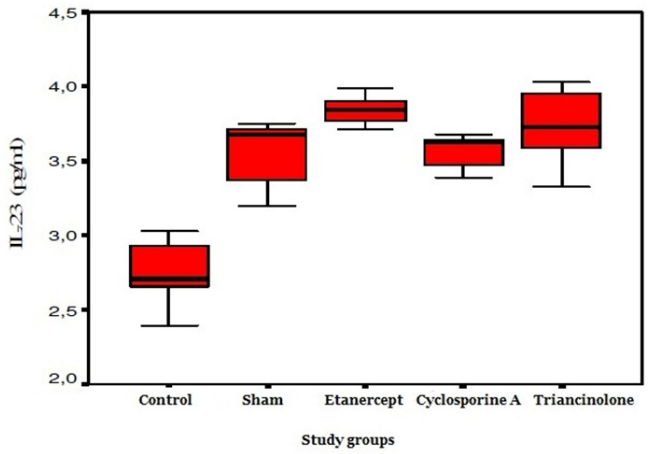

Figure 1: The graphic presents the comparison of the mean vitreous IL-23 levels in the study groups.

IL: Interleukin

in various disorders mediated by excess TNF-α such as uveitis [5-9,43-45].

In rats formed EAU, TNF-α antagonists decreased the severity of uveitis [47]. Etanercept treatment in the patients with RA decreased serum IL-23 levels [43,44]. In another study, it was observed that the etanercept treatment suppressed the proliferation of Th17 in psoriasis patients and suggested that it was probably related to the decrease in the level of IL-23 [45]. In our study, we observed that etanercept did not affect vitreous IL-23 levels in EAU model. These results contradict with the thought that anti-TNF therapy to suppress IL-23 synthesis. This may be caused by a diversity in cytokine cascade due to a change in Th polarization in various diseases such as RA and psoriasis.

Cyclosporine A is a T cell-specific immunosuppressant, which affects the early phase of the immune response via the blockade of the synthesis and release of IL-1 from by macrophages and IL-2 from by Th cells. CsA has been shown to be effective in the treatment of immune-mediated ocular diseases such as uveitis [47-50]. IL-23 is synthesized by macrophages and dendritic cells. CsA affects the functions of dendritic cells [51]. However, in our study, we also found that CsA did not affect IL-23 levels in EAU.

IL-23 leads to synthesis the inflammatory cytokines through IL-12Rβ1 receptors. Glucocorticoids inhibit Th cells and antigen-presenting cells and the expression of various cytokines released by T1 and T2 lymphocytes and eventually suppresses the inflammation. Thus, they have been widely used uveitis [52-54]. Dexamethasone treatment has been shown to decrease the expression of IL-12Rβ1 [55]. In *in vitro* studies, it has been observed that the cytokine synthesis induced by IL-23 was suppressed when dexamethasone was added to medium [55]. In our study, we found that TA did not statistically significantly affect IL-23 levels. This is compatible with that fact of the TA acts decreasing the expression of IL-12Rβ1 but not inhibiting the IL-23 synthesis. Reduction of receptor expression with TA has been provided the blockade of the inflammatory effects of IL-23, however, this has not affected the IL-23 levels.

Despite it was provided significant clinical improvement after etanercept, CsA and TA treatments in EAU, drugs failed to provide a reduction in IL-23 level. In conclusion, we consider that IL-23 does not affect only Th17 proliferation and it may affect other pathways in the inflammatory cascade in uveitis.

As a result, etanercept, CsA and TA failed to suppress vitreal IL-23 in EAU model. Further studies are needed to understand the exact effects of etanercept in the suppression of the inflammation.

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