The Effects of Intraocular Injection of Interleukin-13 on Endotoxin-Induced Uveitis in Rats

Claire Lemaitre,1,2 Brigitte Tbillaye-Goldenberg,1 Marie-Christine Naud,1 and Yvonne de Kozak1

PURPOSE. Interleukin (IL)-13 is a strong immunomodulatory cytokine that inhibits macrophages from secreting proinflammatory mediators. This study was conducted to investigate the effect of intraocular injection of IL-13 on the development of endotoxin-induced uveitis (EU) in the Lewis rat.

METHODS. One injection into the anterior chamber of recombinant human IL-13 (6 ng in 10 μl saline) was performed either simultaneously with a single injection of lipopolysaccharide (LPS) from Salmonella typhimurium into the footpad or 6 hours before the IL-13 injection. EU was evaluated by slit lamp examination at 6, 16, and 24 hours after LPS injection. Counts of inflammatory cells were performed on cryostat sections after specific immunostaining. Anterior chamber paracentesis was performed, and kinetic analysis of the IL-13 injected in the anterior chamber was performed by ELISA. Cytokine and chemokine expression in iridociliary body and the retina was evaluated by reverse transcription-polymerase chain reaction.

RESULTS. A significant inhibition of ocular inflammation was observed in IL-13-treated rats at 16 and 24 hours after LPS injection. Unilateral injection of IL-13 inhibited EU only in the injected eye. High levels of IL-13 were detected in the aqueous humor at 2 hours after local IL-13 injection to remain high up to 18 hours. In contrast, IL-13 was not detected in the corresponding sera. Quantitative analysis of inflammatory cells in ocular tissues showed a significant decrease in OX-42+ cells (microglia, activated macrophages, dendritic cells, and polymorphonuclear leukocytes) and ED1+ cells (monocytes-macrophages and dendritic cells) in treated rats. A decreased expression of TNF-α, IL-1β, IL-6, monocyte chemoattractant protein (MCP)-1, and macrophage inflammatory protein (MIP)-2 mRNAs was observed in the iris-ciliary body and the retina from IL-13-treated rats, whereas IFN-γ was upregulated in the iris-ciliary body.

CONCLUSIONS. Injection of IL-13 into the anterior chamber may inhibit the ocular inflammation induced by LPS injection by reducing intraocular cytokine and chemokine mRNA expression in ocular tissues. (Invest Ophtalmol Vis Sci. 2001;42:2022–2030)

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2022

Materials and Methods

Animals

Inbred male adult 8-week-old Lewis rats (Jean-Pierre Ravaut, Institut National de la Recherche Agronomique, Nouzilly, France) were used. Animals were maintained in a 12-hour light-12-hour dark cycle. Food and water were supplied ad libitum. Animals were cared for in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Indeed, the design of our experiments consisting

of bilateral injection of the immunoregulatory cytokine IL-13 did not affect vision of the rats and did not induce any discomfort. Our treatment using IL-13 injection into the anterior chamber inhibited the inflammation induced by the footpad injection of LPS.

**Induction of EIU**

Rats were injected into one footpad with 350 μg/kg of LPS from *Salmonella typhimurium* (Sigma Chemical Co., St Louis, MO) in 0.1 ml of sterile pyrogen-free saline. This dose of LPS takes into account the weight of the animals and corresponds approximately to the dose of 100 to 200 μg of LPS currently used to induce EIU in rats.

**Intraocular Injection of Saline or IL-13 into the Anterior Chamber**

Anterior chamber paracentesis, or injection into the anterior chamber, can cause inflammation and damage to the ocular structures. To assure the harmlessness of the intraocular injection, we first tested the effect of the injection of sterile pyrogen-free saline into the anterior chamber. Rats were anesthetized with intraperitoneal injection of pentobarbital (40 mg/kg; Nembutal; Abbott, Saint-Remy sur Avre, France), the pupils of the right eye were dilated with an instillation of 1 drop 5% tropicamide (Ciba Vision, (40 mg/kg; Nembutal; Abbot, Saint-Remy sur Avre, France), the pupils of the injection of sterile pyrogen-free saline into the anterior chamber. To examine the harmlessness of the intraocular injection, we first tested the effect of injection of sterile pyrogen-free saline into the anterior chamber.

**Protocols of Injection of IL-13 into the Anterior Chamber**

<table>
<thead>
<tr>
<th>Protocols</th>
<th>Injection in the Footpad</th>
<th>Injection into the Anterior Chamber</th>
<th>Time from LPS Injection</th>
<th>Aqueous Humor Puncture*</th>
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</thead>
<tbody>
<tr>
<td>1a</td>
<td>Saline +</td>
<td>OD/IL-13 + OS/OS</td>
<td>−6 Hours Simultaneous</td>
<td>24</td>
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<tr>
<td>1b</td>
<td>+</td>
<td>OD/OS</td>
<td>+</td>
<td>24</td>
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<td>2a</td>
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<td>3a</td>
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<td>6, 16, 24</td>
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<tr>
<td>3b</td>
<td>+</td>
<td>OD/OS</td>
<td>6, 16, 24</td>
<td>4, 4, 5</td>
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* Aqueous humor was obtained at different time intervals from LPS injection in the footpad.

TABLE 1. Protocols of Injection of IL-13 into the Anterior Chamber

**Inhibition of EIU by Intraocular IL-13**

The intensity of clinical ocular inflammation was scored on a scale of 0 to 5. Animals were examined at the slit lamp by a masked investigator and the degree of inflammation was scored at 6, 16, or 24 hours after LPS injection, as previously described.32

**Histopathology**

At the time of death, eyes were collected, fixed in Bouin solution for 24 hours, and embedded in paraffin. Sections were made at different levels through the pupillary–optic nerve plane and stained with hematoxylin-eosin for histologic examination.

**Immunohistochemistry: Inflammatory Cell Counting**

Encuclated eyes were collected, fixed in 2% paraformaldehyde and stored at −20°C. The eyes were embedded in optimal cutting-temperature (OCT) compound (Tissue-Tek; Miles Inc., Elkhart, IN) and 10-μm frozen anteroposterior sections were prepared at the optic nerve level on gelatin-coated slides for immunohistochemical analysis.35

Sections were incubated with the following primary antibodies: mouse monoclonal antibody ED1 (Serotec, Oxford, UK; recognizing a cytoplasmic antigen in rat monocytes, macrophages, and dendritic cells) and mouse monoclonal antibody OX42 (Serotec; a marker of rat C3Bi receptor; β-chain CD11a, a protein present on macrophage subset microglia, dendritic cells, and polymorphonuclear leukocytes). Biotinylated sheep anti-mouse immunoglobulin G and fluorescein-conjugated streptavidin (Amersham, Little Chalfont, UK) were then applied. Controls involved the omission or replacement of the primary antibody with rabbit preimmune serum at the same dilution. Sections were viewed under the appropriate excitation filters of a photomicroscope (Optiphot-2; Nikon, Tokyo, Japan). To quantify EIU, all immunopositive cells were counted on the whole ocular section, and the cell number was expressed as the mean ± SEM of total cell number per animal.35

**RNA Isolation and RT-PCR**

Total RNA from the retina and the iridociliary body was isolated from freshly enucleated eyes 24 hours after LPS injection by the acid guani-
Kinetics of IL-13 in the Aqueous Humor and Serum

A study of the kinetics of the injected IL-13 was achieved by titration of the rhIL-13 in aqueous humor and serum at 2, 6, and 18 hours after injection of rhIL-13 or saline into the anterior chamber and LPS or saline into the footpad (Table 2). Control rats were either naive rats or rats injected with saline into the anterior chamber before LPS injection or rats that received IL-13 into the anterior chamber without LPS injection. Blood was obtained by cardiac puncture and aqueous humor was collected as previously described. Levels of IL-13 were measured by ELISA kits according to the manufacturer's instructions. In each experiment, the values were related to a standard preparation of IL-13 diluted from 1000 pg/ml to 15.6 pg/ml. Data are presented as mean ± SEM. * Number of aqueous humor samples; each sample was obtained from the aqueous humor of four pooled eyes.

<table>
<thead>
<tr>
<th>Injection into the Anterior Chamber</th>
<th>Injection into the Footpad</th>
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<td>IL-13</td>
<td>Saline</td>
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<tr>
<td></td>
<td>2 h</td>
</tr>
<tr>
<td>+</td>
<td>3495 ± 69</td>
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<td>n = 5*</td>
<td>n = 2</td>
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Levels of IL-13 were measured by ELISA kits according to the manufacturer's instructions. In each experiment, the values were related to a standard preparation of IL-13 diluted from 1000 pg/ml to 15.6 pg/ml. Data are presented as mean ± SEM. * Number of aqueous humor samples; each sample was obtained from the aqueous humor of four pooled eyes.

Protein Determination in Aqueous Humor

At the time of death (2, 6, and 18 hours after injection of IL-13 or saline into the anterior chamber), aqueous humor was collected from each eye of each animal and pooled. Protein concentration was determined in 1 μl of each aqueous humor sample by using Bradford assay with γ-globulin as a standard (Bio-Rad, les Ulis, France).

Statistical Analysis

Data are presented as mean ± SEM. Statistical analysis was performed using the nonparametric Mann-Whitney test (clinical and histologic score of EIU) and the Student’s t test for ELISA values. P < 0.05 was considered significant.

Results

Effect of IL-13 when Injected into the Anterior Chamber

Protocols refer to those shown in Table 1. To determine whether IL-13 induces any inflammation when injected into the eye, IL-13 was administered into the right eye and saline into the left eye, simultaneously with saline injected into the footpad (protocol 1a) or 6 hours before (protocol 1b). No clinical difference between the eyes could be detected at clinical and histologic examination performed 24 hours after saline footpad injection (not shown). This indicates that IL-13 injection does not provoke inflammatory cell infiltration and allows its use to be considered in local immunotherapy.

Effect of Unilateral Anterior Chamber Injection of IL-13 Performed Simultaneously with LPS Injection into the Foot or 6 Hours before

When IL-13 was injected into the right eye 6 hours before LPS injection (protocol 2b), a trend to a decrease of the clinical disease was observed 24 hours after LPS injection compared with control left eye injected with saline (not shown). Simultaneous injection of IL-13 into the right anterior chamber and LPS into the footpad (protocol 2a) caused a significant decrease in clinical EIU in the IL-13–injected eye compared with the left eye injected with saline (Fig. 1). This suggests that the benefit of IL-13 is related to a local inhibitory effect, rather than to a systemic activity.

Effect of IL-13 Treatment in Both Eyes on Clinical EIU and Inflammatory Cell Infiltration

In the subsequent experiments (protocols 3a and 3b), both eyes of rats were injected with IL-13 and the results compared with those in control animals with saline injected in both eyes. To evaluate the kinetics of action of IL-13, rats were killed 6, 16, and 24 hours after simultaneous injection of IL-13 or saline into the eyes and LPS into the footpad. At clinical examination 6 hours after LPS injection, before the onset of clinical uveitis in control eyes, no significant difference was observed between the two groups (data not shown, n = 8). Sixteen hours after LPS induction of uveitis, significantly decreased ocular inflammation was detected in the IL-13–treated rats compared with the saline control groups (P = 0.01). Indeed, 6 (35%) of 18 treated rats showed low-grade clinical EIU, with a score of 1 or less, whereas a high level of inflammation was observed in control animals with saline injected into the anterior chamber (16 [89%] of 18 rats with EIU scored as 1 or more). In all control animals (n = 5...
injected in the footpad with LPS alone, EIU scored at 1 or more developed (Fig. 2A). Twenty-four hours after induction of uveitis, the inhibitory effect of IL-13 injection on the disease was confirmed, because the inflammation was significantly lower in the treated group ($P < 0.0016$) than in the control group. A clinical score of 1 or less was observed in 11 (58%) of 19 treated rats, whereas 17 (85%) of 20 control animals had EIU scored at 1 or more (Fig. 2B).

The clinical inhibitory effect of IL-13 treatment was confirmed by counting the inflammatory cells present in ocular tissues of saline- or IL-13–injected rats. Six hours after LPS injection, very few inflammatory cells were present in the eyes of both control and treated rats with no significant difference between the two groups (data not shown). In the groups of rats killed 16 hours after LPS injection, a low number of OX42$^+$ and ED1$^+$ cells was found in IL-13–treated eyes compared with control animals injected with saline, but the difference was not significant at that time, with the exception of OX42 in the posterior chamber ($P = 0.02$; not shown). At the peak of the inflammatory reaction, 24 hours after LPS injection, counting of immunostained cells on cryostat sections showed a heavy infiltration of OX42$^+$ cells and a less significant number of ED1$^+$ cells in the different ocular tissues of control rats. Compared with control animals, the OX42$^+$ and ED1$^+$ infiltration was significantly decreased in the IL-13–treated group in anterior and posterior segments of the eye (Figs. 3A, 3B, Fig. 4).

**Kinetics of IL-13 in Aqueous Humor**

The injection of IL-13 into the anterior chamber allowed the detection of high amounts of IL-13 in the aqueous humor (2018–4173 pg/ml) sampled at 2, 6, or 18 hours after simultaneous injection of LPS or saline into the footpad (Table 2). It was interesting to note that IL-13 was not detected in the serum of corresponding rats. This suggests that IL-13 injected into the aqueous humor has not reached the general circulation during this period. It must be stated that the values of IL-13 were obtained from pooled aqueous humor of four eyes and may not represent the IL-13 profile of individual rats.

**Cytokine Profile Analysis by RT-PCR**

The effect of local injection of IL-13 on the expression of different cytokines implicated in ocular inflammation was investigated by semiquantitative RT-PCR, 24 hours after LPS injection, in three groups of rats: five rats with LPS injected in the footpad and two groups of five rats with LPS injected into the footpad simultaneously with an injection of saline or IL-13 into the anterior chamber (Fig. 5). mRNA expression was determined in the iris-ciliary body and in the retina. Results of two rats in each group are shown in this study and are representative of the results found in each group of rats. Injection of LPS into the rat footpad induced the expression of proinflamma-

**A 16 h after LPS injection**

**B 24 h after LPS injection**

**FIGURE 2.** Effect of intraocular injection of IL-13 in both eyes on clinical EIU evaluated 16 (A) and 24 (B) hours after LPS injection. IL-13 significantly decreased the clinical intensity of LPS-induced ocular inflammation. Data are mean ± SEM. Control saline-injected rats, $n = 5$; IL-13–treated rats, $n = 5$. 

**FIGURE 1.** Unilateral injection of IL-13 into the anterior chamber performed simultaneously with LPS injection into the footpad suppressed clinical EIU in the IL-13–injected eye compared with the left eye injected with saline. Data are mean ± SEM; $n = 4$ rats in each group.
IL-13 injection. MIP-2, of which equal low amounts were found after saline or cytokine mRNAs was also inhibited in the retina, except for aqueous humor. It is notable that the expression of these detected in the iris-ciliary body of rats injected with IL-13 in the expression being increased only in the retina. This indicates that the needle trauma was sufficient to induce an inflammatory reaction, and consequently the effect of IL-13 injection on EIU was compared with the effect of saline injection. Reduced expression of TNF-α, IL-1β, IL-6, MCP-1, and MIP-2 mRNA was detected in the iris-ciliary body of rats injected with IL-13 in the aqueous humor. The expression of these cytokine mRNAs was also inhibited in the retina, except for MIP-2, of which equal low amounts were found after saline or IL-13 injection. Because IFN-γ has been shown to be expressed in iris-ciliary body during EIU, we looked also for the effect of IL-13 on the expression of this cytokine’s mRNA in ocular tissues. A surprising finding was that although IL-13 treatment increased the expression of IFN-γ mRNA in the iris-ciliary body, no IFN-γ was detected in the retina.

**DISCUSSION**

EIU is an acute inflammatory response localized to the eye with general clinical manifestations observed depending on species and probably on the implicated mediators. In humans, LPS is responsible for septic shock. In animals, general clinical manifestations are observed depending on species and probably on the implicated mediators. Pulmonary, cardiovascular, renal, digestive, and ocular manifestations can occur, with hyperthermy and general discomfort. In the eye, mRNAs of proinflammatory cytokines, chemokines, and mediators such as NO, prostaglandins, leukotrienes, and activated coagulation cascade have been shown to play a critical role in the induction and perpetuation of ocular inflammation. The clinical onset occurs when organs are overwhelmed by inflammation and fail to fulfill their normal function.

Because systemic administration of IL-13 inhibits ocular inflammation in EIU, our purpose in this work was to evaluate the efficiency of local injection of IL-13. We demonstrated that local administration of IL-13 did not provoke an ocular inflammation. On the contrary, the anterior chamber injection of IL-13 performed concomitantly with the injection of LPS in rats caused a significant clinical inhibition observed 16 and 24 hours after LPS injection, with the times corresponding to the peak of the disease. These results were confirmed by cellular counts that showed that inflammatory cell infiltration (ED1+ and OX42+ cells) was inhibited 16 to 24 hours after injection of LPS, indicating that local administration inhibited EIU as efficiently as systemic injection. However, no effect of local IL-13 could be detected on the protein exudation in the aqueous humor (data not shown), which is consistent with the results observed after systemic IL-13 injection.

To explain the inhibitory effect of IL-13, we first determined the amount of IL-13 present in the eye after IL-13 injection into the anterior chamber and the kinetics of its elimination. The injection of IL-13 into the anterior chamber allowed high amounts of IL-13 to be present from 2 hours up to 18 hours after LPS injection into the footpad. This suggests that IL-13 evacuation from the anterior chamber through the trabecular meshwork was not accelerated by the early opening of the ocular blood barriers and by the incoming aqueous flow secreted by the inflammatory ciliary body. Unilateral injection of IL-13 decreased the inflammation only in the injected eye, and IL-13 was not detected in the serum of corresponding rats. These observations suggest that the effect of our treatment originates from the local presence of IL-13 in the eye and is not dependent on the systemic passage of IL-13.

What is the mechanism for local IL-13 efficacy in our experiments? Compared with systemic administration of IL-13 (three injections necessary for efficacy), our results show that one local administration caused an immediately very high IL-13 concentration in aqueous humor that remained high for at least 18 hours. IL-13 could decrease by its effect on CD14, the first increase of cytokines and chemokines that precedes the clinical manifestations. IL-13’s effect on inflammatory mediators could also involve an effect on transcriptional factors. Many cytokines are under the transcriptional control of nuclear factor (NF)-κB, and IL-13 has been shown to suppress NF-κB translocation through augmenting the presence of IkBα.

In the present study, compared with saline-injected rats, the injection of IL-13 into the anterior chamber simultaneously with injection of LPS into the footpad decreased the expression of TNF-α, IL-1β, and IL-6 mRNAs in the iris-ciliary body. In contrast, in our previous report, the first subcutaneous injec-

**FIGURE 3.** Effect of intraocular injection of IL-13 on ocular inflammatory cell infiltration, 24 hours after LPS injection. Cells were counted on cryostat sections at the optic nerve level after specific immunostaining. Treatment with IL-13 inhibited OX42+ (A) and ED1+ (B) cell infiltration in all segments of the eye: cornea-anterior chamber (cornea/ac) iris-ciliary body (iris/cb) and vitreous-retina (v/retina). Data are mean ± SEM. Control rats, n = 5; IL-13-treated rats, n = 5.
tion of IL-13 was performed before LPS injection and resulted in enhanced expression of TNF-α and IL-6 mRNA in ocular tissues. This is consistent with in vitro results reported by Minty et al., who showed that when IL-13 is administered before the LPS stimulation of monocytes, TNF-α and IL-6 are primed, whereas simultaneous administration with LPS inhibits IL-1, IL-6, and TNF-α. It is important to note that in the present study, MCP-1 and MIP-2 mRNAs, chemokines regulating the traffic of leukocytes from the blood to the tissues, were downregulated. The decreased expression of TNF-α and IL-1β by IL-13 could have inhibited the expression of MCP-1 and MIP-2 mRNAs, providing decreased infiltration of the iris-ciliary body by macrophages and neutrophils during EIU.

The expression of IFN-γ mRNA in ocular tissues during EIU suggests that T cells may play a role in the pathogenesis of LPS-induced uveitis. In this context, we measured the effect of IL-13 injection on the expression of IFN-γ mRNA in the iris-ciliary body and the retina. The IL-13 injection increased the IFN-γ mRNA level in the iris-ciliary body compared with that in saline-injected control animals. A similar situation was observed after intraocular injection of IL-12, which inhibited EIU and increased the levels of IFN-γ in aqueous humor, and after systemic injection of IFN-γ in experimental autoimmune uveoretinitis, which conferred resistance to EAU. Contradictory effects of IFN-γ have been reported. T-cell depletion has been shown to induce an amelioration of EIU in mice and high levels of IFN-inducible protein (IP)-10 have been detected in the aqueous humor of patients with anterior uveitis. In contrast, the inhibitory effect of IFN-γ was attributed in part to a diminished migration of macrophage-monocytes by downregulation of C5a receptors, as shown in streptococcal wall-induced arthritis in rats.

In an interesting observation, the injection of IL-13 into the anterior chamber promoted inhibition of the expression of cytokine and chemokine mRNAs in the retina as well, except for MIP-2. Indeed, MIP-2 mRNA expression in the retina from IL-13-injected rats was equivalent to that observed in saline-injected rats, suggesting that this chemokine could be less involved in the recruitment of inflammatory cells in the posterior segment. The effect of anterior chamber injection of IL-13 on proinflammatory cytokine and chemokine mRNAs expressed in the retina suggests that IL-13 was able to diffuse

**Figure 4.** Histolopathologic features of inflammatory cell infiltration in ocular tissues of a rat with IL-13 injected into the right eye and saline into the left eye 24 hours after LPS injection (protocol 2a). (A–D) Saline-injected eye showed a heavy infiltration by inflammatory cells in the ciliary body (A), the internal layers of the retina (B), the vitreous body (C), and the optic nerve (D). (E–H) In the IL-13-treated eye, there was considerable reduction of cellular infiltration of the ciliary body (E) and complete inhibition of inflammation in the retina (F), the vitreal body (G), and the optic nerve (H). Magnification, ×660.
FIGURE 5. Semiquantitative expression of TNF-α, IL-1β, IL-6, IFN-γ, MCP-1, and MIP-2 mRNA in iris-ciliary body (iris/cb) and retina of saline- and IL-13–treated rats. Experiments were performed 24 hours after LPS injection into the footpad in three groups of rats; five rats were injected in the footpad with LPS alone and two groups of five rats received a footpad injection of LPS and simultaneous injection of saline or IL-13 into the anterior chamber. Results in two rats in each group are shown and are representative of results found in all rats. Data represent the ratio of cytokine mRNA expression to β-actin in each reverse-transcribed sample. Lane 1: rats injected in the footpad with LPS alone; lane 2: rats with a footpad injection of LPS and simultaneous saline injection into the anterior chamber; lane 3: rats with a footpad injection of LPS and simultaneous IL-13 injection into the anterior chamber.
from the anterior segment to the posterior segment of the eye through the zonular fibers, which do not constitute a tight barrier, providing significant inhibition of the inflammatory cell infiltration in the retina and in the vitreous, as shown in this study.

Thus, the anti-inflammatory effect of IL-13 in this model could be related to its potent effect of downregulation of the synthesis of proinflammatory cytokines by cells of the monocyte-macrophage lineage and polymorphonuclear cells that play a key role in ocular inflammation. Indeed, EIU inhibition has been obtained by preventing macrophage and polymorphonuclear cell infiltration by the use of monoclonal anti-CD11-CD18 antibodies that prevent extravasation and homing of polymorphonuclear cells or by using injections of CL2MDP-embedded liposomes, which are highly toxic for macrophages. By its early presence in the eye, IL-13 could also have impeded leukocyte rolling on the endothelia of the iris and retinal venules, and, at later stages of EIU, IL-13 could have inhibited the secretion of proinflammatory cytokines and chemokines by a local action directly on the inflammatory cells and/or on ocular resident cells. Different cytokines and chemokines, such as IL-8, MIP-1α and -1β, MCP-1, IP-10, and RANTES, are increased in the aqueous humor of patients with uveitis. In human disease, systemic therapies (steroids and immunosuppressors) are very commonly used in the treatment of recurrent and/or severe uveitis that threatens vision. However, such treatments induce iatrogenic morbidity with endocri

References


Inhibition of EIU by Intracocular IL-13 2029


