ELSEVIER

Suppression of Experimental Autoimmune Uveoretinitis by Anti-αβ TCR Monoclonal Antibody

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Purpose: To evaluate the effects of anti-αβ T cell receptor monoclonal antibody (R73) on the induction of experimental autoimmune uveoretinitis (EAU) in rats.

Methods: Lewis rats in which EAU was induced were treated with R73. All rats were examined for the clinical course of EAU, pathological findings of the globe, delayed-type hypersensitivity, and the interleukin-2 (IL-2) gene and protein expression in the eye.

Results: The R73 treatment was effective for delaying EAU onset, decreasing the severity of EAU, and suppressing delayed-type hypersensitivity to the antigen. IL-2 gene and protein expression was reduced by R73 treatment in the anterior and posterior segments of the eye.

Conclusion: R73 treatment is effective for suppression of the development of EAU, inhibiting IL-2 expression in the eye. **Jpn J Ophthalmol 2002;46:518–524** © 2002 Japanese Ophthalmological Society

Key Words: R73, Anti-αβ TCR monoclonal antibody, experimental autoimmune uveoretinitis, interleukin-2, delayed-type hypersensitivity.

Introduction

Experimental autoimmune uveoretinitis (EAU), an experimental model of the human ocular inflammatory disease, is an autoimmune disease induced by immunization with retinal autoantigens.[1,2] The exact mechanism of EAU is still controversial. Previous studies revealed, however, that EAU is primarily helper T (Th) cell-mediated,[3–5] and that genetic susceptibility to EAU in Lewis rats is closely related to elevated Th1 responses, while genetic resistance does not correlate to elevated Th2 responses.[6]

Helper/inducer T cells express predominantly CD4 on their surfaces. These surface molecules are localized near the site of T cell receptors that recognize I-A antigen. Helper/inducer T cells recognize antigens that are presented by macrophages or other antigen-presenting cells in the context of major histocompatibility complex class II gene products, known as I-region-associated antigens. Various immunosuppressive therapies that utilize anti-I-A monoclonal antibody (mAb),[7] anti-CD4 mAb,[8] anti-ICAM-1 mAb and anti-LFA-1 mAb[9] have been applied to suppress EAU based on these mechanisms. Anti-αβ TCR mAb (R73) therapy, however, has not been conducted yet on EAU in Lewis rats.

R73 is specific for a framework component of αβ T cell receptor, and has been reported to suppress the development of experimental autoimmune encephalitis[10] and adjuvant arthritis.[11] Moreover, R73 treatment was applied in the field of transplantation and prevented allograft rejection in heart,[12–15] skin,[16] small bowel,[17] kidney,[18] and cornea.[19]

In this study, we determined whether R73 could suppress the development of EAU in Lewis rats. We further investigated local cytokine expressions with or without R73 treatment. Our results showed that R73 treatment was effective for the suppression of EAU in rats.

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Materials and Methods

Inbred strains of female Lewis rats RT1^{le} weighing approximately 250 g (Charles River Japan, Kanagawa) were maintained in our facility and assigned randomly to control or treatment group. All animals were treated in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Induction of EAU

A 20-mer peptide of bovine S-Ag, BSA 35, was a gift from Dr. Gregerson (University of Minnesota, Minneapolis, MN, USA). The peptide was emulsified (1:1) in complete Freund's adjuvant (CFA; Difco, Detroit, MI, USA), containing *Mycobacterium tuberculosis* H37Ra at concentration of 2.0 mg/mL. A total of 0.1 mL per rat, containing 30 μg of S-antigen peptide, was injected into one hind footpad.

Treatment Protocols

The mAb-treated rats received 1 mg/day of R73 intraperitoneally. Initially, the rats that received R73 in a total dose of 4 mg were divided into four groups as follows. Control group received no treatment. Pretreatment group received R73 on days −8, −6, −4, and −2 before S-antigen peptide injection; early-treatment group received R73 on days 0, 2, 4 and 6; late-treatment group received R73 on days 8, 10, 12, and 14 after S-antigen peptide injection. Secondly, the rats that belonged to the intensive-treatment group received 3 mg/day of R73 on days 8, 10, 12, and 14 for a total dose of 12 mg. The mAb was purified from ascites using a protein G column.

Evaluation Protocols

Rats were kept under observation until day 30 after S-antigen peptide injection. The clinical severity of EAU and the onset day were recorded. The eyes were enucleated and processed for histopathological examination on day 30. In the control and intensive-treatment groups, some animals were sacrificed on day 20 for the immunological study. Some eyes were frozen for immunohistochemical examination. Other eyes were applied for the examination of aqueous humor that was used for the quantification of interleukin (IL)-2 by enzyme-linked immunosorbent assay (ELISA). In additions, iris and chorio-retinal tissues were examined for the detection of cytokine expression by mRNA analysis.

Evaluation of EAU Development

Clinical signs of EAU were monitored daily under an operating microscope. The onset of clinical EAU was determined when inflammatory cells or fibrins were detected in the anterior chamber. As for the grading of EAU, clinical scores were graded into four categories. grade 0: no inflammation, grade 1: mild inflammation with small amounts of fibrins, grade 2: moderate inflammation with hypopyon, grade 3: severe inflammation with fibrin and hypopyon and invisible iris pattern.

Eyes enucleated on day 30 were histologically examined. Sections stained with hematoxylin-eosin were examined under a light microscope. Inflammation was graded as follows: grade 0: no inflammatory cell infiltration and no destruction of retina, grade 1: minimal cell infiltration in retina and choroid but no destruction, grade 2: partial and mild destruction of outer retina, grade 3: moderate destruction of outer retina, grade 4: broad and severe destruction of outer retina and partial destruction of inner retina, grade 5: complete destruction of entire retina.

Indirect Immunoperoxidase Technique

The biotin-conjugated mAbs for immunostaining were mouse anti-rat IL-2 mAb (A38.3, 20 μg/mL) (PharMingen, San Diego, CA, USA). The immunoperoxidase technique was performed as follows. Frozen specimens were sectioned at 7 μm by a cryostat, then fixed in 4% paraformaldehyde for 1 hour. The mAbs were applied to tissue sections over night. After three washes in phosphate-buffered saline (PBS), mAb-labeled sections were exposed to horseradish peroxidase-labeled streptavidin for 20 minutes. The sections were incubated for 15 seconds in 3,3-diaminobenzidine, and then counterstained with Mayer's hematoxylin for 5 seconds. Slides were mounted in xylol and coverslipped. The eyes enucleated on day 20 were examined by immunohistochemical study.

Assay for Delayed-type Hypersensitivity

Delayed-type hypersensitivity (DTH) responses to S-antigen peptide were determined by measuring ear swelling as follows. On day 29, 200 μg/20 μL S-antigen peptide was injected into the right pinnae. PBS was injected into the left pinnae. After 24 hours, ear thickness was measured with a low-pressure micrometer (Mitsutoyo, Tokyo). DTH-dependent ear swelling was calculated according to the following formula: specific ear swelling = [(24-hour measurement of right ear − 0-hour measurement of right ear) − (24-hour measurement of left ear − 0-hour measurement of left ear) × 10^{-3} mm.

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ELISA

Aqueous humor samples were titrated for rat IL-2 by ELISA. We used the immunoassay kit, Cytoscreen® (BioSource International, Camarillo, CA, USA) for quantifying rat IL-2 according to the manufacturer's protocol. Briefly, diluted samples were added to polyvinylchloride plates coated with an antibody for rat IL-2. Then, biotinylated anti-rat IL-2 solution was added to each well and the plate was incubated at room temperature for 3 hours. After four washes, Streptavidin-HRP Working Solution was added to each well, and then the plate was incubated at room temperature for 30 minutes, followed by washing. Stabilized chromogen was added to each well, after which the plate was incubated at room temperature for 30 minutes in the dark, and then Stop Solution was added to each well. The photodensity of the reaction product was measured as absorbance at 450 nm.

Semi-quantitative Reverse Transcriptase-Polymerase Chain Reaction

Total RNA was extracted by the acid guanidine method as described previously.[20] The homogenized excised iris and chorio-retina obtained from 6 eyes were processed together as a group. The RNA pellet was resuspended in 50 μL of water. First-strand cDNA was synthesized using Superscript® II RNase H-Reverse Transcriptase (Life Technologies, Rockville, MD, USA). Polymerase chain reactions (PCR) consisted of 1% cDNA, 10 mM Tris-Cl (pH 8.3), 50 mM KCl, 1.5 mM $MgCl_2$, 0.2 mM dNTPs, 20 pmol oliogonucleotides and 2.5 U Ampli *Taq* Gold® (Roche Molecular Systems, Branchburg, NJ, USA) in 50 μL reaction volume. Primer sequences of GAPDH (223 bp) were as described previously.[21] The primer for IL-2 had the following sequences: IL-2 (233 bp), 5′ primer-GCAGGCCACAGAATTGA AAC and 3′ primer-AGATGGCTATCCATCTCCTC. After incubation at 95°C for 10 minutes, for the detection of GAPDH, the amplification was done at 94°C for 30 seconds and 60°C for 30 seconds, and for IL-2, the amplification was done at 94°C for 30 seconds, 51°C for 15 seconds and 72°C for 15 seconds in a Gene Amp PCR System 2400® (Perkin Elmer Cetus, Emeryville, CA, USA). PCR products were separated on 3% agarose gels and visualized on ethidium bromide. As described previously,[19] an optical scanner was used to quantify the density of the gel bands and standardize them with those for GAPDH in PCR products. The linear amplified curve of the PCR product of each sample was examined in three-cycle intervals. The band density of each cytokine was compared to that of the GAPDH PCR product.

Statistical Analysis

The statistical comparisons were carried out using Mann Whitney *U*-test. Analysis of variance and Fisher's PLSD method were used to compare the results of four groups in incidence, onset, severity and the DTH of EAU treated with R73 in a total dose of 4 mg.

Results

Clinical and Pathological Findings on EAU with R73 Treatment

Figure 1 shows the clinical course of EAU in each group that was administered a total dose of 4 mg. Averaged EAU onset days in the control (n = 12), pretreatment (n = 12), early-treatment (n = 10), and late-treatment groups (n = 10) were 13.3 ± 1.4 (mean ± SD), 14.4 ± 1.3, 15.8 ± 1.8, and 18.2 ± 0.6, respectively. The late-treatment group showed significantly delayed EAU onset days as compared with the other three groups ($P < .01$). However, all rats including the late-treatment group rats developed EAU and there was no significant difference in histopathological severity among these groups (data not shown).

Because the late treatment appeared to delay the onset most effectively, we tried to reduce the severity of EAU by increasing the dosage from 1 mg/day

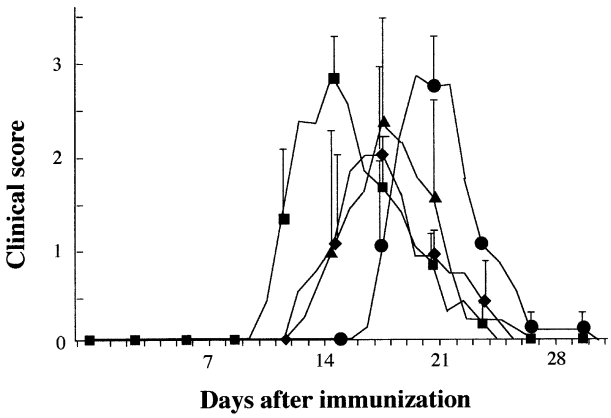

Figure 1. Clinical course of experimental autoimmune uveoretinitis (EAU) in rats that received R73 in a total dose of 4 mg per rat. EAU onset was significantly delayed in the late-treatment group ($P < .01$). Control (■): no treatment, pretreatment (◆): received R73 on days −8, −6, −4, −2 before S-antigen injection, early-treatment (▲): received R73 on days 0, 2, 4, 6 after S-antigen injection, late-treatment (•): received R73 on days 8, 10, 12, 14. Data points represent the mean (± SD) of the averaged score.

to 3 mg/day. There was no obvious adverse side effect noticed in the intensively treated rats. Figure 2 shows the clinical course of EAU in the control and intensive-treatment groups. In the intensive-treatment group, 1/8 eyes did not develop EAU. The average EAU onset days were 13.3 ± 1.4 in the control group (n = 10) and 22.5 ± 3.6 in the intensive-treatment group (n = 8). There was a significant difference between the control and intensive-treatment groups ($P < .01$). As shown in Figure 3, the severity of EAU was also decreased histopathologically as compared with the control group. There was a significant difference in averaged pathological scores between the control and intensive-treatment groups (3.5 ± 0.5 vs. 2.5 ± 0.9, respectively).

DTH Assay

DTH responses to S-antigen peptide were examined in the control and intensive-treatment groups on day 29 after immunization. DTH responses to S antigen peptide were significantly suppressed in the intensive-treatment group as compared with those in the control group (Figure 4).

Immunohistochemical Study

Figure 5 shows the representative photograph of IL-2 expression in the infiltrating cells on day 20 after immunization. In the control group (n = 3), many IL-2-positive infiltrating cells were observed in the chorio-retinal tissue and vitreous (Figure 5A). In contrast, fewer IL-2-positive infiltrating cells were detected in the intensive-treatment group (n = 3) (Figure 5B).

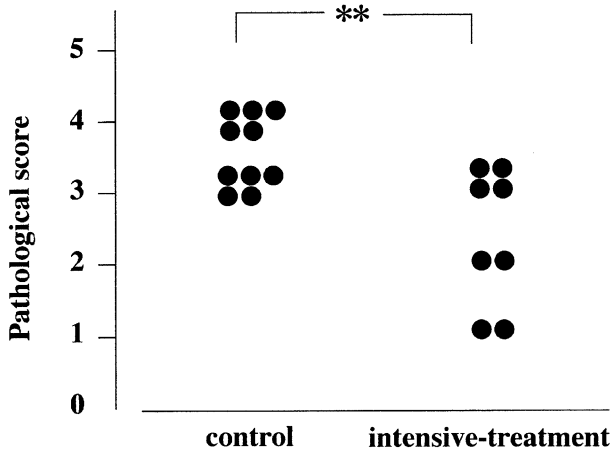

Figure 3. Histopathological score of experimental autoimmune uveoretinitis (EAU). In the intensive-treatment group, the average pathological score was significantly reduced as compared with the control group (**$P < .01$).

IL-2 Concentration in the Aqueous Humor

IL-2 concentration in the aqueous humor was evaluated by ELISA. Approximately 20 μL of aqueous humor was obtained from 1 eye. The averaged IL-2 concentrations obtained from the control (n = 4) and intensive-treatment groups (n = 4) were 431.5 ± 106.5 pg/mL and 145.1 ± 39.1 pg/mL (mean ± SD),

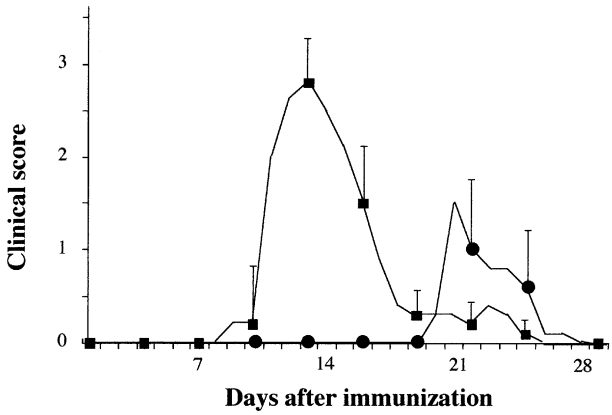

Figure 2. Clinical courses of experimental autoimmune uveoretinitis (EAU) in rats that received R73 in a total dose of 12 mg per rat. The onset of the intensive-treatment group was significantly delayed as compared with that of the control group. Control (■): no treatment, intensive-treatment (•): received R73 on days 8, 10, 12, 14. Data points represent the mean (± SD) of the averaged score.

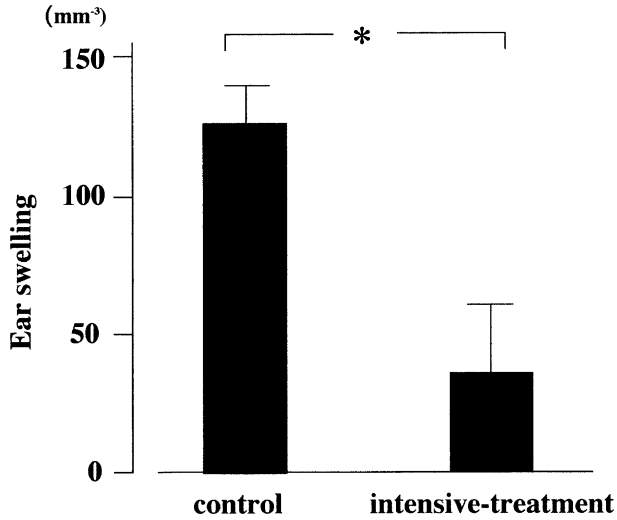

Figure 4. Delayed-type hypersensitivity (DTH) responses to S-antigen peptide. In the intensive-treatment group, DTH responses were significantly suppressed as compared with those in the control group (*$P < .05$).

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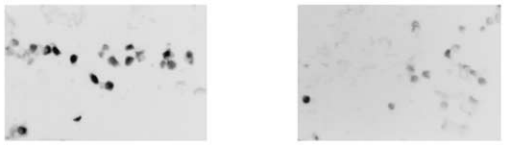

A : control B : intensive-treatment

Immunohistochemical staining in the chorioretinal tissue

Figure 5. Immunohistochemical staining of the infiltrating cells in the chorio-retinal tissue and vitreous. (**A**) In the control group, many interleukin (IL)-2-positive cells infiltrated into the chorio-retinal tissue and vitreous. (**B**) IL-2-positive infiltrating cells were few in the intensive-treatment group. Original magnification ×400.

respectively. IL-2 concentration in the intensive-treatment group was significantly lower than that of the control group ($P < .05$).

IL-2 Gene Transcription Level in the Iris and Chorio-retina

IL-2 gene transcription levels were analyzed in the iris and chorio-retinal tissues, separately. GAPDH was detected in all samples (30 cycles in the iris; 33 cycles in the chorio-retina). In the iris, the IL-2 gene transcription level in the intensive-treatment group was 5-fold lower than that in the control group (37 cycles). In the chorio-retina, IL-2 gene was detected in the control group, but not in the intensive-treatment group (41 cycles) (Figure 6).

Discussion

In this study, we evaluated the immunosuppressive effects of αβ T cell receptor-targeted therapy in a rat EAU model. In the aggregate, we showed that R73 treatment decreases the pathological inflammatory processes of EAU in rats. Its immunosuppressive effects were evidenced by decreased DTH responses in the treated rats. IL-2 gene and protein levels in treated eyes were also suppressed by R73.

R73 treatment efficacy has been already reported in some experimental models. In a rat experimental autoimmune encephalitis model, R73 treatment before immunization, prevented the development of inflammation.[10] Moreover, pretreatment with R73, suppressed cardiac allograft rejection and induced immunological tolerance.[13] According to these previous findings, we expected that R73 treatment before immunization would have a potent immunosuppressive effect on EAU. Unexpectedly, pretreatment with R73 did not express obvious suppressive effects on EAU. It could be due to a simple reflection of the fact that the dosages of mAb in this study were not enough to prevent EAU.

Helper T lymphocytes are divided into two groups, the Th1 and Th2 subsets, based on the cytokine profiles they produce. In the other studies of EAU of Lewis rats, interferon-gamma, IL-2, and IL-4 mRNA expressions peaked during the active phase and declined in parallel with lymphocyte number as the inflammation resolved. IL-10 mRNA levels increased rather slowly, reaching the maximum at later stages of EAU.[22] Our findings demonstrate that R73 treatment inhibits IL-2 gene and protein expressions of both anterior and posterior segments of the eye. This low level of Th1 cytokine coincides well with the downregulation of DTH responses in the intensive-treated rats in our study. To our knowledge, Th1/Th2 balance under R73 therapy has not been investigated yet in autoimmune disease. In organ transplantation, the switch from Th1 to Th2 induced by the R73 treatment has been reported to be the key factor to explain the graft acceptance.[15,18] In another report, Th1/Th2 balance was found not to be associated with the fate of the transplanted organ.[14] Our results in this study support the contention that R73 targeted therapy suppresses Th1 cytokines preferentially. A greater number of IL-10-positive cells were detected in the intensive-treatment group, rather than in the control group (unpublished observation). It remains unknown, however, how Th2 cytokines play a role in this R73 therapy.

R73 treatment was reported to reduce the severity of adjuvant arthritis[11,23] and collagen-induced arthritis,[24] but not Yersinia-induced arthritis.[25] We used an adjuvant in the immunization of EAU, and the severity of adjuvant arthritis was reduced in the intensive R73 treatment group (unpublished observation). This result is consistent with the previous findings.[11]

It is important to address the question of why this target therapy did not suppress EAU completely. It could merely be due to the fact that more intensive therapy was required to completely suppress EAU. For example, Uchio et al reported that the development of EAU could be completely prevented by the administration of anti-ICAM-1 antibody twice a week from day 0 to day 14 rather than semi-weekly administration of the antibody from day 0 to day 7, or from day 10 to day 17.[9] Yet there is the possibility that another T cell subset population is involved. Although the major TCR monoclonal antibody subsets in EAU were αβ T cells, in other autoimmune models, which include autoimmune orchitis and experimental

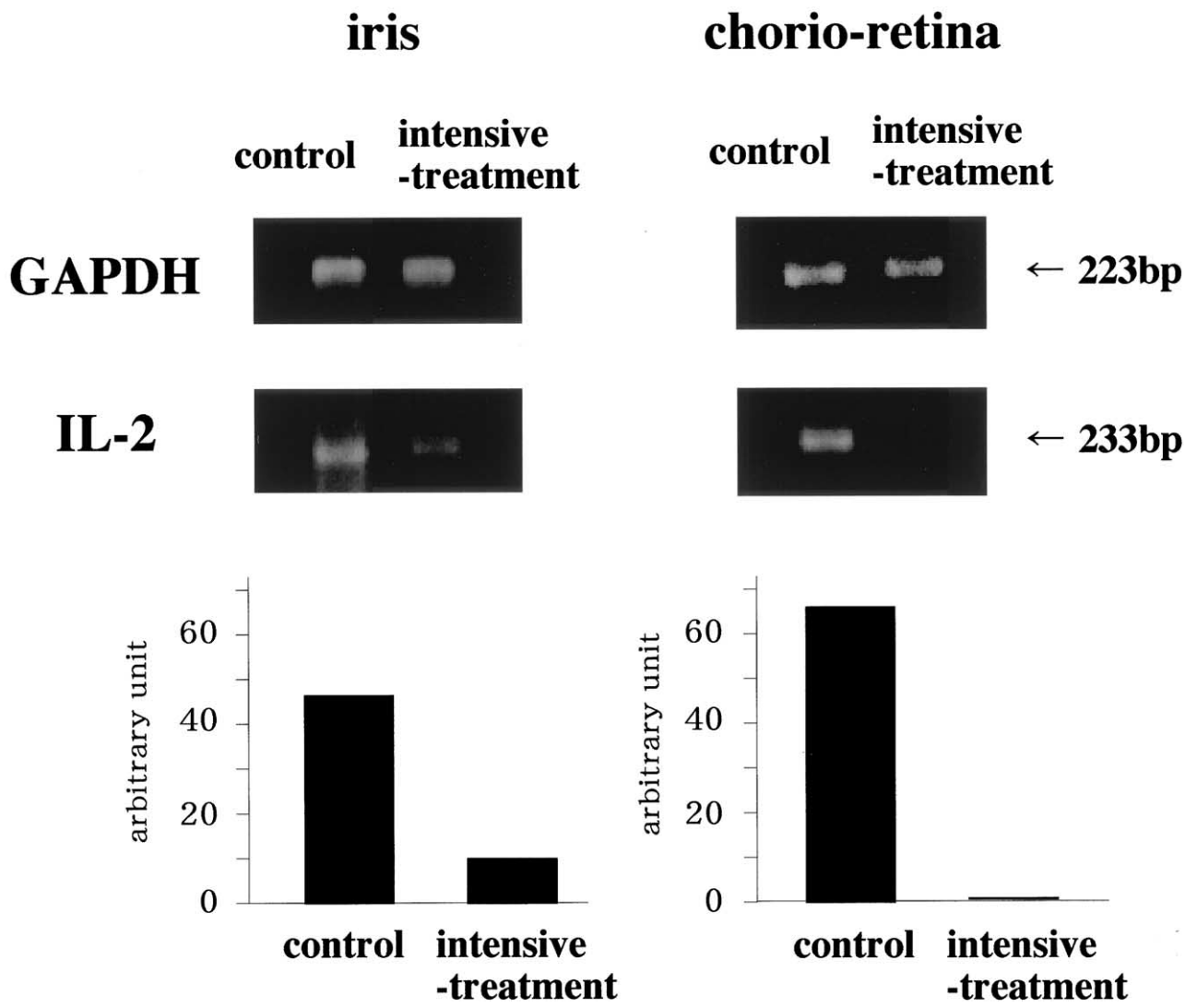

Figure 6. Interleukin (IL)-2 gene transcription level with semi-quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) in the iris and chorio-retinal tissues. The linear amplified curve of the PCR product of each sample was examined in three-cycle intervals. The band density of IL-2 was compared to that of the GAPDH RT-PCR product. Ethidium bromide-stained gel showing RT-PCR products and densitometric analyses normalized to GAPDH are shown. In the both iris and chorio-retinal tissues, the IL-2 gene transcription level was suppressed in the intensive-treatment group as compared with that in the control group. Data are representative of two experiments. Vertical axis indicates arbitrary unit.

allergic encephalomyelitis, γδ T cell responses were also noted in the process of inflammation.[26,27] Our results suggest that, even though predominant T cell subsets are composed of αβ T cells, suppression of this T cell subset population alone is not sufficient to terminate ocular inflammatory processes like EAU. γδ T cell subset may also be associated with the outcome of inflammatory processes in this model indirectly.

In summary, our findings showed that R73 treatment was effective for the partial prevention of EAU as evidenced by suppressed clinical and pathological findings, and the reduced DTH responses. IL-2 gene and protein expression levels were reduced in both the anterior and posterior segments of the eye by R73 treatment.

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