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Intraocular Levels of Interleukin 17A (IL-17A) and IL-10 as Respective Determinant Markers of Toxoplasmosis and Viral Uveitis

Arnaud Sauer,[a,b] Odile Villard,[b] Catherine Creuzot-Garcher,[c] Christophe Chiquet,[d] Jean-Paul Berrod,[e] Claude Speeg-Schatz,[a] Tristan Bourcier,[a] Ermanno Candolfi[b]

Service d'Ophtalmologie, Centre Hospitalier Universitaire de Strasbourg, Strasbourg, France[a]; Institut de Parasitologie et de Pathologie Tropicale, EA 7292, Fédération de Médecine Translationnelle, Université de Strasbourg, Strasbourg, France[b]; Service d'Ophtalmologie, Centre Hospitalier Universitaire de Dijon, Dijon, France[c]; Service d'Ophtalmologie, Centre Hospitalier Universitaire de Grenoble, Grenoble, France[d]; Service d'Ophtalmologie, Centre Hospitalier Universitaire de Nancy, Nancy, France[e]

Uveitis is a potentially blinding inflammatory disease. Thirty to 50% of uveitis cases are considered idiopathic. The present study sought to determine the intraocular cytokine patterns in the different etiological types of uveitis in order to better understand their immunological regulation and to determine whether the cytokine pattern may be a useful diagnostic tool. From a multicenter institutional prospective study, the clinical and biological data from patients with uveitis of various etiologies, determined after a complete workup, were compared with those from a control group of cataract patients. A multiplex assay was used to assess the profiles of 27 cytokines and chemokines in aqueous humor samples from these patients. In total, 62 patients with infectious or noninfectious uveitis and 88 controls were included. After a complete workup, the cause of uveitis remained unknown in 25 patients (40% idiopathic uveitis). Interleukin 1β (IL-1β) levels were markedly increased in viral uveitis, as were IL-10 levels, whereas IL-17A levels were augmented in toxoplasmic uveitis. Based on the cytokine pattern, the patients were reassigned to specific groups. At the end of the study, the diagnosis of idiopathic uveitis was still valid in only 11 patients (18%). The observation that some markers are specific to certain diseases enables a better understanding of the disease pathogenesis and paves the way for new diagnostic methods aimed to identify inflammatory markers, which may perhaps be targeted by therapy.

Uveitis is a potentially blinding inflammatory disease affecting individuals of all ages. Uveitis accounts for 5 to 20% of legal blindness in both the United States and Europe and perhaps for as much as 25% of blindness in the developing world (1, 2). Infectious uveitis is more common in the developing world, accounting for 30 to 50% of all uveitis cases (3, 4). The most common infectious uveitis etiologies include toxoplasmosis, tuberculosis, onchocerciasis, cysticercosis, leprosy, and leptospirosis (2). In developed countries, infectious uveitis, mainly due to herpesvirus infection and toxoplasmosis, accounts for a much smaller number of cases, with other causes like tuberculosis and syphilis being even less common (1, 5). The most common causes of noninfectious uveitis include Fuchs heterochromic iridocyclitis, HLA-B27-associated uveitis, intermediate uveitis, birdshot chorioretinopathy, sympathetic ophthalmia, sarcoidosis, multifocal choroiditis, Vogt-Koyanagi-Harada (VKH) syndrome, serpiginous choroiditis, and Behçet's disease. There are distinct regional differences in the distribution of noninfectious uveitis: sarcoidosis is more common in the United States, Japan, and the Netherlands, whereas Behçet's disease is a leading cause in Turkey, Greece, China, Japan, Iran, and Saudi Arabia, VKH syndrome in Asian or Eurasian countries, and birdshot chorioretinopathy in Western countries (1–5). Despite huge advances in diagnostic techniques, numerous cases of uveitis are still labeled "idiopathic" (35 to 50%).

Specific $CD4^+$ T helper (Th) cell-mediated immune responses have been increasingly thought to play a central role in uveitis pathogenesis. $CD4^+$ Th cells play a crucial part in regulating immune responses by orchestrating the function of other immune cell types. When activated by pathogens, naive $CD4^+$ T cells differentiate, within a specific cytokine environment, into different subsets with distinct effector functions aimed to activate and mobilize other cell types in order to effectively clear invading pathogens. Based on cytokine profiles, the existence of two distinct effector Th subsets was initially proposed: (i) Th1 cells that produce gamma interferon (IFN-γ) activate macrophages and are responsible for cell-mediated immunity against intracellular pathogens and (ii) Th2 cells that induce strong antibody responses by B cells and eosinophil activation (6, 7). Recently, this paradigm has been updated following the discovery of interleukin 17 (IL-17)-producing Th17 cells and T regulatory cells. Th17 cells represent a subset separate from Th1 and Th2 cells, with distinct effector functions. Numerous studies have confirmed the central role of Th17-type cytokines in autoimmune pathology (8, 9), although these cytokines may prove beneficial in certain infec-

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Address correspondence to Arnaud Sauer, arnaud.sauer@chru-strasbourg.fr.

T.B. and E.C. contributed equally to this article.

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tious diseases (10). A pathogenic role for local IL-17A in ocular toxoplasmosis was demonstrated in a recent study (11).

While the aqueous humor (AqH) cytokine and chemokine concentrations are elevated in both infectious and noninfectious uveitis, a further in-depth analysis may clarify the mechanisms of uveitis-related ocular damages and enable a better understanding of the disease pathogenesis, according to the pathogens or autoantigens involved (6, 12, 13). The understanding of immunopathological events may facilitate the discovery of new and targeted approaches to diagnostic methods and immune therapy (11, 14). In this study, we used a multiplex assay to assess the profiles of 27 cytokines and chemokines in AqH samples from patients with uveitis of various etiologies, in comparison with those of a control group of cataract patients.

TABLE 1 Etiologies in 62 patients with acute uveitis[a]

Cause of uveitis	No. (%) of patients
Toxoplasmosis	12 (19)
Virus	14 (23)
HSV	8 (13)
VZV	5 (8)
CMV	1 (2)
Systemic disease	11 (18)
HLA-B27	6 (10)
Sarcoidosis	2 (3)
Lymphoma	2 (3)
Syphilis	1 (2)
Idiopathy	25 (40)

[a] A positive diagnosis was made after a complete biological and clinical workup excluding cytokine level determination.

MATERIALS AND METHODS

Patients and control subjects. In a prospective multicenter study, 62 patients with active uveitis seen at the university hospitals of Strasbourg, Dijon, Grenoble, and Nancy (France) between June 2008 and September 2011 were included. These patients were part of a prospective multicenter study benefiting from funds made available by Protocole Hospitalier de Recherche Clinique (PHRC 3964). All of the patients underwent a full clinical examination to determine the nature of their disease and associated systemic illnesses. A medical history and review of systems were obtained. A complete biological workup was done to assess the diagnosis of the uveitic disease: *Treponema pallidum* particle agglutination (TPHA) and venereal disease research laboratory (VDRL) tests, a tuberculin purified protein derivative test, and tests for HLA-B27, angiotensin-converting enzyme, rheumatoid factor, antinuclear antibodies, granular-staining cytoplasmic antineutrophil antibodies (c-ANCA), serum antibodies to herpes simplex virus (HSV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and varicella-zoster virus (VZV), Lyme disease, HIV, toxoplasma, and toxocara. Chest radiographs or computed tomography (CT) scans to rule out sarcoidosis and tuberculosis and sacroiliac spine radiographs to demonstrate HLA-B27 disease were performed. For the diagnosis of infectious uveitis, biological proof on ocular samples was required. Patients who underwent cataract extraction with no history of uveitis served as a control group.

An anterior chamber puncture and serum sampling were conducted by means of limbic paracentesis using a 30-gauge needle attached to a tuberculin syringe after the application of the topical local anesthetic oxybuprocaine hydrochloride 0.4% (Benoxinate; Chauvin Pharmaceuticals Ltd., Kingston, United Kingdom). The anterior chamber puncture was carried out before initiation of treatment or at the beginning of the surgical procedure for patients who underwent cataract surgery. Overall, 150- to 350-μl samples of AqH were analyzed for diagnostic purposes. The diagnosis of ocular toxoplasmosis was confirmed using at least one of the following methods: (i) a local specific IgG antibody assay with the Goldmann-Witmer-Desmonts (GWD) coefficient ($C = \geqq 3$), the modified GWD coefficient, or immunoblotting of paired AqH and serum samples; (ii) a local specific IgA assay; or (iii) PCR amplification of *Toxoplasma* DNA in AqH samples (15). Viral uveitis due to herpes simplex virus type 1, cytomegalovirus, or varicella-zoster virus was confirmed by PCRs as previously described (16). The samples used for multiplex analyses were snap-frozen and maintained at −80°C until use.

The protocol followed the tenets of the Declaration of Helsinki and was approved by the local ethics committee. All patients provided written informed consent.

Cytokine assays. The Bio-Plex human 27-Plex (Bio-Rad, Marne-la-Coquette, France) assays were used in order to measure cytokines and chemokines (IL-1β, IL-1Rα, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12[p70], IL-13, IL-15, IL-17, fibroblast growth factor [FGF], eotaxin, granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF], IFN-γ, gamma interferon-induced protein 10 (IP-10), monocyte chemoattractant protein 1[MCP-1], macrophage inflammatory protein 1 alpha [MIP-1α], MIP-1β, platelet-derived growth factor BB (PDGF-BB), RANTES, tumor necrosis factor alpha [TNF-α], and vascular endothelial growth factor [VEGF]) levels in AqH samples. This technology allows for measuring multiple analytes in a single 50-μl sample. The analysis was performed following the manufacturer's instructions, as previously described (11, 17). Data were analyzed using Bio-Plex Manager software v1.1.

Statistical analysis. Values are given as individual cytokine or chemokine levels plus means, medians, and standard deviations (SD). The Mann-Whitney test was used to compare means from two independent groups. The two-way analysis of variance (ANOVA) test was employed to compare mean titers of immune mediators obtained by Bio-Plex analysis in the different patient groups. All statistical analyses were performed and graphs were generated using GraphPad Prism software v5 (GraphPad Software, San Diego, CA). A P value of <0.05 was considered statistically significant.

RESULTS

In total, 62 patients with infectious or noninfectious uveitis and 88 controls were included. Uveitis was related to toxoplasmosis ($n = 12$), viral infection ($n = 14$, including herpes simplex virus, $n = 8$; varicella-zoster virus, $n = 5$; and cytomegalovirus, $n = 1$), systemic inflammatory disease ($n = 11$, including HLA-B27-associated uveitis, $n = 6$; sarcoidosis, $n = 2$; and lymphoma, $n = 2$), or syphilis ($n = 1$). After a complete workup, the cause of uveitis remained unknown for 25 patients (40.3%) (idiopathic uveitis). Causes of uveitis are shown in Table 1.

Cytokine patterns in each uveitis group. For cytokine pattern analysis, patients were divided into five groups: controls (C) ($n = 88$), toxoplasmic uveitis (TU) ($n = 12$, 19%), viral uveitis (including PCR-confirmed HSV-, CMV-, or VZV-associated uveitis) (VU) ($n = 14$, 23%), systemic inflammatory disease-related uveitis (SIDU) (including sarcoidosis, HLA-B27, and lymphoma; $n = 11$, 18%), and idiopathic uveitis (IU) ($n = 25$, 40%). Means and standard deviations of cytokine and chemokine concentrations (pg/ml) in AqH samples for each patient group are shown in Table 2. A column designated Cutoff that contains the average values plus 3 SD obtained in controls is included in Table 2. Cases with

TABLE 2 Cytokine and chemokine concentrations in aqueous humor from controls and patients with toxoplasmic uveitis, viral uveitis, systemic inflammatory disease-related uveitis, and idiopathic uveitis[a]

Cytokine	Result (pg/ml) for cataract controls (n = 88)	Cutoff[b] (mean + 3 SD)	Result (pg/ml) for patients with[c]:			
			TU (n = 12, 19%)	VU (n = 14, 23%)	SIDU (n = 11, 18%)	IU (n = 25, 40%)
IL-1β	8.9 (15.1)	54.2	16.0 (4.2)	61.5 (23.1)	47.8 (5.7)	36.4 (29.2)
IL-1Rα	23.5 (51.7)	178.9	83.2 (43.2)	40.5 (41.4)	32.0 (34.8)	28.4 (34.6)
IL-2	1.7 (5.1)	17.0	12.5 (5.2)	45.6 (18.2)	48.0 (9.3)	34.0 (28.7)
IL-15	12.7 (12.7)	50.8	55.6 (49.2)	94.4 (81.9)	130.8 (47.8)	47.5 (62.2)
IFN-γ	5.9 (6.1)	24.2	213.6 (119.1)	42.2 (19.6)	63.1 (3.7)	121.8 (126.1)
TNF-α	15.0 (15.5)	61.5	21.9 (6.0)	46.8 (14.5)	42.2 (5.4)	41.9 (21.3)
IL-12(p70)	15.9 (20.1)	76.2	21.5 (12.6)	262.4 (150.1)	129.4 (18.6)	45.1 (45.7)
IL-6	37.9 (37.4)	150.1	475.6 (328.8)	8,580 (4,220)	15,517 (1,940)	6,594 (7,099)
IL-7	8.6 (10.4)	39.8	12.8 (6.9)	30.9 (9.5)	33.9 (5.4)	23.5 (15.2)
IL-4	6.0 (5.6)	22.8	18.3 (14.4)	293.4 (165.9)	63.9 (13.7)	69.7 (128.8)
IL-5	0.6 (2.1)	6.9	22.5 (8.9)	61.5 (23.1)	3.4 (1.0)	10.4 (9.4)
IL-13	11.6 (15.8)	59	17.6 (13.3)	262.4 (150.1)	469.5 (262.0)	232.0 (275.8)
IL-17	17.8 (9.7)	46.9	82.6 (18.3)	28.9 (10.2)	36.0 (9.3)	38.5 (28.9)
IL-10	28.0 (27.8)	111.4	56.5 (29.0)	164.9 (34.3)	63.7 (17.6)	86.8 (94.0)
IL-9	13.3 (10.3)	57.2	25.6 (5.9)	31.1 (14.0)	36.6 (7.5)	17.2 (11.3)
IL-8	88.9 (119.1)	446.2	975.3 (773.4)	2,751 (1,835)	404.0 (255.1)	1,387 (2,347)
MIP-1β	4.8 (6.7)	24.9	43.4 (30.3)	61.7 (23.9)	51.6 (6.3)	33.9 (20.9)
MIP-1α	109.9 (122.6)	477.7	725.7 (658.5)	1,317 (2,027)	388.0 (48.7)	511.8 (1,332)
MCP-1	190.3 (69.0)	397.3	1,176 (495.5)	3,943 (4,673)	7,042 (779.8)	3,904 (4,137)
IP-10	27.1 (37.7)	140.2	12,164 (6,424)	13,958 (4,978)	11,044 (1,829)	5,625 (5,527)
G-CSF	8.7 (20.3)	69.6	360.5 (336.6)	3,344 (4,420)	7,101 (810.9)	3,398 (4,126)
GM-CSF	227.5 (283.4)	1,077.7	68.3 (15.0)	128.3 (114.7)	23.7 (11.1)	17.6 (20.6)
RANTES	10.1 (12.4)	47.3	211.4 (168.5)	228.0 (240.3)	91.5 (12.6)	42.9 (38.8)
Eotaxin	1.2 (4.0)	13.2	32.1 (34.8)	57.1 (18.7)	49.9 (10.6)	17.6 (20.6)
FGF	37.7 (41.9)	163.4	57.5 (39.3)	73.9 (43.5)	56.5 (26.4)	49.8 (46.9)
VEGF	463.3 (322.6)	1,431.1	632.8 (392.4)	2,437 (1,462)	1,449 (263.8)	727.8 (531.8)
PDGF-BB	5.6 (7.1)	26.9	35.4 (18.9)	84.5 (65.6)	64.5 (9.2)	30.4 (30.1)

[a] Results are means (SDs) unless otherwise indicated.
[b] The cutoff was established by calculating the average value obtained for each cytokine in cataract controls and adding 3 SD.
[c] TU, toxoplasmic uveitis; VU, viral uveitis (including PCR-confirmed HSV-, CMV-, or VZV-associated uveitis); SIDU, systemic inflammatory disease-related uveitis (including sarcoidosis, HLA-B27, and lymphoma); IU, idiopathic uveitis. Gray shading represents cases with average values higher than the cutoff.

average values higher than the cutoff are indicated. IL-1β levels were markedly increased in viral uveitis, as were IL-10 levels, whereas IL-17A levels were augmented in toxoplasmic uveitis. IL-1β, IL-10, and IL-17A levels in each patient are shown in Fig. 1. Since IL-1β and IL-10 were significantly increased in the viral uveitis group and IL-17A was increased in the toxoplasmic uveitis group, a complete reanalysis of the patients with presumed uveitis was carried out.

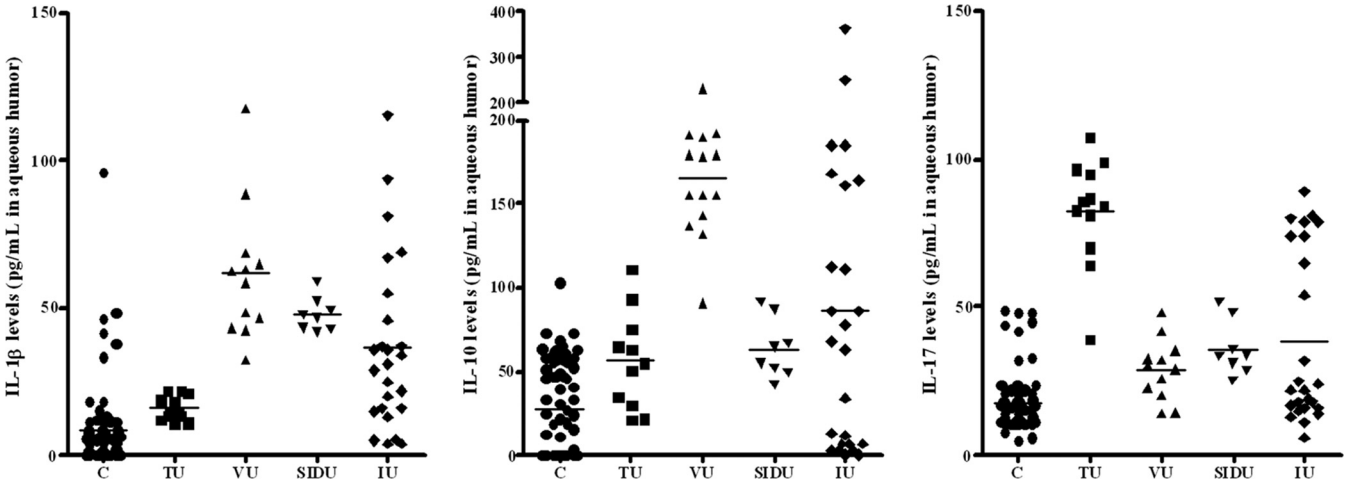

FIG 1 Intraocular concentrations of IL-1β, IL-10, and IL-17A in controls (C) (n = 88) and in patients with toxoplasmic uveitis (TU) (n = 12, 19%), viral uveitis (VU) (including PCR-confirmed HSV-, CMV-, or VZV-associated uveitis; n = 14, 23%), systemic inflammatory disease-related uveitis (SIDU) (including sarcoidosis, HLA-B27, and lymphoma; n = 11, 18%), and idiopathic uveitis (IU) (n = 25, 40%).

TABLE 3 Bioclinical detailed data for patients with initially presumed idiopathic uveitis and secondarily classified in the ocular toxoplasmosis group in consideration of IL-1β, IL-10, and IL-17A levels

Patient no.	Intraocular cytokine level (pg/ml)[a]			Clinical finding		Result for biological workup					
						Serology[b]					
	IL-1β	IL-10	IL-17A	Ocular features	Systemic features	*Toxoplasma*	HSV	EBV	VZV	CMV	Other
1	13	7	79	Retinochoroiditis	None	+	−	+	+	+	None
2	36	34	74	Retinochoroiditis	None	+	+	+	+	+	None
3	69	7	89	Retinochoroiditis	None	+	−	+	+	+	None
4	55	3	81	Panuveitis	None	+	+	+	−	+	None

[a] The mean (SD) intraocular cytokine levels for patients with confirmed OT were 16.0 (4.2) pg/ml for IL-1β, 56.5 (29.2) pg/ml for IL-10, and 82.6 (18.3) pg/ml for IL-17A.
[b] +, presence of IgG; −, absence of IgG.

Analysis of patients with initially presumed uveitis in consideration of IL-1β, IL-10, and IL-17A cytokine levels. Patients who were initially presumed to have idiopathic uveitis ($n = 25$) were reanalyzed in terms of IL-1β, IL-10, and IL-17A levels and clinical data (evolution from 3 months to 2 years). Upon consideration of the clinical and biological data, a final reassignment to one of the different disease groups was possible for 14 of these patients. Four patients were assigned to the toxoplasmic uveitis group, 5 to the viral uveitis group, and 5 to the systemic inflammatory disease-related uveitis group. Details are provided in Tables 3 to 6. After detailed cytokine pattern analysis, only 11 patients remained in the idiopathic group, instead of 25 after the first analysis. The sensitivity of the standard tools for positive uveitis diagnosis was estimated to be 60%, while the sensitivity of the two methods (standard tools plus cytokine analysis) reached 82%.

DISCUSSION

This study investigated 62 patients with uveitis. After the standard assessment, a specific etiology was found in 62% of cases, with 38% labeled as idiopathic uveitis. This distribution is consistent with previously published data (1, 18, 19), highlighting the current limitations of the microbiological diagnostic techniques while questioning the criteria applied to systemic inflammatory diseases (20, 21). The first outcome of this study is that cytokine pattern analysis can be used as a diagnostic approach. Thus, analyzing only three cytokines, notably IL-1β, IL-10, and IL-17A, leads to an 82% increase in diagnostic sensitivity. These findings open the way to new diagnostic approaches and should be tested prospectively in a larger patient cohort. Among the uveitis cases with a formal diagnosis, a large portion were of infectious origin (42% of total), while only 18% of cases were related to a systemic inflammatory disease. This distribution probably reflects a bias in recruitment rather than a normal distribution of etiologies in the population. Patients with a known history of HLA-B27-associated arthritis or sarcoidosis were not included in the study, since their uveitis was considered to be related to their systemic disease. The exclusion of these patients has resulted in an overrepresentation of infectious uveitis cases in our cohort.

This study also allowed us to characterize the cytokine spectrum in cataract patients, considered free of any ocular inflammation, which thus represents the composition of normal AqH. The distribution of cytokines in 88 controls was very homogeneous, regardless of age and eye disease history (glaucoma, age-related macular degeneration, or diabetic retinopathy). As previous studies have shown, some cytokines or chemokines, such as IL-1β, IL-1Rα, TNF-α, IL-12(p70), IL-7, IL-10, IL-17, IL-9, IL-15, MIP-1α, MIP-1β, and MCP-1, are present in the eye without any inflammation. Growth factors like VEGF or FGF are also detectable in AqH of controls (22–26).

In patients with uveitis, irrespective of the cause, the intraocular cytokine network is extremely modified, compared with that of the control group. In addition, cytokine profiles are highly homogeneous within each group with a low interindividual variation, as demonstrated in previous studies (17, 27, 28), except for idiopathic uveitis. By a comparison of the intraocular concentrations of each cytokine in each patient group, some cytokines seem to be particularly overexpressed in certain etiologies of uveitis. The marked increase in IL-17A is characteristic of a *Toxoplasma* infection, because it is not observed in

TABLE 4 Bioclinical detailed data for patients with initially presumed idiopathic uveitis and secondarily classified in the viral uveitis group in consideration of IL-1β, IL-10, and IL-17A levels

Patient no.	Intraocular cytokine level (pg/ml)[a]			Clinical finding		Result for biological workup					
						Serology[b]					
	IL-1β	IL-10	IL-17A	Ocular features	Systemic features	*Toxoplasma*	HSV	EBV	VZV	CMV	Other
5	57	168	25	Anterior uveitis	None	−	+	+	+	+	None
6	115	185	14	Anterior uveitis	None	−	+	+	+	+	None
7	93	251	32	Keratouveitis	None	−	+	+	+	+	None
8	64	164	18	Anterior uveitis; relapse of the disease with positive PCR for HSV in AqH	None	+	+	+	+	+	None
9	81	185	15	Keratouveitis	None	−	+	+	+	+	None

[a] The mean (SD) intraocular cytokine levels for patients with confirmed VU were 61.5 (23.1) pg/ml for IL-1β, 164.9 (34.3) pg/ml for IL-10, and 28.9 (10.2) pg/ml for IL-17A.
[b] +, presence of IgG; −, absence of IgG.

TABLE 5 Bioclinical detailed data for patients with initially presumed idiopathic uveitis and secondarily classified in the systemic inflammatory disorders-related uveitis group in consideration of IL-1β, IL-10, and IL-17A levels

Patient no.	Intraocular cytokine level (pg/ml)[a]			Clinical finding		Result for biological workup					
	IL-1β	IL-10	IL-17A	Ocular features	Systemic features	Serology[c]					Other
						Toxoplasma	HSV	EBV	VZV	CMV	
10	5	3	6	Anterior uveitis	Pneumopathy related to sarcoidosis	−	+	+	+	+	Hypercalcemia-positive ACE[b]
11	20	7	13	Anterior uveitis	Colopathy related to Crohn's disease	−	−	+	+	+	
12	29	3	19	Anterior uveitis	Arthritis related to ankylosing spondyloarthritis	−	−	+	+	−	HLA-B27
13	46	13	22	Anterior uveitis	Arthritis related to ankylosing spondyloarthritis	−	+	+	−	−	HLA-B27
14	31	364	16	Panuveitis	Oculocerebral lymphoma	−	+	+	+	+	Positive cytology

[a] The mean (SD) intraocular cytokine levels for patients with confirmed SIDU were 47.8 (5.7) pg/ml for IL-1β, 63.7 (17.6) pg/ml for IL-10, and 36.0 (9.3) pg/ml for IL-17A.
[b] ACE, angiotensin-converting enzyme.
[c] +, presence of IgG; −, absence of IgG.

uveitis of other etiologies (29). This result is consistent with a recently published animal study employing direct intraocular injection of tachyzoites of the avirulent type II PRU strain of *Toxoplasma gondii*. This study demonstrated the deleterious role of IL-17A in terms of pathology and parasite control while confirming the central role of IFN-γ in limiting parasite proliferation (11). The confirmed presence of IL-17A in infected eyes is of particular interest, since this cytokine is known to induce and mediate proinflammatory responses and autoimmune diseases. The role of IL-17A in infectious diseases is ambiguous, ranging from antipathogenic activity to tissue destruction. As has been previously shown, early neutrophil induction during *T. gondii* infection is dependent on IL-17-mediated signaling. A diminished response in *IL-17R*$^{-/-}$ mice was associated with failure to produce the MIP-2 chemokine early in infection. *T. gondii* infection was reported to induce a strong and early neutrophil response (30). The neutrophils clear the parasites during the initial infection stages so that adaptive immunity, which is induced later, is not overburdened. A possible countereffect is that neutrophil recruitment may be responsible for retinal damage.

Concerning viral uveitis, cytokine profiles were also homogeneous. No significant differences were noted between herpetic uveitis and zoster uveitis. Increases in IL-1β and IL-10 were particularly noteworthy and appeared to characterize viral uveitis. IL-10 is an especially attractive candidate for affecting pathogens, as it can dramatically inhibit the proinflammatory environment. IL-10 has been shown to suppress the T-cell response and favor viral replication. The ability of IL-10 to potently suppress the cellular immune response and increase the host susceptibility has made it a strategic target for intracellular human pathogens (31). The immunosuppressive ability of IL-10 has been demonstrated in mice infected with cytomegalovirus (CMV) (32, 33). Increased IL-10 is also thought to play an essential part in persistent infections caused by viruses, bacteria, and parasites. Pathogens, such as CMV and Epstein-Barr virus (EBV), have been shown to induce IL-10 synthesis and encode their own IL-10 homologues (34, 35). HSV, which is also responsible for uveitis, does not encode an IL-10 homologue, nor does it directly induce significant IL-10 levels in T cells. In an elegant example of convergent evolution, HSV has instead developed an alternative strategy. By differentially targeting intracellular signaling pathways, HSV transforms an activating stimulus into the isolated synthesis of an immunosuppressive cytokine that favors viral replication. To achieve selective T-cell receptor (TCR)-stimulated IL-10 synthesis, HSV was shown to markedly remodel intracellular signal pathways in T cells by simultaneously inhibiting signaling through the linker for activation of T cells (LAT) while inducing signaling through p38 and Jun N-terminal protein kinase (JNK) (31).

In conclusion, this study has precisely described the cytokine spectrum found in the AqH of uveitis patients. The observation that some markers are specific to certain diseases is of major interest, for it enables a better understanding of the disease pathogenesis. Moreover, this finding paves the way for new diagnostic methods aimed to identify inflammatory markers, the elevation of which is specific to a certain etiology, as it the case in ocular lymphoma. Finally, this work may open the way toward new diagnostic and therapeutic approaches targeting specific markers in each etiology.

TABLE 6 Bioclinical detailed data for patients with idiopathic uveitis

Patient no.	Intraocular cytokine level (pg/ml)[a]			Clinical finding		Results for biological workup					
						Serology[b]					
	IL-1β	IL-10	IL-17A	Ocular features	Systemic features	*Toxoplasma*	HSV	EBV	VZV	CMV	Other
15	16	12	74	Panuveitis	None	+	+	+	+	+	None
16	5	86	22	Panuveitis	None	−	+	+	+	+	None
17	4	0	24	Panuveitis	None	+	+	+	+	+	None
18	4	0	18	Panuveitis	None	−	+	+	+	+	None
19	16	112	54	Anterior uveitis	None	+	−	+	+	−	None
20	22	161	17	Panuveitis	None	−	−	+	+	+	None
21	67	86	65	Anterior uveitis	None	+	−	+	+	+	None
22	37	68	79	Anterior uveitis	None	+	+	+	+	+	None
23	25	78	80	Anterior uveitis	None	−	+	+	+	+	None
24	15	111	11	Panuveitis	None	−	+	+	+	+	None
25	36	63	16	Panuveitis	None	−	+	+	+	+	None

[a] The mean (SD) intraocular cytokine levels for patients with idiopathic uveitis were 36.4 (29.2) pg/ml for IL-1β, 86.8 (94.0) pg/ml for IL-10, and 38.5 (20.9) pg/ml for IL-17A.
[b] +, presence of IgG; −, absence of IgG.

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