Expert Review of Ophthalmology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierl20

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To cite this article: Jorge Gomez Marin, Alejandra de la Torre & Mónica Vargas-Montes (29 Nov 2023): Immunopathogenesis of ocular toxoplasmosis and implications for treatment, Expert Review of Ophthalmology, DOI: 10.1080/17469899.2023.2279178

To link to this article: https://doi.org/10.1080/17469899.2023.2279178

Published online: 29 Nov 2023.

EXPERT REVIEW OF OPHTHALMOLOGY
https://doi.org/10.1080/17469899.2023.2279178

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REVIEW

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Immunopathogenesis of ocular toxoplasmosis and implications for treatment

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ABSTRACT

Introduction: Ocular toxoplasmosis appears after primary infection or during the reactivation of chronic infection by the protozoa *Toxoplasma gondii*. The risk of ocular involvement and the heterogeneity of clinical manifestations, their complications, and the probability of recurrences are linked to polymorphisms in immune response-related genes, cytokine networks, lymphocyte subpopulation, and parasite virulence factors. Appropriate clinical management and evidence-based advisory recommendations for patients require a clear understanding of the immunopathological mechanisms of this parasitic disease.

Areas covered: Narrative review of the scientific literature in human ocular toxoplasmosis related to parasitological and immunological characteristics, genetic polymorphisms linked to ocular involvement, and the clinical correlations of the cytokinome in aqueous humor and experiments with peripheral blood mononuclear cells.

Expert Opinion/Commentary: The greater severity in people infected by South American strains is partly explained by parasite protein kinases interfering with the effector immune functions of interferon-gamma, resulting in lower antiparasitic activity and more significant inflammation. Future therapies should point to the increase in IFN-γ production (for example, by stimulating CD4+ memory T cells subset). Thus, immune-based interventions could be promising in inducing an appropriate response for treating and preventing ocular damage and recurrences. Drugs targeting tissue cysts responsible for reactivations are a current priority.

PLAIN LANGUAGE SUMMARY

Ocular toxoplasmosis is a persistent eye condition affecting patients' visual health and quality of life. This disease may manifest after a primary infection or during the reactivation of a latent infection by the protozoan *Toxoplasma gondii*. In our opinion, based on the principle of precaution, all recent primary infections, symptomatic or asymptomatic, caused by *Toxoplasma*, should be treated, as routine screening of the susceptibility genetic factors remains unavailable. Clinicians often encounter inquiries about the source of the infection, the factors contributing to ocular involvement (which, in the majority of the population, approximately 90%, remains asymptomatic), the likelihood of recurrent episodes, and the potential expansion of ocular damage. Current scientific knowledge indicates that genetic determinants governing specific immune responses, particularly the ability to produce protective cytokines while restraining inflammatory responses, may contribute to understanding the development and characteristics of ocular toxoplasmosis in humans. The role of genetic polymorphisms has been substantiated by the analysis of cytokine profiles in aqueous humor and experimental investigations using human peripheral blood mononuclear cells (PBMCs). In South America, where virulent strains of *Toxoplasma* prevail, the disease can manifest itself more severely. Numerous parasite protein kinases function as virulence factors, impeding the effector immune functions of interferon-gamma, decreasing antiparasitic activity, and exacerbating inflammation. The interaction between infection by virulent strains and genetic host susceptibility factors intervene in the magnitude of retinochoroidal damage.

In light of these insights, developing new therapies becomes imperative for managing and preventing recurrent ocular toxoplasmosis. Additionally, pursuing drugs capable of eradicating tissue cysts responsible for recurrences and reactivations is a current research priority.

ARTICLE HISTORY
Received 31 July 2023
Accepted 31 October 2023

KEYWORDS
Ocular toxoplasmosis; cytokines; lymphocyte subpopulations; uveitis; *Toxoplasma gondii*; virulence; interferon gamma

1. Introduction: epidemiology and risk factors for ocular toxoplasmosis

Ocular toxoplasmosis results from retinal infection by the protozoan parasite *Toxoplasma gondii* [1]]. This successful ubiquitous apicomplexan protozoan can infect various vertebrate hosts, considered the most frequent zoonotic disease worldwide [2–4]. The infection is cosmopolitan but is more prevalent in tropical and subtropical regions, where environmental conditions favor the parasite's survival, especially the humidity and a high rate of precipitations [5–8]. An umbrella review concluded that in the human general population, the global seroprevalence reach 42%, varying largely according to geographical regions [2]. It is generally estimated that one-third of the human population has had the infection [9].

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Article highlights

- Ocular toxoplasmosis develops in around one-tenth of people after a primary infection.
- Susceptibility to developing ocular toxoplasmosis and its severity result from the interplay between host genetic factors and parasite virulence.
- The most critical genetic markers related to susceptibility to ocular toxoplasmosis are polymorphisms in the IFN γ promoter region.
- Future treatments with molecules that block inflammatory pathways could be adjuvant treatments, but the essence of curative treatment is the elimination of tissue cysts.
- Medications targeting tissue cysts responsible for recurrences are a current priority.

Although this high prevalence of the infection in the human population, the development of symptoms such as ocular clinical manifestations are relatively low, estimated to range from 1% to 18% of all *Toxoplasma* infections [1,10]. In recent years, some reports indicate a decline in the prevalence in the general population in Europe and North America [11] but not in South America [12]. Parallelly, the incidence of ocular toxoplasmosis was reported to decline in some places in North America [13] but increased in South America over the years [14]. It should be noted that climate change would impact the trends in the risk of infection for many regions of the world, and an increase in toxoplasmosis frequency can be expected for the years to come [15–17].

Toxoplasmosis in humans is a food and waterborne infection [18–21]. The attributable fraction from each factor changes from region to region; thus, infections due to uncooked meat are more common in countries with elevated incomes and low-income countries due to water conditions [22]. Waterborne origin has been linked with outbreaks of ocular toxoplasmosis [23–26]. Congenital transmission from mother to fetus contributes to a lower fraction of ocular toxoplasmosis, with postnatal infection the most critical origin of ocular disease due to toxoplasmosis [7,27].

2. Parasitological, clinical, and pathological characteristics of human ocular toxoplasmosis

Toxoplasma can infect almost any cell type, unlike other protozoa that cause human diseases such as *Plasmodium* or *Leishmania*, invading specific cell lineages [28]. However, humans' most common clinical damage is observed in the eye and brain [29]. During the acute phase of the disease, *Toxoplasma* multiplies actively within cells in the tachyzoite stage with rapid replication [30]. After the host develops an immune response parasite turns to a stage with slower proliferation, the bradyzoite, residing within a cyst tissue [30,31]. This infection characteristic is crucial to understanding clinical consequences, such as reactivation and subsequent recurrence of ocular lesions [32].

The most prominent clinical characteristic of toxoplasmosis as a human disease for immunocompetent individuals is neurotropism, with the eye and brain as primary targets for damage [33,34]. Our classical view that chronic infection is asymptomatic and without significant consequences for most infected people has recently been challenged [35–37]. Voluminous and cumulative evidence indicates that chronic infection can lead to mental disease [37,38]. Although the clinical and pathological characteristics of immunodeficient individuals with toxoplasmosis differ, the brain and eye remain the main sites of disease manifestations [39].

One clinical key feature of ocular toxoplasmosis is that it is unilateral for most (~70%) of the immunocompetent hosts in primary and during recurrent episodes in the posterior eye segment [40]. The infection can cause visual impairment and ocular complications, including retinal scars, retinal detachment, cataracts, glaucoma, and vision loss [39,41–43]. The severity, recurrences, and location of the lesions within the eye can vary, leading to a wide range of clinical manifestations [39,42,43].

One crucial question is how many infected people have the parasite in the eye and how many result in retinochoroiditis. Eye fundoscopy screening in the general population can indicate how many seropositive people have retinochoroidal scars in the population [44,45]. This kind of screening has the advantage of identifying people unaware of the presence of retinal scars because they are peripheral or because of a lack of access to visual health care [7]. The reports of eye fund screening for chorioretinal scars [46] showed a prevalence ranging between 0.6% in Maryland, United States [47], and 17.7% in Brazil [44]. However, fund eye screening has the problem that up to 30% of retinal lesions seen as typical of toxoplasmosis can originate from other microorganisms [48]. Another source of information comes from the reports of ocular involvement during outbreaks [27,49] as occurred in Canada [47], Brazil [49] and India [23]. The rates of ocular involvement in these outbreaks ranged between 2.7% to 19% [1]. The most critical data to date comes from Brazil through a longitudinal follow-up, where the risk of new chorioretinal lesions after diagnosis was 6.4 per 100 persons/year [27].

Another work was made in *postmortem* specimens from bank eyes from two cities in Brazil [46]. The eyes were collected consecutively from deceased persons, and the overall prevalence of retinal scars in 270 eyes was 10% [46]. After that, PCR analysis for *Toxoplasma* was performed in 57 eyes, and different prevalences were found according to the city: in Joinville, in southern Brazil, it was 87% (13/15), and in São Paulo, 7% (3/42). The eyes from Joinville tested positive for parasite DNA had a 1:1 correlation with seroprevalence, which may indicate that no apparent barrier to parasite entry into the eye existed in this geographic region [46]. Even more interesting was that the 16 eyes that were positive by PCR did not have any chorioretinal scar, indicating that bearing parasite infections in their eyes do not force the development of ocular lesion, like the finding that only 30%–50% of AIDS *Toxoplasma* seropositive patients experience recrudescent ocular or brain disease [50].

The data from the studies based on eye screening, outbreaks, and eye banks can give us a picture of what can occur after a primary *Toxoplasma* infection and, at the same time, can answer some crucial questions. The parasite, after infection, can arrive in the eye and remain as tissue cysts without triggering retinal damage for most people. This can be

explained by an efficacious local immune response mediated by innate (Figure 1a) and adaptative (Figure 1b) immune response [32,51]. Although some people presumably can eliminate the parasite and become seronegative for antibodies and even revert to a negative T cell response [52] this is not a general situation, as can be deducted from the high rate of reactivation and the association of an increased risk of ocular toxoplasmosis reactivation with age [53]. Two additional facts indicate that persistent cyst tissue in the eye is responsible for reactivation: the lack of acute markers for most acute episodes (~80%) of ocular toxoplasmosis [5,54–56] and the presence of parasite DNA in eye bank specimens [46]. Our estimation of the mean length of specific IgM after primary infection is two years in the Colombian population [57] therefore, we can

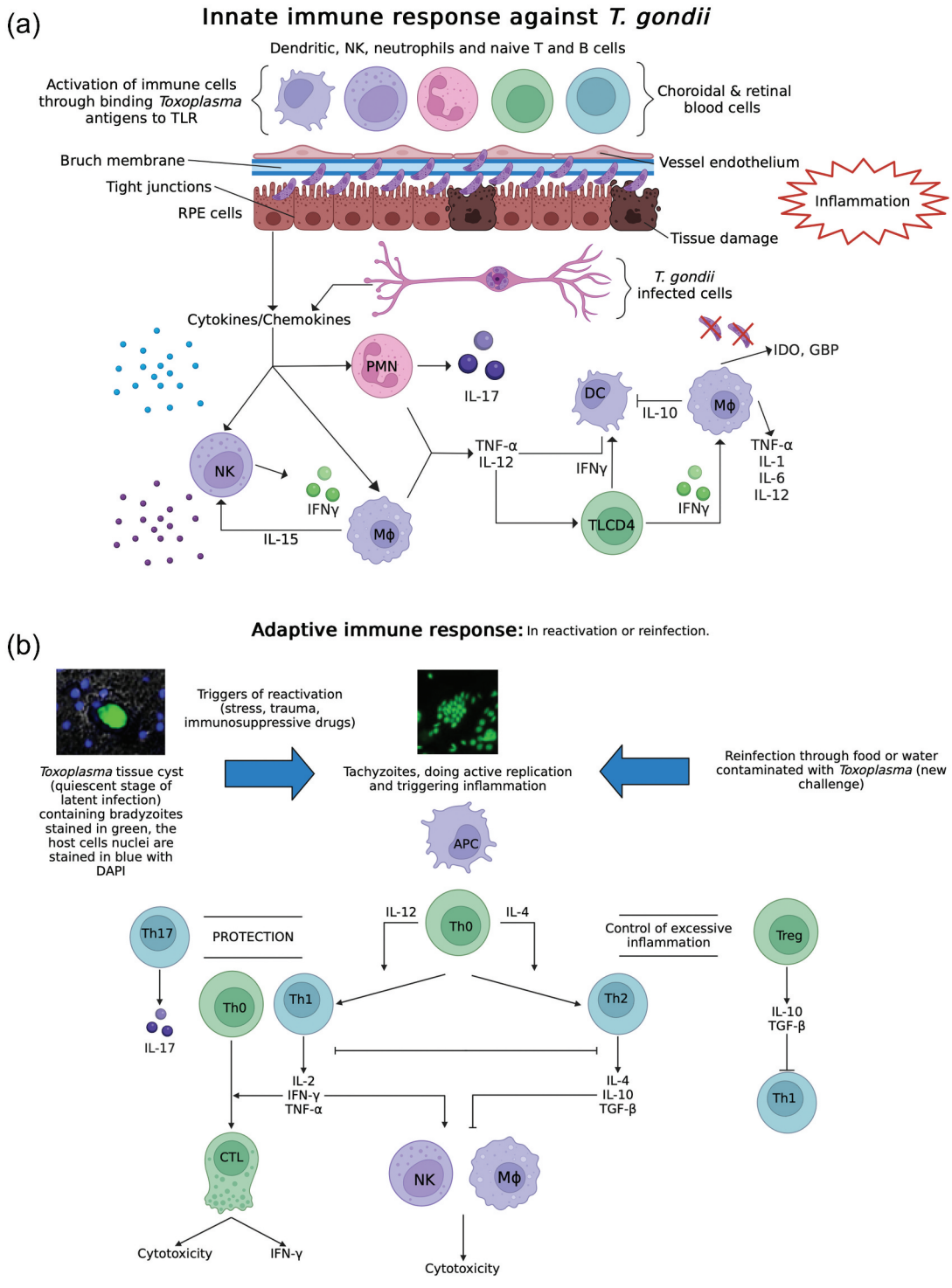

Figure 1. Scheme of the innate and adaptive immune response occurred during human ocular toxoplasmosis. Created with BioRender.com. a. local innate immune response components in the human eye responsible for the control of the *Toxoplasma gondii* retinal infection. b. Local adaptative immune response in the human eye responsible for controlling the *Toxoplasma gondii* retinal infection. Abbreviations: TLR: toll-like receptors, NK: natural Killer cells; RPE: retinal pigmentary epithelium; IDO: indoleamine Oxygenase; GBP: guanylate binding proteins; PMN: polymorph mononuclear cells; MΦ: macrophages.

estimate that, at least in Colombian patients, when active retinochoroiditis manifests, this occurs after infection was acquired more than two years before.

When infection leads to retinal damage, the pathological description can inform what cells are affected by the main characteristics of the inflammatory reaction [28]. Helenor Wilder accomplished the first description of the pathological changes induced by toxoplasmosis in 1952 in a case series of 53 enucleated eyes with granulomatous lesions where central necrosis and the presence of tachyzoites of *T. gondii* were consistently found in the necrotic areas [58]. The lesions comprised focal necrotizing retinitis, characterized by inflammation and tissue damage with mixed inflammatory reactions, mainly lymphocytes and monocytes [58]. In pathological material, a well-demarcated area of coagulative necrosis is observed with adjacent choroiditis, vasculitis, hemorrhage, and vitritis [40,57]. Viable tachyzoites and tissue cysts may be found in superficial layers of the infected retina, along with an intense mononuclear inflammatory cell reaction seen in the involved retina and adjacent choroid and vitreous [40].

One interesting noninvasive imaging technique providing *in vivo* information is optical coherence tomography (OCT), an interferometric, noninvasive optical tomographic imaging technique offering micrometer penetration [59]. The results of this technique have demonstrated the involvement of retinal layers during acute episodes of ocular toxoplasmosis [60,61]. Typical OCT findings in toxoplasmic chorioretinitis are the retinal pigment epithelium proliferation and hyperpigmentation, an increased backscatter from the choroid consistent with pigmentary atrophy, and the preferential involvement and thinned of superficial layers of the retina, which is consistent with the preference of toxoplasmosis for neural tissue [59]. In one study from Brazil, in all patients at the active lesion site, the inner retinal layers were abnormally hyper-reflective with thickening of the posterior hyaloid as well as of the subjacent choroid, and changes at the retinal pigmentary epithelium in two-thirds of the patients [62]. At the same time, only one-fifth had subretinal fluid [62]. The recent introduction of optical coherence tomography angiography demonstrated that retinal vasculitis is another common finding of ocular toxoplasmosis, in addition to typical focal necrotizing retinitis [60,63].

Additional data come from *ex vivo* cups of the human eye [64] This model provides essential information that indicates tachyzoites of *T. gondii* cross the vascular endothelium to access the human retina by at least three routes: inside leukocytes that migrate to the retina, as a transmigrating tachyzoite, and after infecting endothelial cells [64]. The retinal Müller glial cells are the preferred initial host cells; then, by invading retinal pigment epithelial cells, the secretion of growth factors is altered and induces the proliferation of adjacent uninfected epithelial cells [64]. Indeed, this model gave a very realistic dynamic view of the eye invasion process.

3. The role and mechanisms of parasite strains diversity and virulence in ocular toxoplasmosis severity

The clinical forms of ocular toxoplasmosis in immunocompetent people infected in South America are more severe than in other continents [65–68]. This has been linked to infection with virulent strains [68,69]. Notoriously, *Toxoplasma* has a biphasic distribution of the parasite population [70]. The strains in the northern hemisphere have a clonal distribution and are less polymorphic; in contrast, the parasite strains from South America are more diverse genetically and have virulent alleles more frequently than strains from other continents [71–73]. This can be explained because the most probable apparition of *Toxoplasma* species was in South America, specifically, the Colombian Atrato region, as deduced from the phylogeographic analysis [74]. In South America, parasite dissemination occurred through slow feline dispersion in a wild environment, keeping remarkable genetic polymorphism and conserving virulent alleles. In contrast, the species was transmitted faster through domestic cats associated with human populations in Africa, Asia, and Europe privileging attenuated clonal species [74–76]. The virulent alleles are related to genes coding for protein kinases derived from the organelle rhoptry of the parasite [77]. Some groups of rhoptry-derived protein kinases fundamentally affect the host immune response. For instance, ROP16 coopts the intracellular signaling of STAT proteins necessary for the IFN-mediated response [78–80] and ROP18 inhibits the host proteins that lyse the parasite vacuole [81].

The first demonstration of the pertinence of *Toxoplasma* virulent factors in humans described a higher inflammatory response in patients harboring strains with the ROP18 virulent allele [82]. While any strain can induce ocular damage in human toxoplasmosis, more severe clinical forms are related to infections by strains from serotype I [76]. This serotype possesses the virulent versions of many rhoptry proteins, being the ROP5, the critical locus for virulence [83].

4. Cytokine networks in ocular toxoplasmosis

An essential element in the immune response is how cells communicate with each other to activate or regulate inflammatory processes through networks of cytokines [84]. These networks have been studied in patients with ocular toxoplasmosis, allowing us to know which cytokines are involved in the inflammatory and reactivation processes of ocular toxoplasmosis [85]. The eye has a specific and independent intraocular immune response, making it an immunologically privileged organ [86]. For this reason, exploring and comparing the systemic and intraocular cytokine network response are fascinating topics in ocular toxoplasmosis [87].

The role of cytokines in toxoplasmic uveitis is complex because the predominance of a particular set of cytokines varies according to the time, the intensity of the antigenic stimuli, and the simultaneous presence of cytokines with antagonistic effects [88]. It should be remembered that the immune response looks for an equilibrium between the efficacious inhibitions of the parasite's replication or its destruction and the control of an excessive detrimental inflammatory response [89,90]. Therefore, mapping the cytokine levels in the eye (cytokinome) can enhance our understanding of the disease's mechanisms and help develop targeted treatments [85]. Examining cytokine levels might also help predict relapses and monitor disease activity in patients with uveitis [84,91]. For this reason, some studies have sought to generate

a methodology to determine the degree and patterns of cytokine secretion in uveitis, considering its potential clinical utility and the knowledge it can provide about the immunopathogenesis of this condition [69,84,92].

In this sense, some studies have measured several intraocular cytokines/chemokines in patients diagnosed with OT in the aqueous humor [66,93]. Correlations were evaluated between cytokine/chemokine levels, type of inflammatory response (Th1, Th2, Th17, Treg), and clinical characteristics [68,94–96]. A predominant Th2 response was associated with more severe clinical features [68,85]. The presence of VEGF and IL-5 was related to a higher number of recurrences [85]. Growth factors (VEGF, FGF, PDGF-β) were related to more lesions [85]. Patients infected by type-I/III strains had a particular intraocular cytokine pattern related to more severe clinical characteristics [85]. Additional studies of the aqueous humor cytokinome showed slight differences between primary acquired ocular toxoplasmosis and recurrent cases [93].

In addition, it has been described that severe ocular lesions occur from a combination of host gene susceptibility and exposure to more aggressive strains [69]. The parasite and its host's relationship could affect clinical presentation, treatment, and prognosis [97]. In this context, host cytokines and promoter sequences polymorphisms have been studied and observed more frequently in individuals with ocular lesions than controls in the same geographical areas [98–102].

Considering the characteristics in different geographical regions, comparing the cytokine profile in the eye between French and Colombian patients revealed that Colombian patients exhibited an intraocular polarized Th2 cytokine response [85]. Similarly, Colombian patients with ocular toxoplasmosis displayed a peripheral Th2-skewed response [103]. The peripheral immune response also showed a significant increase in IL-6, IL-10, and TGF-β mRNA levels in the patients with ocular toxoplasmosis compared to the chronically infected individual without ocular lesions and negative controls [104]. TNF-α and IL-12 mRNA levels were up-regulated in patients with ocular lesions but did not reach statistical significance. Furthermore, IL-27 and IFN-γ mRNA levels were higher in patients with ocular toxoplasmosis than in negative controls, and these differences were statistically significant [104].

South American patients experience more severe clinical symptoms than European patients, including higher levels of inflammation, more lesions, and larger lesion sizes [68]. This could be attributed to the South American strains' ability to weaken the protective effect of IFN-γ by manipulating the immune response through a Th2 cytokine profile and upregulation of IL-17 [105]. IL-17, produced by Th17 and Müller cells, negatively impacts IFN-γ production, decreasing the protective immune response against *Toxoplasma gondii* [105].

The production of IFN-γ by human peripheral blood mononuclear cells (PBMC) in response to intracellular pathogens like *T. gondii* is influenced by both genetic factors, such as polymorphisms in the IFN-γ gene and genes that inhibit IFN-γ synthesis like IL-10 [69,106,107]. Other factors, including DNA methylation, posttranscriptional mechanisms like miRNA modification of IFN-γ mRNA, the type of infection (congenital or acquired), and the presence of ocular or cerebral lesions, also affect IFN-γ production [108,109]. Patients with ocular hypertension associated with ocular toxoplasmosis who produce high levels of intraocular IFN-γ during reactivation of toxoplasmic retinochoroiditis can be identified as high releasers of IFN-γ by PBMCs in cytokine release assays [106]. These assays can also help to identify patients with acquired ocular toxoplasmosis who exhibit low release of IFN-γ [106]. This patient group has a higher risk of experiencing extended disease progression and severe complications. Including local strains in the cytokine release assay when using *T. gondii* lysates is recommended [106].

Moreover, the release of IFN-γ by Natural Killer cells (NK cells) plays a crucial role in innate immunity during *T. gondii* infection. Interleukin 12 (IL-12) is a critical cytokine that promotes the generation of IFN-γ by NK cells. Various studies have demonstrated the influence of cytokines on NK cell activation, with IL-2 being an important stimulatory factor [110].

Focusing on the interferon role, an *in vitro* model examined the immune interaction among retinal cells, specifically concentrating on the involvement of type I and III interferons in the barrier function [111]. It was shown that IFN-γ influenced the parasite proliferation, and the regulation of the barrier function of the outer blood-retinal barrier (oBRB) is associated with type I and III interferons producing IFN-λ1 in a manner independent of STAT1 [111]. These findings may help identify potential immunological targets related to these interferons and provide possible treatment options for this ocular disease [111].

In conclusion, the information provided by studies focused on evaluating the network and kinetics of intraocular cytokines (Figure 1a and b) in humans has contributed the most to understanding what happens in real-life scenarios within the eyes of individuals infected with *Toxoplasma gondii*. This information has been precious in studying and comparing ocular immune responses of cytokines among patients infected with parasite strains in various geographic areas, considering that the local response in an immunologically privileged organ like the eye provides the most specific information about what occurs at the local level. Investigating the cytokinome within the eye can enhance our comprehension of the mechanisms underlying the disease and aid in developing precise and advanced targeted therapies. This information could also potentially facilitate the prediction of relapses and enable the monitoring of disease activity in patients with ocular toxoplasmosis.

5. Immunogenetics studies

The fact that most people who acquire toxoplasmosis do not develop ocular disease is a solid argument for considering individual susceptibility [112,113]. Certain genetic predisposition variations have been associated with an increased likelihood of developing ocular involvement. Table 1 summarizes the polymorphisms by cytokine that showed significant association with ocular toxoplasmosis. Many polymorphisms related to recurrences, like IL-1α −889 C/T [101], IL-10

-1082A/G [69,102] and IFN-γ +874 T/A [101,121], should be considered indicative biomarkers for prophylaxis against recurrences [133,134]. The findings of theses immunogenetic studies confirm the importance of gene regulation in the immune response and the development of toxoplasmic retinochoroiditis [112,113]. However, due to the intricate nature of the immune response to parasites, it is improbable that genetic variation at a single location can fully explain the differences in immune responses and clinical manifestations among hosts [112,113]. Understanding disease susceptibility and genetic factors is essential for the functional assessment of disease-related gene variations [112,113]. Most studies analyze the putative association between the frequency of the gene polymorphisms and the presence of the disease. Still, very few go until the demonstration of how the specific polymorphisms affect the synthesis or activity of the cytokine [112,113].

Important and notoriously, in the + 874 site of the promotor for IFN γ (SNP rs24305619), the T/A or A/A polymorphisms are present in 95% of Colombian cases with ocular toxoplasmosis. In contrast, in people without ocular toxoplasmosis, 80% have the TT or TA alleles [98]. In Santa Rita de Cassia, in Brazil, 91% of patients had T/A or A/A polymorphisms but with a similar frequency of theses alleles in community seropositive controls; however, no IgM was performed to establish that non-recent infections were present, and no follow-up was reported to show apparition of ocular lesions in this high prevalent region [101]. The + 874 site of the IFN γ promotor is a NFkB binding site [135], and in health volunteers, the presence of the T allele was associated with increased IDO activity [136]. The significance of these polymorphisms was proved by *T. gondii* stimulation in *ex vivo* experiments, showing that the leukocytes from people with ocular toxoplasmosis possessing the T/A allele significantly produced less IFN γ than those with the T/T allele [137]. The polymorphisms in this genetic locus are associated with susceptibility to severe infections by many microorganisms [135,138,139].

6. Lymphocyte subpopulations

The studies about lymphocyte subpopulations (CD4+ memory, effector) are the start point to understanding how cytokines synthesis is modulated. Still, most of the studies in ocular toxoplasmosis remain in the initial characterization of the systemic $CD4^+$ and $CD8^+$ T cell immune responses and the cytokines they produce [140–142]. In addition, other leukocytes are essential in this landscape, including Natural Killer (NK) cells and neutrophils [110,143,144]. All these leukocyte subsets can produce interferon-gamma (IFN-γ), providing a significant response against the parasite and mediating host resistance [145]. Consistently, human eyes removed from patients with ocular toxoplasmosis showed a heterogeneous leucocytic infiltrate [32,146,147].

Also, in the eye environment, it is essential to consider the retinal pigment epithelium (PE), which modulates the activation status of multiple lymphocyte subsets and reduces intraocular inflammation [148]. Therefore, regarding $CD8^+$ T cells, a key lymphocyte population controlling the infection against *T. gondii*, a recent study explored the interaction between human $CD8^+$ T cells and retinal PE in the setting of T. *gondii* tachyzoite infection [145]. The authors exposed confluent human retinal PE monolayers to GT-1 strain tachyzoites and subsequently co-cultured the cell monolayers with $CD8^+$ T cells obtained from human peripheral blood [64]. They found a reduced production of IL-2 (an indicator of T cell activation) in T cells and observed differential expression of the immunomodulatory marker (programmed cell death-ligand 1, PD-L1 transcript), which increased in retinal PE cells infected with the parasite [64]. Since PD-L1 inhibits T cell activation, its elevated levels in retinal PE cells were expected to inhibit IL-2 production by CD8+ T cells [64]. This finding could support what was previously suggested about how retinal PE cells can convert $CD4^+$ T and $CD8^+$ T cells into T regulatory cells, along with expressing TGFβ and through the expression of ligands for programmed cell death pathways, such as FAS ligand (FasL) and PD-L1 [64]. We recently confirmed these results by analyzing the expression of $CD8^+$ T – cell exhaustion immunomodulatory markers in peripheral blood mononuclear cells (PBMCs) from patients with ocular toxoplasmosis, and we found that the gene expression of PD-1 (programmed cell death 1 protein) was higher in ocular toxoplasmosis compared to asymptomatic or uninfected individuals [149]. Additionally, membrane expression of PD1 was observed in the central memory $CD8^+$ T lymphocytes subset, and most patients with ocular toxoplasmosis showed a total exhaustion phenotype [149]. Also, when PBMCs were stimulated *ex vivo* with total antigen from *T. gondii*, it was found an inverse correlation between the exhaustion markers and clinical characteristics (lesion size, recurrence index, and number of lesions), suggesting that PD-1 expression could have a beneficial role during immediate response to a new challenge and therefore by controlling an excessive inflammatory response [149].

Similar research, using PBMCs from patients with toxoplasmic retinochoroiditis and after stimulation with *T. gondii* antigen, found that $CD4^+$ and $CD8^+$ T cells were the main sources of IL-10 cytokine, but also for IFN-γ and TNF-α, other lymphocyte populations were a relevant source of inflammatory cytokines [150]. Interestingly, a negative correlation was observed between ocular lesion size and IL-10 expression by $CD4^+$ lymphocytes. Therefore, this study showed that T cells are the main lymphocyte populations expressing IL-10 and its protective role for excessive damage in patients with toxoplasmic retinochoroiditis [150]. Besides the IL-10 response from $CD4^+$ T lymphocytes, it has been detected the IL-17A production by resident retinal cells rather than infiltrating T cells in the eye [151]. The observed distribution and early secretion of IL-17A in the eye led to suspect that resident cells, such as glial cells and astrocytes, may be responsible for this early production of IL-17A [151]. Local IL-17A production by resident cells plays a central role in the pathology of ocular toxoplasmosis [151,152]. The balance between Th17 and Th1 responses, by regulating especially IFN-γ levels, is crucial for the outcome of infection [151,152].

Additional key cytokines participating in this cellular response involve IL-23, which induces the proliferation of IL-17-producing cells, and IL-27, counterplayer to IL-

Table 1. Genetic polymorphisms associated to ocular toxoplasmosis.

Immune molecule	Author, year, Country (Reference)	Case and control definition	Immunogenetic Findings	Treatment impact	Relation with serum levels	Interest as biomarker in personalized medicine
IL-1α	Wujcicka W et al, 2015, Poland [114]	Cases: fetuses congenitally infected with *Tg* Controls: Uninfected control cases	The allele C in the IL1α −889 C/T did not show a difference in the frequency of the congenital toxoplasmosis infection.	NI	NI	-
	Cordeiro et al, 2008, Brazil [115]	Cases: **OT** with anti-*Toxoplasma* IgG positive Controls: Toxoplasma IgG positive without ocular lessons Recurrence: patient with **OT** and new active the focus of retinal necrosis after three months of an active episode with anti-*Toxoplasma* IgG positive	IL-1α −889 C/T genotype and allele were unrelated to TR occurrence. However, genotype and allele presented significant differences in patients with recurrence and without them.	NI	NI	Future biomarker for prophylactic therapy. More studies evaluating cytokine levels are needed.
	Naranjo-Galvis et al, 2018, Colombia [98]	Cases: Confirmation by aqueous humor, Goldmann-Witmer coefficient Controls: 22 with uveitis but without **OT** and 94 healthy controls.	The IL-1α −889 G/A and IL-1α−889T/C were not related to **OT**.	NI	NI	-
	Mantilla-Muriel et al., 2020, Colombia [69]	Cases: OT patients (13 confirmed, two co-infections- and eight unconfirmed cases) Controls: 20 individuals chronically infected with Toxoplasma but without ocular involvement.	IL-1α (−889 G/A) when compared within the group of patients with OT was not associated with characteristic clinical manifestations nor the number of vitreous cells, retinal lesions, lesion size (in disc diameters), and recurrences.	NI	NE	-
IL-1β	Naranjo-Galvis et al, 2018, Colombia [98]	Cases: Confirmation by aqueous humor, Goldmann-Witmer coefficient Controls: 22 with uveitis but without **OT** and 94 healthy controls.	*The IL-1β−31 G/A was loosely related to **OT**. *Haplotype GAA of IL-1β gene promoter polymorphism (rs16944,rs1143634, andrs1143627) seems to be related to **OT**. *IL-1β +3954 G/A, IL-1β −511 G/A were not related with **OT**.	NI	NI	-
	Cordeiro et al, 2008, Brazil [115]	Cases: **OT** with anti-*Toxoplasma* IgG positive Controls*: Toxoplasma* IgG positive without ocular lessons Recurrence: patient with **OT** and new active the focus of retinal necrosis after three months of an active episode with anti-*Toxoplasma* IgG positive	IL-1β +3954 C/T genotype and allele were unrelated to TR occurrence. Also, genotype and allele did not present significant differences in patients with and without recurrence.	NI	NI	-
	Wujcicka W et al, 2015, Poland [114]	Cases: fetuses congenitally infected with *Tg* Controls: Uninfected control cases	The allele C in the IL1β +3954 C/T was more frequent in the congenital toxoplasmosis infection than in the controls. ($P \leq 0.05$)	NI	NI	-
	Mantilla-Muriel et al., 2020, Colombia [69]	Cases: OT patients (13 confirmed, two co-infections- and eight unconfirmed cases) Controls: 20 individuals chronically infected with *Toxoplasma* but without ocular involvement.	IL-1β (+3954 G/A, −511 G/A, −31 G/A) did not show an association with characteristic clinical manifestations nor with the number of vitreous cells, number of retinal lesions, lesion size (in disc diameters), and number of recurrences.	NI	Serum IL-1β levels did not correlate with the total number of retinal lesions, age, recurrences, vitreous cells, and lesion size in disc diameters.	-
	Rocha-Araujo et al. 2023. Brazil [116]	Cases G1: Patients with OT lesions and positive serology Controls G2: Patients with positive serology but without OT lesions Controls G3: Patients without OT lesions and without positive serology.	IL-1β-511C/C was found to be a protective factor against OT lesions (OR 0.28, 95% CI 0.08–0.78 for G1 vs G2) and (OR 0.29, 95% CI 0.09–0.82 for G1 vs G3).	NI	NI	-

(*Continued*)

Table 1. (Continued).

Immune molecule	Author, year, Country (Reference)	Case and control definition	Immunogenetic Findings	Treatment impact	Relation with serum levels	Interest as biomarker in personalized medicine
IL-6	Wujcicka W et al, 2015, Poland [114]	Cases: fetuses congenitally infected with *Tg* Controls: Uninfected control cases	The IL-6 – 174 G/C increased risk (OR of 4.2) for congenital toxoplasmosis. The allele C in the IL-6 – 174 G/C was more frequent in congenital toxoplasmosis than in controls. ($P \leq 0.05$)	NI	NI	-
	Cordeiro et al, 2013, Brazil [117]	Cases: **OT** with anti-*Toxoplasma* IgG positive Controls: *Toxoplasma* IgG positive without ocular lesson Recurrence: patient with **OT** and new active the focus of retinal necrosis after three months of an active episode with anti-*Toxoplasma* IgG positive	The IL-6 – 174 G/C and IL-6 low producer allele C related to the occurrence of TR ($P = 0.001$ and $P = 0.01$). However, they were not associated with recurrence.	NI	NI	-
IL-10	Naranjo-Galvis et al, 2018, Colombia [98]	Cases: Confirmation by aqueous humor, Goldmann-Witmer coefficient Controls: 22 with uveitis but without **OT** and 94 healthy controls.	*The IL-10 – 1082A/G was significantly more prevalent in **OT** patients than controls with an OR 5.27(BONF = 3.48) *Haplotype 'GG' and 'GA' of IL-10 gene promoter polymorphism (rrs1800896 and rs1800871) seem to be related to **OT**. *The IL-10 – 1082 G/A was significantly less prevalent in **OT** patients.	NI	NI	-
	Cordeiro et al, 2008, Brazil [102]	Cases: **OT** with anti-*Toxoplasma* IgG positive Controls: *Toxoplasma* IgG positive without ocular lesson Recurrence: patient with **OT** and new active focus of retinal necrosis after three months of an active episode with anti-*Toxoplasma* IgG positive	*The IL10 – 1082 A/G may be related to TR ($P = 0.004$) *Patients with allele IL10 – 1082 (AA +AG genotypes) have an OR of 2.55 to have TR than the control subjects.	NI	NI	-
	Rocha-Araujo et al. 2023. Brazil [116]	Cases G1: Patients with OT lesion and positive serology Controls G2: Patients with positive serology but without OT lesion Controls G3: Patients without OT lesion and positive serology.	IL-10 –1082 did not show any association with OT	NI	NI	-
	Mantilla-Muriel et al., 2020, Colombia [69]	Cases: OT patients (13 confirmed, two co-infections- and eight unconfirmed cases) Controls: 20 individuals chronically infected with *Toxoplasma* but without ocular involvement.	IL-10 -1082A/G did not correlate with characteristic clinical manifestations or the number of vitreous cells, retinal lesion, lesion size (in disc diameters), or recurrences. IL-10 -819 G/A was associated with the bilateral presentation of OT; however, it did not show differences in the number of vitreous cells, number of retinal lesions, lesion size (in disc diameters), or recurrences.	NI	The levels of IL-10 in serum showed a strong positive correlation between serum levels, the number of recurrences, and the size of the lesions in disc diameters.	Future biomarker for prophylactic therapy
IL-12	Mantilla-Muriel et al., 2020, Colombia [69]	Cases: OT patients (13 confirmed, two co-infections- and eight unconfirmed cases) Controls: 20 individuals chronically infected with *Toxoplasma* but without ocular involvement.	IL-12 + 169774 G/T showed an association with synechia presentation of OT; however, it did not show differences in terms of the number of vitreous cells, number of retinal lesion, lesion size (in disc diameters), and number of recurrences.	NI	NE	-

(*Continued*)

Table 1. (Continued).

Immune molecule	Author, year, Country (Reference)	Case and control definition	Immunogenetic Findings	Treatment impact	Relation with serum levels	Interest as biomarker in personalized medicine
IL-17	Mantilla-Muriel et al., 2020, Colombia [69]	Cases: OT patients (13 confirmed, two co-infections- and eight unconfirmed cases) Controls: 20 individuals chronically infected with *Toxoplasma* but without ocular involvement.	IL-17 R + 18661C/T did not correlate with characteristic clinical manifestations nor the number of vitreous cells, retinal lesions, lesion size (in disc diameters), and recurrences.	NI	NE	-
TNF-α	Abu et al, 2016, Ghana [118]	Cases: **OT** with anti-*Toxoplasma* IgG positive Controls*: Toxoplasma* IgG positive without ocular lesion	TNF-α-308 genotype, alleles, and allele carriage analysis did not show a relation with TR	NI		
	Cordeiro et al, 2008, Brazil [119]	Cases: **OT** with anti-*Toxoplasma* IgG positive Controls: *Toxoplasma* IgG positive without ocular lesson Recurrence: patient with **OT** and new active the focus of retinal necrosis after three months of an active episode with anti-*Toxoplasma* IgG positive	The TNF-α −308 G/A did not show a relation with TR occurrence or recurrence.	NI	NI	-
	Naranjo-Galvis et al, 2018, Colombia [98]	Cases: Confirmation by aqueous humor, Goldmann-Witmer coefficient Controls: 22 with uveitis but without **OT** and 94 healthy controls.	The TNF-α −238 G/A, TNF-α −308 G/A, TNF-α −1031T/C, TNF-α −857C/T, and TNF-α −863C/A were not associated with **OT**	NI	NI	-
	Mantilla-Muriel et al, 2020, Colombia [69]	Cases: OT patients (13 confirmed, two co-infections- and eight unconfirmed cases) Controls: 20 individuals chronically infected with *Toxoplasma* but without ocular involvement.	TNF-α −1031T/C, −308 G/A, −238C/T, −857 G/A did not show an association with characteristic clinical manifestations nor with the number of vitreous cells, number of retinal lesion, lesion size (in disc diameters), and number of recurrences. TNF-α −857 G/A, in the allele G/G, is associated with more retinal lesions. But don't associate with other clinical characteristics, number of vitreous cells, lesion size (in disc diameters), or recurrences.	NI	The levels of TNF-α in serum showed a strong negative correlation between serum levels and age. Additionally, they demonstrated a strong positive relationship between higher serum levels and a greater number of vitreous cells.	-

(*Continued*)

Table 1. (Continued).

Immune molecule	Author, year, Country (Reference)	Case and control definition	Immunogenetic Findings	Treatment impact	Relation with serum levels	Interest as biomarker in personalized medicine
IFN-γ	Albuquerque et al, 2009, Brazil [120]	Cases: **OT** with anti-*Toxoplasma* IgG positive Controls: *Toxoplasma* IgG positive without ocular lesion	*The IFN-γ +874T/A did not find a difference with the controls. *The IFN-γ +874T/T has more risk of presenting TR than controls with positive serology (OR 2.62)	NI		-
	Aleixo A et al, 2019, Brazil [121]	Active case: active toxoplasmic retinochoroiditis according to the criteria described by Holland with anti-*Toxoplasma* IgG positive Recurrence: Active retinochoroiditis associated with a retinal scar in either eye.	IFN-γ +874 T/A had more risk of recurrence (HR: 1.49)	All have been treated for 30 to 45 days.	Future biomarkers for prophylactic therapy	Future biomarkers for prophylactic therapy
	Neves et al, 2012, Brazil [122]	Cases: Acute acquired toxoplasmosis (AAT) with *Toxoplasma* IgG positive Controls*:* *Toxoplasma* IgG positive without ocular and ganglionar toxoplasmosis.	IFNγ +874T/A, there was no association between polymorphism and the presence of symptoms. Nevertheless, a possible relation of A-allele was observed with prolonged illness, and T-allele was more frequent in severe disease.	NI	NI	-
	Peixe et al, 2014, Brazil [123]	Cases: **OT** with *Toxoplasma* IgG positive and type of retinal lesion Controls: *Toxoplasma* IgG positive without **OT.**	*The IFN-γ polymorphism rs2069718 is related to the most severe scar lesions. It was evidenced that the G allele was higher in the group with type A scar lesions than in the control group. Also, The GG genotype was associated with a higher risk of type A scar lesion than the allele A positive genotype (OR = 3.31). On the other hand, the presence of the A allele in either homozygosity or heterozygosity seems to be protective. (AA vs. GG: OR = 0.36; AG vs. GG: OR = 0.28). *The IFN-γ polymorphism rs3181035, least severe scar lesions. I was evidenced that the C allele was significantly lower in the group with type C scar lesions than in the control group. The homozygous or heterozygous T allele was associated with increased susceptibility (TT vs. CC: OR = 4.8; CT vs. CC: OR = 2.8), whereas the presence of the homozygous C allele seemed to be protective (OR = 0.33).	NI	For SNP rs2069718, higher levels of IFN-γ production were observed in individuals with homozygous AA and GG genotypes, who presented the most severe scar lesions (type A). Also, patients with intermediate-severity (type B) scar lesions exhibited a correlation. However, in the SNP rs3181035, IFN-γ production levels were lower in the group with type east severe scar lesions (Type C).	Future biomarkers for prophylactic therapy.
	Naranjo-Galvis et al, 2018, Colombia [98]	Cases: Confirmation by aqueous humor, Goldmann-Witmer coefficient Controls: 22 with uveitis but without **OT** and 94 healthy controls.	The IFN-γ +874A/T (rs2430561) was significantly more prevalent in **OT** patients than controls with an OR 4.2 (BONF = 6.07)	NI	NI	-
	Abu et al, 2016, Ghana [118]	Cases: **OT** with anti-*Toxoplasma* IgG positive Controls: *Toxoplasma* IgG positive without ocular lessons	IFN-γ +874T genotype, alleles, and allele carriage analysis didn't show a relation with TR	NI	NI	-
	Mantilla-Muriel et al, 2020, Colombia [69]	Cases: OT patients (13 confirmed, two co-infections- and eight unconfirmed cases) Controls: 20 individuals chronically infected with *Toxoplasma* but without ocular involvement.	IFN-γ (+874T/A) did not show an association with characteristic clinical manifestations nor the number of vitreous cells, retinal lesions, lesion size (in disc diameters), and recurrences.	NI	The levels of IFN-γ in serum showed a strong negative correlation between serum levels and age. Additionally, they demonstrated a strong positive relationship between higher serum levels and a more significant number of vitreous cells.	-

(*Continued*)

Table 1. (Continued).

Immune molecule	Author, year, Country (Reference)	Case and control definition	Immunogenetic Findings	Treatment impact	Relation with serum levels	Interest as biomarker in personalized medicine
CCR5	Faria Junior et al, 2018, Brazil [124]	Group 1: **OT** with anti-*Toxoplasma* IgG positive Group 2: *Toxoplasma* IgG positive without ocular lessons Group 3: No **OT** and Toxoplasma IgG negative	CCR5 59,029 A/G was a risk factor of **OT** (OR 2.41) but must have CCR5/CCR5 genotype	NI	NI	-
P2RX7	Jamieson et al., 2010, United States [125]	Cases: Congenital *Tg* Controls: Parents	Association between P2RX7 polymorphisms (C (+) G(-) allele at SNP rs1718119 and rs2230912 with a risk of ocular disease (OR 3.0) and (OR 5.99)	NI	NI	-
	Mantilla-Muriel et al, 2020, Colombia [69]	Cases: OT patients (13 confirmed, two co-infections- and eight unconfirmed cases) Controls: 20 individuals chronically infected with Toxoplasma but without ocular involvement.	P2RX7 1,718,119 G/A; 1621,388 C/T; 2230,912 C/T did not show an association with characteristic clinical manifestations nor with the number of vitreous cells, number of retinal lesions, lesion size (in disc diameters), and number of recurrences.	NI	NE	-
ALOX12	Wilota et al., 2014, United States [126]	Cases: Congenital toxoplasmosis	rs6502997, rs312462, rs6502998, and rs434473 were related with congenital toxoplasmosis	NI	NI	-
TLR2	Peixoto-Rangel et al, 2009, Brazil [127]	Cases: **OT** with anti-*Toxoplasma* IgG positive Controls: Toxoplasma IgG positive without ocular lessons Familiar relation	The polymorphisms rs3804099, rs5743708, rs4986790, and rs4986791 did not show a relation with **OT**.	NI	NI	-
TLR5	Peixoto-Rangel et al, 2009, Brazil [127]	Cases: **OT** with anti-*Toxoplasma* IgG positive Controls: Toxoplasma IgG positive without ocular lessons Familiar relation	The polymorphism rs1341987 and rs1053954 did not show a relation with **OT**.	NI	NI	-
TLR9	Peixoto-Rangel et al, 2009, Brazil [127]	Cases: **OT** with anti-*Toxoplasma* IgG positive Controls*: Toxoplasma* IgG positive without ocular lessons Familiar relation	The polymorphism rs352140 evidenced a relation with the presence of **OT** (Specifically, the allele C had an OR of 7), but the rs5743836 of the allele A didn't show a relation with **OT**.	NI	NI	-
	Mantilla-Muriel et al, 2020, Colombia [69]	Cases: OT patients (13 confirmed, two co-infections- and eight unconfirmed cases) Controls: 20 individuals chronically infected with *Toxoplasma* but without ocular involvement.	TLR-9 352,140 C/T did not correlate with characteristic clinical manifestations nor the number of vitreous cells, retinal lesions, lesion size (in disc diameters), and recurrences.	NI	NE	-
NOD2	Dutra et al, 2013, Brazil [128]	Group 1: Asymptomatic with *T. gondii* seropositivity Group 2: Active **OT** with *Tg* seropositivity Group 3: Presumed **OT** with *Toxoplasma* seropositivity Group 4: Asymptomatic with *Toxoplasma* sero negative Familiar relation	*The polymorphism rs2076753 did not show an association with **OT** *The polymorphism rs2111235: did not show an association with **OT** *The polymorphism rs3135499 was associated with **OT**, but the homozygous genotype CC is associated with protection.	NI	They did not identify differences in IFN-γ and IL-2 levels produced by Th1 cells when comparing patients with active ocular toxoplasmosis (AOT) or presumed ocular toxoplasmosis (POT) with asymptomatic individuals. However, an increase in interleukin IL-17A production was observed in patients with POT or AOT. In patients with POT or AOT, the main cellular source of IL-17A was CD4+ CD45RO+ T-bet- IFN-γ- T-helper 17 cells.	-
NALP1	Witola et al., 2011, United States [129]	Cases: Congenital toxoplasmosis	NALP1 rs8081261 and rs11652907 were related to congenital infection	NI	There was no observed upregulation of the proinflammatory cytokines interleukin-1β (IL-1β), IL-18, and IL-12 following T. gondii infection in monocyte cells with NALP1 silencing.	-

(*Continued*)

Table 1. (Continued).

Immune molecule	Author, year, Country (Reference)	Case and control definition	Immunogenetic Findings	Treatment impact	Relation with serum levels	Interest as biomarker in personalized medicine
HLA B35	Demarco et al., 2012, Brazil	Cases: Patients with AIDS and **OT** with *Toxoplasma* IgG positive Controls: Patients with AIDS and *Toxoplasma* IgG positive without **OT**. Recurrence: satellite lesions	*The HLA-B35 and AIDS patients have more risk of **OT** (RR 2.56). *The without HLA-B35 and AIDS patients have less **OT** risk (RR 0.42).	NI	NI	-
MICA	Ayo et al., 2015, Brazil [130]	Cases: **OT** with *Toxoplasma* IgG positive Controls: *Toxoplasma* IgG positive without **OT**. Recurrence: satellite lesions	* The MICA × 002~HLA-B × 35 haplotype increased the risk of **OT** (OR 2.20) but lost significance in the multivariate analysis * The MICA × 008~HLA-C × 07 haplotype decreased the risk of **OT** (OR 0.009) but lost significance in the multivariate analysis * The MICA~HLA-B and MICA~HLA-C haplotypes showed no significant difference comparing primary manifestations and t recurrent manifestations of **OT**.	NI	NI	-
KIR	Ayo et al., 2016, Brazil [131]	Cases: **OT** with *Toxoplasma* IgG positive Controls: *Toxoplasma* IgG positive without **OT**. Recurrence: satellite lesions	*The activation of KIR3DS1 increased the risk of **OT** vs. controls (OR 2,15) and recurrence vs. controls (OR 3.25), but the significance last was lost with the Bonferroni correction. *The activation of KIR2DS2 decreases the risk of **OT** vs. controls (OR 0.55), but the significance last was lost with the Bonferroni correction. *The activation of KIRD and HLA ligands (KIR3DS1-Bw4-80Ile and KIR2DS1+/C2++ KIR3DS1 +/Bw4-80Ile+) increased the risk of **OT** vs. controls (OR 5.56), also related with recurrence of **OT** vs. controls (OR6.50) *The inhibitors of KIRD and HLA (KIR2DL3/2DL3-C1 /C1 and KIR2DL3/2DL3-C1) decreased the risk of **OT** vs. controls (OR 0.19) and also recurrence vs. controls (OR 0.09) *The KIR3DS1−/KIR3DL1+/Bw4-80Ile+ combination was associated as a protective factor for **OT** vs. controls (OR 0.52), recurrent vs. controls (OR 0.13), and recurrence and primary manifestations (OR 0.20)s.	NI	NI	Future biomarkers for prophylactic therapy. More studies evaluating cytokine levels are needed. Contrasting results with those of Perce da Silva 2023 [132]
	Perce-da-Silva DS, 2023, Brazil [132]	Active case: active toxoplasmic retinochoroiditis according to the criteria described by Holland with anti-*Toxoplasma* IgG positive Recurrence: Active retinochoroiditis associated with a retinal scar in either eye.*n* = 274 patients and 45 of them followed more than 4 years	* KIR2DL2 were related with less frequent recurrence and less progresión of recurrence (HR 0.63) *Possible mechanism through protective effect on T cells enabling longer survival if they carry KIR2DL2 and therefore exert stronger protection	NI	NI	Future biomarkers for prophylactic therapy

NI: No information; NE: Not evaluated; TR:Toxoplasmic Retinochoroiditis; OT: Ocular toxoplasmosis.

17 May 2001regulate Th1-cell-mediated responses in ocular toxoplasmosis [51]. The importance of these cytokines in experimental models of uveitis and encephalitis has been reported. $CD4^+CD25^+$ regulatory T-cells may control the local inflammatory response and protect the host against collateral inflammatory tissue damage. The responses of these cells to ocular infection by *T. gondii* may be suitably tailored to cope with either an acquired or a congenital origin [51]. On the other side, the beneficial or pathogenic roles of the cytokines produced by Th1 and Th17 cells and the protective and homeostatic roles of IL-10, TGF-β, and IL-27 in modulating the hypersensitivity responses induced by *T. gondii* are generally recognized [153]. The IFN-γ and IL-17 cytokines produced by Th1 and Th17 cell responses were analyzed in patients with active ocular toxoplasmosis or presumed ocular toxoplasmosis. The authors found an increased IL-17A production in both groups of individuals, where the main cellular source of IL-17A was CD4(+) CD45RO (+) T-bet (-) IFN-γ (-) T-helper 17 cells [151]. Furthermore, they found that the NOD2 gene influences the production of IL-17A by $CD4^+$ T lymphocytes and might contribute to the development of ocular toxoplasmosis [154].

Regarding other cell populations involved in the immune response inside the eye, it has been found the involvement of neutrophils in retinal inflammation in the setting of ocular toxoplasmosis [155]. Neutrophils generated more reactive oxygen species when co-cultured with infected versus uninfected retinal pigment epithelial cells (ARPE-19 cells) [155]. Infected ARPE-19 cells also induced neutrophils to produce inflammatory cytokines, like TNF-α and IL-1β, but this effect was not replicated in primary cells for TNF-α and proved to be donor-dependent for IL-1β [155]. These results suggested infiltrating neutrophils contribute to retinal damage in ocular toxoplasmosis [64].

Finally, the NK cells have also been involved in the presentation and diagnosis of ocular toxoplasmosis; a recent study found these cells as part of the putative biomarkers for early diagnosis and prognosis of congenital ocular toxoplasmosis [156]. The analysis of *in vitro T. gondii*-specific $IL5^+CD4^+$ T-cells and IFN-γ^+NK-cells displayed a high accuracy for early prognosis of the ocular lesion in infants with congenital toxoplasmosis attaining a global diagnostic accuracy of 0,8 and 0,9, respectively [156]. The authors concluded about the relevance of employing the elements of the cell-mediated immune response as biomarkers with the potential to endorse early diagnosis and prognosis of congenital ocular toxoplasmosis to contribute to precise clinical management and effective therapeutic intervention [156].

In Table 2, we summarize the evidence of T lymphocyte subpopulations; the most striking characteristic of ocular toxoplasmosis patients is that during the active phase of infection, it would be necessary to stimulate CD8+ effector subset cells expressing CD244 to limit the damage caused by inflammation [149]. Contrarily, during the chronic phase, the CD8+ central memory subset expressing CD160+ should be limited [149].

7. Trigger signals for reactivation

Recurrences of lesions are present in patients with ocular toxoplasmosis in 56% in South America, in 46% in Europe and 39% in North America [161]. How a quiescent parasite tissue cyst in the retina becomes active is a central question (and an anguish factor for patients and their families). Some clear conditions that trigger recurrences (or worsening clinical picture) are the use of subconjunctival steroids [162], early initiation of steroids without antiparasitic drug [163,164], pregnancy [165] age [53] and ocular trauma [166]. These triggers are related to an immunosuppressive status like immunosenescence [167] or alteration in the blood-retinal barrier [66], pointing to the critical maintenance of a protective local immune response [64]. We found that

Table 2. CD8+ T lymphocyte subpopulations and exhaustion phenotype in patients with ocular toxoplasmosis.

T cell subpopulations	Normal Activities	Altered cell phenotype in ocular toxoplasmosis	Complementary information	References
CD3+ CD8+ effector T cells (CD45RA +CCR7−)	Production of cytokines such as IFN-γ and tumor necrosis factor (TNF)-α and/or cytolytic mechanisms (1). Functional effector T cells can transiently express inhibitory receptors during activation (2).	Lower intensity (MFI) of the exhaustion marker CD244 (2B4 inhibitory receptor) in most of the ocular patients compared with uninfected individuals (3).	Intensity of exhaustion markers correlated negatively with more severe clinical characteristics (3). Exhaustion phenotype during active infection and memory T-cell response is necessary to limit microorganisms ocular damage and inflammation (4).	1 [157] 2 [158] 3 [149] 4 [159]
Central memory T cells (T cm) (CD3+CD8+ CD45RA-CCR7 +)	Memory cell subpopulation that can recirculate through secondary lymphoid organs and function as a reservoir of antigen-specific T cells (5).	Higher percentage of CD160+ cells (exhaustion marker) in individuals with ocular lesions (3).	The majority of OT patients had a total exhaustion phenotype mediated by increased CD160 expression (3). Increased CD160 expression was related to cytokine unresponsiveness in ocular toxoplasmosis (3).	3 [149] 5 [160]
Effector memory T cells (Tem) (CD3+CD8+ CD45RA- CCR7-)	Cells that recirculate between the blood and the body and can respond rapidly against reinfection by producing effector cytokines (4).	High percentage of PD1+ cells (inhibitory receptor) in ocular patients compared to uninfected patients (3).	T-cell exhaustion phenotype is heterogenous within the group with ocular toxoplasmosis (3). PD-1 expression is necessary during active infection to control parasite damage (3).	3 [149] 4 [160]

drinking boiled water, a protective factor against reinfection, was associated with a lower rate of recurrences [168]. Secondary infection with a different strain can lead to a superinfection status where CD8 T cell IFN-γ response is impaired [169]. The risk of recurrence is higher immediately after an active episode with a clustering pattern [66,170,171]. [165,170]

In our opinion, based on the physiopathological factors involved in this disease, ocular toxoplasmosis should always be treated with a combination of steroids and antiparasitic drugs, even for small lesions, because at the moment it is not possible to predict who or when an individual with ocular lesions will have recurrences [66,162]. The steroids reduce the time to clearance of the vitreous and enhance lesion size regression, shortening the time for visual recovery [172]. In turn, antiparasites will inhibit parasite replication, limiting additional tissue damage and probably potentializing the host immune response by limiting the production of parasite virulence factors [173,174]. The lack of evidence of efficacity of antiparasites in ocular toxoplasmosis is because not appropriate outcome have been defined to evaluate the benefit of therapy, thus antiparasite treatment should be given with the aim of reducing the risk of recurrences after treatment [171,172,175].

8. Implications for current and next-generation treatments

The understanding of the role of different cells of the immune system to control invasion and permanence of the parasite within the cells of the retina has illuminated the search for new therapeutic strategies improving the efficacity of the antibiotics traditionally used to treat the active disease or reduce recurrences [32,176,177]. A potential therapeutic target is studying and understanding inflammatory pathways and cytokine networks [64,177]. Blocking inflammatory molecules may help arrest excessive inflammation and subsequent retinal damage [94,105]. However, much remains to be discovered in this intricate mechanism that becomes even more complicated if we consider the characteristics of the eye as an immunologically privileged organ [148,178]. The crucial cytokine defending the host retinal cells against *T. gondii* is IFN γ [145]. But, the potential activation of other IFNs like the type I (α and β) or type III (λ) pathways are also under study [111]. However, some *in vitro* results show that inhibition of type I IFN can be beneficial [179]. The apparent contrary effect of cytokines in different *in vitro* and *in vivo* models of infection can be explained by considering that the positive or detrimental effect of one given cytokine depends on the stage of the infection and the fine-tuning of their levels [153,180]. Additionally, while targeted cytokine inhibitors can mitigate tissue destruction mediated by higher cytokine production, cytokine-targeted therapeutics' effectiveness is difficult to predict due to disease heterogeneity [181]. To establish the IFN type, the stage of the infection will be beneficial, and the clinical criteria to be applied is critical for future immune therapies [181].

The IL-17 axis, as a potent inflammatory agent in ocular toxoplasmosis, leading to severe inflammation and subsequent tissue damage, is, in theory, an attractive target for inhibitory antibodies [95,105,152]. Currently, several available therapies, particularly monoclonal antibodies like ixekizumab, brodalumab, and secukinumab, that target the IL17 pathway, are being evaluated or used to treat autoimmune diseases such as psoriasis [182,183], ankylosing spondyloarthritis [184] and ustekinumab targeting the IL-23/IL-17 axis used in psoriatic arthritis, Crohn's disease, and uveitis [185]. However, the potential use of these medications in controlling intraocular inflammation secondary to *T. gondii* has not been studied. The possible side effects of these therapies in this parasitic infection are unknown, especially in patients infected with virulent strains that downregulate the IL17 secretion and yet present severe tissue damage [68].

Targeting other molecules like IL6, a pleiotropic cytokine involved in the inflammatory process, including intraocular inflammation, using monoclonal antibodies such as tocilizumab could offer alternative therapeutic options [186–188].

The role of therapies targeting different molecules, such as IL-5 and growth factors (VEGF, FGF, PDGF-β), that have been related to a higher number of recurrences and more lesions must be elucidated [85]. Anti-IL-5 is used to treat eosinophilic asthma and anti-VEGF as antiangiogenic therapy [189]. Nevertheless, the role of these therapies in ocular toxoplasmosis has not been explored.

While these medications may alleviate inflammation, their effectiveness as antiparasitic agents is not their main activity. Therefore, proper antiparasitic drugs should be included in all these potential treatment regimens. Nonetheless, immune-based treatments could be promising in inducing an appropriate response to prevent tissue damage, reduce recurrences, and hopefully, in the future, limit parasite growth [32].

9. Expert opinion

Altogether, the data from eye fund screening and from outbreaks with ocular involvement in different continents and geographical areas (such as India, Canada, United States, Colombia, or Brazil) point to a risk of ocular involvement that can be manifested months after primary infection in around one-tenth of infected people. Some genetic polymorphism exists linked to the susceptibility to develop an ocular episode, especially the + 874 nucleotide of the promotor for IFN γ (SNP rs24305619). Still, it has not been evaluated for use in routine practice. Additional polymorphisms should be explored as biomarkers for recurrence (IL-1α −889 C/T; and IL-10 -1082A/G) and their use as criteria to establish antiparasite prophylaxis. More robust evidence is needed regarding the necessity of treatment of primary infection to reduce the development of ocular toxoplasmosis and a separate risk of later development of mental disease. However, on the precaution principle, in our opinion, we recommend treating acute acquired toxoplasmosis, yet clinical trials are necessary to validate this recommendation for all geographical areas. Although our understanding of the underlying causes of ocular toxoplasmosis has improved, many unanswered questions remain. The complete mapping of the immune response has yet to be entirely recognized.

The ideal in the future is to find an antibiotic that will penetrate cysts containing bradyzoites in the intraocular tissues, which has not been possible until now. Treatments with molecules that block inflammatory pathways can be adjuvant treatments, but the essence of curative treatment is the elimination of tissue cysts. Multiple tests have been proposed by *in vitro* and animal models, but in real life in patients infected with *Toxoplasma gondii*, it has not been possible to eradicate the parasites encysted in the retina that remain latent for the host's entire life.

Funding

This paper was not funded.

Declaration of interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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Acknowledgments

To all our patients, who are also part of the research team and altruistically participated and contributed with their information, clinical samples, and support without awaiting an immediate benefit but always hoping for a future benefit for them and others. To Dr. William Rojas Carabali for help in Figures elaboration.

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