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ORIGINAL ARTICLE

The emerging role of interleukin (IL)-1 in the pathogenesis and treatment of inflammatory and degenerative eye diseases

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Abstract Interleukin (IL)-1 plays a key role in the pathogenesis and thereafter in the search for specific treatments of different inflammatory and degenerative eye diseases. Indeed, an overactivity of IL-1 might be an initiating factor for many immunopathologic sceneries in the eye, as proven by the efficacy of the specific IL-1 blockade in different ocular diseases. For instance, the uveitis in monogenic autoinflammatory disorders, such as Blau syndrome and cryopyrin-associated periodic syndrome, or in complex polygenic autoinflammatory disorders, such as Behçet's disease, has been successfully treated with IL-1 blockers. Similarly, therapy with the IL-1 receptor antagonist anakinra has proven successful also in scleritis and episcleritis in the context of different rheumatic conditions. Moreover, interesting findings deriving from animal models of ocular disease have set a rational basis from a therapeutic viewpoint to manage patients also with dry eye disease and a broadening number of ocular inflammatory and degenerative conditions, which start from an imbalance between IL-1 and its receptor antagonist.

Keywords Diabetic retinopathy · Dry-eye · Keratitis · Macular degeneration · Scleritis · Uveitis

Introduction

Other than being single entities, ocular disorders may cover a small sector of a bigger picture complicating systemic inflammatory diseases. Patients affected by rheumatologic disorders frequently complain about ocular symptoms, including red and dry-eye, foreign-body sensation, pruritus, pain, photophobia, and visual impairment that sometimes result in a complete vision loss. A multitude of structures involving episclera, sclera, ocular adnexa, corneal, and uveal tissues can be subject to an irreversible damage. Ophthalmic complications might be either disease-related or treatment-related as in the case of chloroquine, hydroxychloroquine, corticosteroids, and bisphosphonate administration [1]. A careful ophthalmologic examination is the starting point for an accurate early diagnosis and prompt or adequate treatment to preserve visual function [2]. What makes the eye a unique site is its immune-privileged background designed to maintain tolerance and protection against exogenous agents. In this regard, several mechanisms cooperate to create a favorable immune privilege: (i) principally the absence of bold and lymphoid vessels, (ii) the anterior chamber-associated immune deviation, that controls the proinflammatory milieu, and (iii) retinal protection identified in phagocytosis of damaged receptors and retinal pigment epithelium, which also construct the retina-blood barrier [1].

Given the deleterious ocular and systemic side effects of glucocorticoid therapy and development of novel, effective,

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relatively safe and more targeted biotherapies, it is possible that eye involvement in many rheumatologic disorders might take advantage from these new bioengineered molecules. Interleukin (IL)-1 blockade has provided interesting and promising results in both preclinical or experimental animal models of different ocular inflammatory diseases [3–5] and also from case series [6] or clinical trials [7, 8].

IL-1 is the prominent cytokine implicated in the pathogenetic mechanisms of inflammatory diseases ranging from autoinflammatory disorders (AIDs) to diabetes and ischemic heart disease [9]. Significant higher levels of IL-1 family, involving IL-1β, IL-1 receptor antagonist (Ra), IL-37, and IL-36Ra, have been demonstrated in the aqueous humor of subjects with human leukocyte antigen (HLA)-B27-associated acute anterior uveitis (AAU) compared to idiopathic AAU or control groups. Except for IL-18 levels, all other IL-1 family members showed a marked difference between serum and aqueous humor levels in favor of the latter, suggesting a specific intraocular immune response in HLA-B27-associated AAU or, at least, a more severe intraocular inflammatory phenotype [10]. Severe uveitis may recognize a possible role of in situ secretion of IL-1β in the retina by dendritic cells, macrophages, and neutrophils, indicating the relevance of IL-1 signaling in experimental autoimmune uveitis**.** The authors suggested the potential therapeutic protagonism of IL-1 blocking agents for uveitis as well as for other ocular inflammatory diseases [11]. Interestingly, a substantial impact of IL-1 was also hypothesized in age-related macular degeneration (AMD), as shown by a dose-dependent reduction on neovascular choroidal area in a rodent model of laser-induced choroidal neovascularization during intravitreal treatment with anakinra (ANA), the recombinant IL-1 receptor antagonist [12].

We herein discuss about the role of IL-1 blockade in several ophthalmologic conditions related and unrelated to a host of systemic inflammatory disorders.

The search engine PubMed was employed to retrieve the most suitable papers written in English using the following terms: "anakinra," "canakinumab," or "gevokizumab" each combined with "uveitis," "scleritis," "keratitis," "episcleritis," "diabetic retinopathy," and "age-related macular degeneration." Relevant data were selected and rearranged according to the predetermined structure of the manuscript.

Uveitis

Ocular middle layer inflammation should be carefully evaluated in patients affected by any kind of uveitis due to its potential short- and long-term complications that may determine a severe visual impairment. Macular edema, epiretinal membrane, cataract and glaucoma are, in fact, events that may often complicate the clinical scenario and impair visual acuity. As a matter of fact, uveal inflammation can accompany several systemic diseases, including juvenile idiopathic arthritis, sarcoidosis, multiple sclerosis, connective tissue disease-associated vasculitis, and Vogt-Koyanagi-Harada disease [39]. In addition, the expanding group of monogenic autoinflammatory disorders (AIDs) has also been associated with uveitis. In particular, AIDs represent a class of inherited conditions characterized by seemingly unprovoked recurrent inflammatory episodes in the absence of pathogens, autoreactive T cells and autoantibodies [40]. Blau syndrome (BS), also called early-onset sarcoidosis (EOS) in its sporadic variant, displays a clinical diversity that often outbreaks with atypical or incomplete manifestations if compared to the classic triad characterized by joint, skin and eye stigmata. In 2007, based on their findings, Aróstegui et al. proposed IL-1 as a central cytokine involved in BS pathogenesis. They reported a clinical improvement after administering ANA in one patient affected by BS with severe uveitis refractory to systemic corticosteroids; plasma levels of proinflammatory cytokines were also normalized under ANA treatment [13].

Ocular involvement in BS can be overwhelming and particularly resistant to conventional treatments. Simonini et al. described one case of severe complicated panuveitis nonresponsive to corticosteroids, immunosuppressants (mycophenolate mofetil), adalimumab, infliximab, and abatacept. In this case, the human monoclonal antibody targeting IL-1® canakinumab (CAN), at the monthly dosage of 2 mg/kg, prevented ocular flares without the need of pulse steroid therapy; the drug also influenced gene expression profile, as the upregulated innate immunity gene transcripts were normalized only after the first CAN injection [14].

Genetic and pathogenic findings have provided the biologic rationale to antagonize IL-1 in another autoinflammatory condition named "chronic infantile neurologic cutaneous articular (CINCA) syndrome" [41]. Despite having conjunctivitis as a main ocular feature, CINCA patients may sometimes display severe ocular manifestations, such as corneal infiltrates or uveitis [15, 42]. Daily injections of ANA (1 mg/kg/day) or regular CAN injections (150 mg given subcutaneously every 6 weeks) have shown to rapidly and strikingly determine a compelling clinical improvement in all disease manifestations, including ophthalmologic signs like conjunctivitis, corneal infiltrates, uveitis and refractory bilateral panuveitis [15, 16]. However, posologic adjustments should be contemplated for an optimal IL-1 blockade since standard doses of CAN may inadequately control disease activity in the most severe CINCA patients [43] (Table 1).

Behçet's disease (BD), after being historically cataloged as a separate nosographic entity, has now been recently classified among AIDs as a complex polygenic and multifactorial systemic condition [44]. Although many BD cases are well-managed with standardized therapies, unresponsive or difficult-to-treat patients represent a tough challenge in the rheumatologic and ophthalmic clinical practice, especially if

Table 1 Interleukin-1 inhibition in uveitis associated with different systemic inflammatory disorders

	Anti-IL-1 agent	Type of eye involvement	Outcome measures	Study design
Aróstegui et al. [13]	ANA (3 mg/kg daily)	Refractory U of BS (4 PU and 3 AU), other ocular manifestations[b]	Clinical evaluation and BCVA, blood samples prior and after ANA administration to measure IL-6, TNF, and IL-1β	Retrospective analysis of BS: cohort of 12 patients
Simonini et al. [14]	CAN (2 mg/kg monthly)	Severe PU of BS with retinal detachment	Clinical evaluation and gene expression profile before CAN and monthly thereafter for 5 months	Case report
Teoh et al. [15]	ANA (1 mg/kg daily)	Bilateral PU in CINCA syndrome	BCVA, OCT findings, resolved vitritis and disk swelling	Case report
Hirano et al. [16]	CAN (150 mg subcutaneously every 6 weeks)	Monolateral recurrent stromal keratitis and anterior uveitis in CINCA syndrome	BCVA, fundus examination, OCT findings	Case report
Gül et al. [17]	Gevokizumab (0,3 mg/kg as a single intravenous infusion; second same dosage in case of relapse)	BD-related uveitis (7 acute posterior uveitis or PU and/or RV)	SLEx followed by fundus photography; laser flare photometry for anterior chamber flare scored by SUN working group grading scheme and Ben Ezra et al. scoring system for retinal findings.	Open-label pilot study
Tugal-Tutkun et al. [18]	Gevokizumab (3 regimens for acute patients and 3 regimens for at-risk patients[a])	BD-related uveitis (18 PU, 3 posterior uveitis)	BCVA, SLEx, indirect ophthalmoscopy for vitreous haze, retinal infiltrates and retinal vasculitis; BenEzra scoring system for retinal findings	Prospective, open-label, randomized, parallel group, phase 2 multicenter trial
Ugurlu et al. [19]	Unresponsive to ANA, CAN single infusion of 150 mg	BD (bilateral PU with hypopyon, RV)	BCVA	Case report
Emmi et al. [20]	ANA (100 mg/daily)	BD (bilateral RV, bilateral vitritis)	BCVA, FA	Case report
Caso et al. [21]	ANA (100 mg/daily)	BD (severe bilateral PU with RV)	CR	Case report
Vitale et al. [22]	CAN (150 mg every 6 weeks)	BD (AU in one patient and monolateral PU in another)	CR	Case series
Emmi et al. [23]	CAN (150 mg/8 week)	BD (bilateral RV)	CR	Case series
Cantarini et al. [6]	ANA (100 mg/day) ANA (150 mg/day) (case 1) CAN (150 mg/8 weeks)	BD (1 RV, 1 bilateral PU and papillophlebitis, 2 AU)	Ophthalmologic evaluation (case 1,4,5,9) and CR	Case series
Emmi et al. [24]	ANA (100 mg/day subcutaneously)	Acute papillitis	BCVA	Case report
Emmi et al. [25]	ANA (100 mg/day) ANA (150 mg/day) CAN (150 mg/8 weeks) CAN (150 mg/6 weeks)	BD-16/30 (8 PU, 3 posterior uveitis, 2 AU, 1 retinitis, 1 papillitis, 1 intermediate uveitis)	CR	Multicenter retrospective study
Brambilla et al. [26]	CAN (2 mg/kg monthly)	JIA-related recurrent uveitis and intermediate idiopathic uveitis	BCVA, IOP, OCT findings	Case series

List of abbreviations: *ANA* anakinra, *CAN* canakinumab, *BS* Blau syndrome, *CINCA syndrome* chronic infantile neurologic cutaneous and articular syndrome, *BD* Behçet disease, *JIA* juvenile idiopathic arthritis, *U* uveitis, *AU* anterior uveitis, *PU* panuveitis, *RV* retinal vasculitis, *CR* clinical response, *BCVA* best corrected visual acuity, *OCT* optical coherence tomography, *FA* fluorescein angiography, *IOP* intraocular pressure, *SAA* serum amyloid-A, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *IL* interleukin, *TNF* tumor necrosis factor, *SUN* Standardization of Uveitis Nomenclature, *SLEx* slit lamp examination

[a] For acute patients, the three regimens were (1) 60 mg IV gevokizumab at entry, 30 mg IV at time of response, and then 30 mg SC every 4 weeks thereafter; (2) 30 mg IV gevokizumab at entry, 30 mg IV at time of response, and then 30 mg IV every 4 weeks thereafter; and (3) 60 mg IV gevokizumab at entry, 60 mg IV at time of response, and then 60 mg SC every 4 weeks thereafter; for risk-patients, the three equivalent regimens were (1) 60 mg IV gevokizumab at entry and then 30 mg SC every 4 weeks thereafter; (2) 30 mg IV gevokizumab at every visit; and (3) 60 mg IV gevokizumab at entry, and then 60 mg SC every 4 weeks thereafter

[b] Recurrent bilateral conjunctivitis, synechiae, bilateral granulomas, cataract and severe refractory ocular hypertension

severe eye involvement is present. Encouraging clinical outcomes of IL-1-suppression in BD-related uveitis have widened the therapeutic armamentarium for BD and offered a great alternative in refractory cases [6, 17, 18, 25]. Gevokizumab, a regulatory therapeutic antibody that modulates IL-1β bioactivity by reducing the affinity for its IL-1RI/IL-1RAcP signaling complex, was the first anti-IL-1 agent to demonstrate efficacy in severe resistant uveitis and retinal vasculitis in an open-labeled pilot study. Moreover, a sustained clinical response was granted despite discontinuation of traditional immunosuppressive drugs [17]. These results were confirmed by an exploratory phase 2 open-label randomized multicenter study; additionally, the need for high-dose corticosteroids was avoided and an impressive safety profile reported no drug-related adverse events [18]. Also, other anti-IL-1 blocking agents like ANA and CAN have proved to be effective in treating BD-related uveitis. In this context, during the last 5 years, several case reports and small case series have been published, all showing a promising result for IL-1® blockade [6, 19–23]. IL-1 targeting molecules have been even administered as first-line biologic therapy in one patient with BD-related acute papillitis and concomitant latent tuberculosis [24]. Of note, infections like tuberculosis restrict biotherapy alternatives, particularly in geographic areas where it still represents an unresolved and diffuse sanitary problem with a considerable social and economic impact. In this respect, anti-IL-1 agents might be a safer option [45]

From a clinical point of view, one of the most interesting studies and, at the same time, the largest in terms of sample size, gave a substantial contribute to this topic. In this retrospective multicenter study, 30 patients receiving ANA or CAN were analyzed to assess efficacy and safety profile of these two drugs. More than half of them had ocular involvement (8 panuveitis, 3 posterior uveitis, 2 anterior uveitis, 1 intermediate uveitis, 1 retinitis, 1 papillitis). Impressive findings on safety recorded only 4 site-injection reactions in ANA-treated patients and no adverse events (AE) for CAN as well as no serious AE for both drugs. Additionally, a good drug retention rate was reported according to the Kaplan-Meier plot. With regard to the optimal dosage, new conceptual aspects emerged: in case of initial inefficacy of ANA, increasing the dose to 150 mg/day could be taken into account before switching to other biologic agents; furthermore, switching to CAN and, in case of incomplete response, shortening the interval between CAN injections from 8 to 6 weeks could be also another valid alternative [25]. More recently, we have evaluated the role of IL-1 inhibitors ANA and CAN in the treatment of BD-related uveitis in a multicenter retrospective observational study. Nineteen BD patients (31 affected eyes) receiving treatment with anti-IL-1 agents were included in the study. At 12 months, intraocular flares significantly decreased from 200/100 patients/year to 48.87/100 patients/year ($p < 0.0001$). The frequency of retinal vasculitis significantly decreased between baseline, 3- and 12-month follow-up evaluations ($p < 0.0001$ and $p = 0.001$, respectively). Moreover, steroid dosage was significantly decreased at 12-month visit compared to baseline ($p = 0.02$). Data from our study showed that treatment with IL-1 blockers ANA and CAN is effective in the management of BD-related uveitis and provides a long-term control of ocular inflammation in refractory and long-lasting BD cases [46].

CAN has also been employed in juvenile idiopathic arthritis-related uveitis and in idiopathic uveitis occurring in pediatric patients. Successful results were granted by achievement of ocular remission with vision improvement and a fine corticosteroid-sparing effect [26]. This drug is thereby proposed as a newer therapeutic option in sight-threatening uveitis refractory to other biologic drugs [14, 26].

With regard to animal models, a couple of studies have supplied interesting findings. Lentiviral vectors containing cDNAs for murine (m) IL-1Ra or mIL-10 were injected into the ocular anterior chamber and effectively treated experimental models of endotoxin-induced uveitis with a significant lower inflammatory cell count and a better preservation of blood-ocular barrier, as demonstrated by a lower aqueous total protein content. A single administration of lentiviral-mediated gene transduction is potentially able to maintain an inflammatory suppression state over recurrent episodes of uveitis [4]. In the context of gene therapy, intravitreal injection of recombinant adeno-associated virus vector encoding IL-1Ra led to a sustained transgene expression in New Zealand white rabbits and a subsequent control of relapse number [5]. This gene therapy acted as an alternative anti-inflammatory treatment. In addition, intraocular delivery of immunomodulatory genes did not interfere with the systemic immune state [4]. These intriguing pathogenetic findings suggest a potential role of IL-1, mainly produced by retinal myeloid cells, in uveitis: targeting IL-1 might prove to be substantially beneficial not only for uveitis, but also for other ocular inflammatory diseases [11, 47](Table 2).

Keratitis

Keratitis presents with ocular pain, red eye, or reduced vision and frequently leads to corneal opacification and thinning or ulceration and sometimes perforation. With regard to rheumatologic disorders, it is typically associated with rheumatoid arthritis [1]. However, keratitis has been also described in different AIDs. Cryopirin-associated periodic syndrome (CAPS) refers to a group of dominantly inherited disorders with three levels of severity, where familiar cold autoinflammatory syndrome (FCAS) and CINCA syndrome lie at the mildest and most severe extremities, respectively. Despite having conjunctivitis as a main ocular feature, an accurate examination can unravel a more serious eye

Table 2 Interleukin-1 inhibition in ocular diseases other than uveitis

	Anti-IL-1 agent	Type of eye involvement	Outcome measures	Study design
Amparo et al. [7]	Topical ANA 2,5%, or 5% 1 drop 3 times daily or vehicle (1% carboxymethylcellulose)	Refractory DED in 75 patients	CFS for corneal epitheliopathy evaluation, proportion of patients achieving complete bilateral CFS clearance after treatment. OSDI for DED-related symptoms. Tear film BUT, VA, Schirmer test	Prospective phase 1/2 randomized double-masked vehicle-controlled clinical trial
Goldstein et al. [8]	Isunakinra (5 mg/mL, 20 mg/mL 1 drop 3 times daily or placebo)	Moderate to severe DED in 74 subjects	BCVA, (SLEx), dilated and undilated ophthalmoscopy, corneal esthesiometry, corneal pachymetry, conjunctival cultures, PK parameters and immunogenicity, CFS and OSDI; Safety measures: AEs reporting, laboratory studies, electrocardiogram (ECG)	Randomized prospective double-masked phase 1a/2b study
Goldstein et al. [27]	Topical EBI-005 Isunakinra (5 mg/l, 3 times daily in blow fill units of 0,3 ml or placebo)	159 moderate to severe allergic conjunctivitis	CAPT, EEC and clinical assessment of ocular itching, ocular tearing and associated nasal symptoms on a 4-point descriptive scale; conjunctival redness and lid swelling on a 5-point scale, follicular/papillary response on a 4-point scale; chemosis and mucous discharge (0 = absent; 1 = present)	Randomized double-blind vehicle-controlled study
Botsios et al. [28]	ANA (100 mg/daily)	RA-related AS (2 diffuse anterior left eye scleritis with development of necrotizing areas and blurred vision in one case)	CR, BCVA	Report of 2 cases
Knickelbein et al. [29]	Gevokizumab (60 mg s.c at baseline and then every 4 weeks)	Eight autoimmune non-infectious non-necrotizing AS (2 with systemic diseases: 1 RA and 1 SLE + Sjögren's syndrome)	BCVA, intraocular pressure, SLEx, funduscopy, standardized scleral photographs, complete blood count with differential, basic metabolic panel, urine pregnancy testing in female participants, vital signs, concomitant medication assessment and urinalysis	Phase 1/2 open label non-randomized prospective single-arm pilot trial
Lequerré et al. [30]	ANA (100 mg/daily)	Three episcleritis out of 4 and 3 papilledema out of 4	Close monitoring of clinical, biochemical and hematological parameters	Case series (family with CAPS)
Espandar et al. [31]	CAN (50 mg s.c every 8 weeks)	Three keratitis in FCAS	CR, BCVA, SLEx	Small case series
Alejandre et al. [32]	ANA (dosage not reported)	MWS-related keratitis	CR, inflammatory markers, SLEx	Concise report
Terrada et al. [33]	ANA (2 mg/kg/day) s.c	Bilateral anterior nummular SK with concomitant bilateral papilledema in CINCA syndrome	CR, inflammatory markers, fundus examination, SLEx	Case report
Hirano et al. [16]	CAN s.c 150 mg every 6 weeks	Monolateral recurrent SK and anterior uveitis in CINCA syndrome	BCVA, fundus examination, OCT findings	Case report

List of abbreviations: *ANA* anakinra, *CAN* canakinumab, *DED* dry eye disease, *CFS* corneal fluorescein staining, *OSDI* ocular surface disease index, *BUT* breakup time test, *BCVA* best corrected visual acuity, *AEs* adverse events, *ECG* electrocardiogram, *SLE* systemic lupus erythematosus, *PK* pharmacokinetic, *CAPT* conjunctival allergen provocation test, *EEC* environment exposure chamber, *CR* clinical response, *RA* rheumatoid arthritis, *FCAS* familial cold autoinflammatory syndrome, *MWS* Muckle-Wells syndrome, *CINCA syndrome* chronic infantile neurologic cutaneous and articular syndrome, *s.c* subcutaneously, *OCT* optical coherence tomography, *SLEx* Slit lamp examination, *AS* anterior scleritis, *SK* stromal keratitis

involvement in some cases, like uveitis and keratitis [32]. In 2014, Espandar et al. reported three FCAS cases with anterior stromal white blood cell infiltration and bilateral central stromal corneal scarring; treatment with CAN stabilized these lesions with no active corneal infiltrate on the following ophthalmic examinations [31]. A concise report described a family with CAPS diagnosed after an ophthalmic evaluation: patients reported a history of keratitis and uveitis and exhibited reticular mid-stromal corneal changes without significant opacification in one case and bilateral central corneal opacification in the other two; two of them started treatment with ANA, which culminated with a complete remission. Interestingly, the authors found a heterozygous germline p.R260W mutation in the *NLRP3* gene and stated that this mutation was associated with high-risk ophthalmic involvement and potential visual loss [32]. IL-1 neutralization was shown to be effective in a young girl diagnosed with CINCA syndrome having an important ocular picture, with the following characteristics: bilateral anterior nummular stromal keratitis (SK) and bilateral papilledema. A remarkable improvement was recorded not only for joint pain and headache, but also for ocular manifestations after 6 months under ANA [33]. Hirano et al. have recently described one case of CINCA-related SK with concomitant anterior uveitis, successfully treated with CAN: antagonizing IL-1β proved to be highly and rapidly effective for all disease-related manifestations. However, the authors noted the lack of awareness for this rare disorder and the consequent diagnostic delay that can result in irreversible damages [16]. Of note, IL-1 has been suggested as a trustworthy target even in infectious SK. In fact, experimental animal models with transgenic mice overexpressing IL-1Ra showed marked resistance to herpetic SK compared to IL-1Ra$^{-/-}$ and control groups. The beneficial effects were thought to originate from a minor polymorphonuclear leukocyte invasion due to reduced chemiotactic signaling, as revealed by low IL-6 and macrophage-inflammatory protein-2 levels in corneal extracts. Levels of vascular endothelial growth factor were also lower in the IL-Ra transgenic mice group. This anti-angiogenetic molecule provided less neovascularization, a crucial step in SK pathogenesis [3]. Proinflammatory cytokines generated in the context of infectious keratitis, especially of bacterial nature, may directly or indirectly contribute to corneal ulcerations through stimulation of polymorphonuclear chemotaxis and activation of tissue-damaging enzymes. In fact, upregulation of IL-1β and downregulation of IL-1Ra play active roles in corneal disease severity induced by *Pseudomonas* strains. Based on their findings, Thakur et al. suggested a potential therapeutic role of recombinant IL-1Ra (rIL-1Ra) in bacterial keratitis. In their acute experimental *Pseudomonas aeruginosa* keratitis, particularly with invasive strains, injected with subconjunctival rIL-1Ra before infection, it was found a remarkable reduced cellular infiltration [48]. Overall, these encouraging findings may indicate the start of a new road for the treatment of this relevant worldwide cause of blindness.

Scleritis and episcleritis

The clinical experience with ANA in the treatment of scleritis is limited to a few reported papers [28, 29]. Different systemic inflammatory disorders such as rheumatoid arthritis, granulomatosis with polyangiitis, Sjogren's syndrome, and spondyloarthropathies can exhibit ocular involvement, especially non-infectious anterior scleritis, a well-recognized severe and potentially sight-threatening manifestation requiring systemic corticosteroids and corticosteroid-sparing therapy with disease modifying antirheumatic drugs or biologic agents. Given its elevated serum levels in diffuse anterior scleritis, IL-1β, among several cytokines, has been implicated in the immunopathogenetic pathways of non-infectious scleritis [29].

Two patients with a history of rheumatoid arthritis affected by diffuse anterior scleritis were successfully treated with ANA after inefficacy of infliximab in one case and a suspected paradoxical response to etanercept in the other one, considered by the authors as possible rare AE. Despite achieving a rapid clinical response with marked amelioration of ocular inflammation following ANA, one patient experienced a relapse upon dose reduction. Considering its short half-life, the posologic scheme required a regular and constant daily compliance [28]. In a phase 1–2 prospective nonrandomized single-center study performed in eight patients suffering from acute non-necrotizing non-infectious anterior scleritis, the majority of eyes met the primary endpoint (78% of response rate) ending up to a clinically meaningful improvement of scleritis. With regard to the safety profile, non-serious AE were reported and 86% of AE were not attributed to IL-1- inhibition [29]. Scleral inflammatory episodes may often be consequence of recurrent disseminating episcleritis. For this reason, episcleral phlogistic events should not be overlooked. In this context, ANA has been administered in two family members affected by atypical form of CAPS with joint destruction, unusual neurologic signs, livedo, episcleritis, and papilledema: this therapy granted timely high and sustained effectiveness by regressing or controlling all manifestations, except for episcleritis in the proband [30].

Dry-eye disease

The Dry Eye workshop defined dry eye as a multifactorial disease of tears and ocular surface, which results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. Tear hyperosmolarity

lies at the pathogenetic crossroad, causing a secondary ocular surface inflammatory response with a well-known signaling pathway involving MAPK and NF-kB, ultimately leading to the generation of proinflammatory cytokines, among which IL-1 holds the way. Despite etiology, intrinsic or extrinsic evaporative dry eye, Sjögren syndrome (SS)-related dry eye or dry eye unrelated to SS, surface inflammatory events are now universally accepted and considered as the turning point in dry eye disease (DED) pathogenesis [49]. Therapeutic alternatives for DED are poor: long-term topical corticosteroid use has a sight-threatening risk of cataract, glaucoma, and infections, while topical cyclosporine A is marked by slow onset of action, tolerability problems, and only partial effectiveness in some patients [34, 50]. Fortunately, interesting findings have set a rational basis from a therapeutic viewpoint [51–53]. In 2001, Solomon et al. hypothesized a key-function disclosed by IL-1 in the keratoconjuctivitis sicca, providing evidence of a consistent association between DED and increased tear fluid levels of IL-1α and mature IL-1β. Even though showing an increase in IL-1Ra levels in the same analyzed specimens, compared to normal controls, IL-1Ra/IL-1α and IL-1Ra/IL-1β ratios were found significantly lower in both DED groups and in patients with meibomial gland dysfunction, respectively [51]. IL-1Ra expression might be an endogenous defensive mechanism, necessary to counteract IL-1 effects in the epithelium of unwounded cornea and in stromal cells after corneal damage [52]. The significantly increased tear levels of IL-1Ra, IL-6, and epidermal growth factor have also encouraged authors to suggest their use as potential biomarkers, especially in moderate forms of evaporative-type DED, where signs do not strongly correlate with symptoms [53]. Promising results were also obtained in an experimental DED mice model with topical IL-1 blockade. Topical formulation containing 5% IL-Ra granted a remarkable decrease in corneal fluorescein staining (CFS), lymphatic growth, central CD11b + cell count and IL-1β expression. Given the effect on CD11b + cells, IL-1Ra might modulate corneal immune response even in other diseases like herpes keratitis and graft rejection [34]. A double-blind randomized prospective trial conducted in patients with meibomian gland dysfunction demonstrated a significant amelioration of corneal epitheliopaty and DED-related symptoms measured with CFS and ocular surface disease index (OSDI) respectively, following treatment with topical IL-1Ra. Despite being employed in 2 different regimens (one with 2,5% ANA and the other with 5% ANA, each 1 drop 3 times daily for 12 weeks), the 5% ANA did not provide additional benefits, implying an optimal pharmacokinetic effect with both concentrations, thereby encouraging the use of lower doses. Moreover, the formulation with higher concentration demands anionic excipients to prevent aggregation and consequently precipitation. The authors also found no influence on intraocular pressure, which is a possible side effect of corticosteroids topical treatment [7]. Since the site of administration is peculiar, several considerations need to be made for the topical biotherapy including pharmacokinetics, agent size and thermal stability, the last being fundamental for treatment compliance. Hou et al. designed a topical formulation that optimizes its pharmacokinetics in terms of clearance and interval between doses, developing a chimera molecule by fusing sequences from IL-1β and IL-1Ra based on their specific receptor affinity. More specifically, site A of IL-1Ra has an affinity 300 fold greater than IL-1β to bind to D1 and D2 domain, while IL-1β, on the other hand, possesses on its B site a 200 fold greater affinity. By combining site A of IL-1Ra with site B of IL-1β, several chimeras were developed. Among different antagonists, 93:60 exhibited much greater affinity for IL-1R1 and its IC_{50} was the lowest among antagonists. The dissociation rate constant was also lower with subsequent increase of its half-life, almost 5 fold (31 h for 93:60 compared to the 6.4 h half-life of IL-1Ra). In other terms, 93:60 was more potent than ANA at reducing corneal staining as well as bringing a substantial improvement on its thermal stability [54]. Formerly known as EBI-005, this engineered protein, now called isunakinra, has been very recently tested in a phase 1a-2b multicenter double-blinded environment trial, where 74 subjects with DED were randomized to either placebo or isunakinra at 5 mg/ml or 20 gm/ml. Isunakinra, a 17.7 kDa protein chimera with agonist-free activity, met both primary and secondary endpoints: in particular, about safety profile and tolerability, isunakinra displayed promising outcomes. The drug did not alter corneal structure, nervous sensitivity and ocular surface flora as assessed by pachymetry, esthesiometry and ocular surface microbiology, respectively. Receptor occupancy was 97% with the low-dose isunakinra, suggesting that administering the increased dose of 20 mg/ml did not provide additional benefits, thereby with irrelevant repercussions on efficacy. Regarding pharmacokinetics and immunogenicity, plasma concentration of isunakinra was below the detection range, indicating no systemic exposure. Only three subjects developed drug-specific autoantibodies, fortunately in low-titer and of non-neutralizing nature. Given the hyperalgesic action of IL-1, positive effects were noted even in ocular pain. Interestingly, the need for artificial rescue tears was lower in patients using topical isunakinra, suggesting that the use of topic biologics can potentially revolutionize treatment for ocular surface diseases.

Sjögren syndrome

SS epitomizes an autoimmune exocrinopathy that causes salivary and lacrimal gland dysfunction, traditionally associated with mononuclear cell infiltration and specific autoantibody positivity. However, innate immune system is also involved in the pathogenetic pathways of SS. In fact, compelling evidence

has emerged about modulations of IL-1 family proteins in SS [55–59]. Increased level of IL-1 in the salivary gland secretion and peripheral blood samples shows that IL-1 acts as a fundamental supervisor in the aberrant immune network that ultimately leads to local and systemic clinical manifestations [55, 56]. A significant increase in tissue and circulating levels of IL-36α [59] and salivary IL-18 was also demonstrated in primary SS. This abnormal cytokine production is initiated by $P2X_7$ receptor-NLRP3 axis, which leads to caspase activation and proteolytic processing of IL-1. Actually, $P2X_7$ receptor activates NLRP3 inflammasome, which in turn is capable of determining mature IL-1β and IL-18 generation [57]. In support of $P2X_7R$ involvement in SS pathogenesis, another study proved a significant higher surface expression of this receptor on peripheral mononuclear blood cells in subjects with primary SS [58]. López-Miguel et al. exposed 40 SS-DED patients to short-term desiccating stress and proved deterioration of the lacrimal function unit accompanied by significant differences in tear IL-1Ra concentrations before and after stress exposure. A significant correlation was found between tear IL-1Ra levels and worsening of corneal staining [60]. Additionally, the same working group has previously reported a consistent and inverse association between IL-1Ra tear levels and Schirmer and break-up time tests [53]. To further support the importance of IL-1 axis in SS and SS-related DED, ANA was shown to be effective in aqueous-deficient DED in animal models that mimic SS by increasing tear secretion, improving surface integrity and reducing irregular glycosylation pattern in globet cells mucins [35]. To overcome the dogmatic view of an exclusive adaptive immunity importance in SS, studies regarding innate immunity have recently opened the door to fascinating novel pathogenetic hypothesis, thereby to potentially new treatment approaches (Table 3).

Future perspectives

IL-1 is an omnipresent inflammatory mediator that has expanded its sphere of influence beyond disorders of rheumatologic concern, passing through cardiovascular diseases and diabetes [61]. Along with uveal phlogosis [39], diabetic retinopathy is recognized as a leading cause of blindness in the Western world, especially in older patients. The inflammatory process consistently influences metabolic disorders such as type 2 diabetes with IL-1β being able to induce apoptosis of pancreatic β-cells and its neutralization has proved to be effective in lowering inflammatory markers and improving glycemic control [62]. However, when dealing with ocular neovascularization, the medical literature reveals conflicting results between preclinical and clinical studies (Table 3). An experimental animal model of alkali-induced corneal injury in IL-1Ra knockout mice displayed enhanced corneal neovascularization and pro-angiogenetic molecule expression [63]. On the other hand, a prospective uncontrolled open-label pilot study using CAN did not meet its primary endpoint concerning the potentially anti-angiogenetic properties of CAN, as the changes in retinal neovascularization area did not reach statistical significance. A local injection might be more appropriate, since a desirable drug concentration into the retinal circulation cannot be obtained with a systemic administration. In fact, it is suggested that systemic doses of CAN may be sufficient to stabilize diabetic retinal neovascolarization (neovascularization elsewhere—[NVE]), but insufficient to induce its complete regression. Additionally, the authors detected by chance an interesting effect on macular edema and an intriguing improvement in HbA1c, the later pursuing a role for beneficial outcomes also in other affected organs [62]. Reducing IL-1 activity may be effective for AMD as well. This complex disorder, in its exudative variant, characterized by choroidal neovascularization, represents a main cause of severe central acuity loss. Inflammatory mediators like IL-1 may play a possible role in exudative AMD by at least partially influencing angiogenesis. In fact, animal models of intravitreal injection of rIL-1Ra provided a dose-dependent reduction of the neovascular area [12].

Furthermore, interesting clues have been risen in a therapeutic viewpoint regarding moderate-to-severe forms of allergic conjunctivitis (AC) refractory to anti-histamines. Many patients indicate symptoms of a late phase response that goes beyond the bounds of mast cells, potentially recognizing IL-1 as a key-cytokine, which drives an important and more pronounced inflammatory response. To overcome the corticosteroid-associated liabilities, EBI-005 was employed in a double-blind randomized placebo-controlled study in 159 patients affected by moderate-to-severe AC. The authors obtained interesting results in terms of safety and efficacy consenting a meaningful statistical improvement in symptoms, such as itching, rhinorrhea and tearing in the conjunctival allergen provocation test group [27]. Surprising results have been also obtained in corneal graft rejection too. Despite being an immune privileged site, due to its avascular nature, the immune response directed by IL-1 remains the primary cause of corneal graft failure. In this regard, a step forward was made to relieve the struggle for a prolonged corneal graft transparency, therefore raising the success rate of corneal transplantation by implementing IL-1Ra gene therapy. Specifically, in murine models, the score of stromal edema, opacity, and neovascularization in the experimental group was lower compared to the control group, the first one displaying also a reduced lymphocyte infiltration and a decreased expression in IL-1 levels [36]. In the context of these animal models, the combination of IL-1Ra with Staphylococcal enterotoxin B (SEB) had demonstrated to further prolong allograft survival due to a hypothetical synergic effect, particularly in high-risk corneal transplantation (Table 3). SEB presents a totally

Table 3 Data on experimental animal models of different ocular disorders and effects of interleukin-1 inhibition

	Anti-IL-1 agent	Type of ocular disease studied	Outcome measures
Biswas et al. [3]	Transgenic mice overexpressing IL-1Ra	HSV-1 induced-SK	Keratitis score, angiogenesis severity with neovascularization index, levels of IL-6, MIP-2 and VEGF, histopathological analysis
Trittibach et al. [4]	Lentiviral vectors containing cDNAs for murine IL-1Ra	Endotoxin (*Salmonella thyphimurium* LPS)-induced uveitis	Histological assessment, aqueous protein concentration, FA
Tsai et al. [5]	Intravitreal injection of recombinant adeno-associated virus vector encoding IL-1Ra	Experimental IL-1α-induced uveitis	Aqueous analysis (cell count and protein concentration) and histopathological examination
Olson et al. [12]	Intravitreal ANA	Exudative AMD induced by laser photocoagulation through Bruch's membrane rupture	Isothiocyanate-Dextran FA
Okanobo et al. [34]	Topical formulation 5% IL-1Ra 1% methylprednisolone, 0.05% CsA	Experimental DED[a]	CFS, RT-PCR for IL-1β, immunohistochemical staining for CD11b+
Vijmasi et al. [35]	Topical ANA	Murine model of autoimmune mediated-dacryoadenitis with aqueous tear deficiency	Lissamine green staining for ocular surface damage, tear secretion assay measured by the mm of wetting of the phenol red thread, lectin-histochemical staining for glycosylation pattern of mucins, immunohistochemical staining and RT-PCR
Yuan et al. [36]	IL-1Ra gene therapy (corneal stromal injection of a recombinant plasmid of pcDNA3.1-hIL-1Ra)	Rat model of corneal graft rejection	Graft histopathology evaluating oedema, lymphocyte infiltration and neovascularization in the corneal stroma, immunohistochemistry
Jie et al. [37]	Subconjuntival IL-1Ra with SEB	Corneal neovascularization induced by intrastromal sutures to establish a high-risk corneal transplantation	Scoring system on a 5-point scale to evaluate stromal opacity through slit-lamp microscope, histopathological examination, immunohistochemical staining of CD4 and CD8 cells, lymphocytes proliferation assay, flow cytometry
Rivera et al. [38]	Intraperitoneal IL-1Ra or rytvela [101.10]	Oxygen-induced retinopathy	Flat mounted retinas labeled with *Griffonia simplicifolia* lectin to examine vascularization, immunofluorescence in retinal cryosections

List of abbreviations: *IL-1Ra* interleukin 1 receptor antagonist, *ANA* anakinra, *SEB* Staphylococcal enterotoxin B, *DED* dry eye disease, *AMD* age-related macular degeneration, *HSV* herpes simplex virus, *LPS* lipopolysaccharides, *SK* stromal keratitis, *MIP-2* macrophage inhibitory protein 2, *VEGF* vascular endothelial growth factor, *FA* fluorescein angiography, *RT-PCR* reverse transcription polymerase chain reaction, *CFS* corneal fluorescein staining, *CD* cluster of differentiation

[a] Controlled environment chamber, topical atropine sulfate 1% and dorsal subcutaneous injections of scopolamine hydrobromide

different immune effect consisting in the bypass of MHC I and MHC II restriction to directly interact with CD4+ and CD8+ subpopulations, and ultimately driving to T-cell deletion and anergy [37]. It is not completely clear from a pathogenetic point of view whether IL-1-blockade effects are confined within its anti-inflammatory setting or they also involve promotion of allo-protective tolerogenic pathways. Different authors have put efforts to elucidate this topic. The positive effect on graft survival is derived principally from its ability to suppress inflammation, since the effect on inducing anterior chamber-associated immune deviation is scant. Nevertheless, IL-1Ra treatment accelerates ocular capacity to induce intracamerally delivered soluble antigen. The failure in promoting allospecific tolerance determines the need for a prolonged IL-1 suppression to prevent graft rejection [64]. Neuroinflammatory course has been recently associated with ischemic retinopathies, such as retinopathy of prematurity, where microglia overreacts during the vaso-obliteration phase and serves as an essential origin of IL-1β. Under hyperoxic stress, microglia display an IL-1β-driven response, thereby an indirect microvascular injury through the release of proapoptotic semaphoring-3A from bordering retinal ganglion cells. With IL-1R antagonism, the microvascular bed remains intact, turning out in a decrease on abnormal

neovascularization and vaso-obliteration. An interesting finding was brought regarding therapeutic aspects. The allosteric modulator of IL-1R 101.10, a small stable peptide, exhibited the same efficacy of rIL-1Ra, while offering several pharmacodymanic and pharmacokinetic advantages due to its selectiveness and size [38]. IL-1Ra is also naturally and locally produced by retinal pigmenting epithelium (RPE) to antagonize pro-inflammatory cytokines, thus suppressing antigen presenting cells. Among its protective mechanisms, RPE causes the suppression of Th1 and Th17 inflammatory T cell effectors in vitro as well as the suppression of B cells and macrophage activation. It also converts T cells in their regulatory subtype. Sugita et al. proved a constitutive mRNA expression of IL-1Ra by RPE cells to inhibit simultaneously activated dendritic cells. This is another feature that enlarges the immunosuppressive intraocular microenvironment stressing the conceptual aspect to contemplate the eye as an immune privilege site [65]. Indeed, ARPE-19, a human RPE cell line, releases IL-6, IL-8, and monocyte chemoattractant protein-1 after necrotic cell induction. These three molecules, considered key-mediators in retinal inflammation, were inhibited by IL-1Ra, presumably via NF-kB signaling, pointing out that IL-1 constitutes a central signal danger released by necrotic RPE, therefore preparing the ground to novel therapeutic implications [66]. It is interesting to mention some intriguing findings obtained in animal models concerning retinitis pigmentosa, where chronic inflammation was suggested to contribute to pathogenesis. Among several cytokines, IL-1β was found to be significantly upregulated. This retinal degenerative disease constitutes a major cause of blindness in adulthood, and chronic inflammation substantially contributes to its physiopathology [67] and closely relates to visual function. Based on these findings, anti-inflammatory treatment may represent a potential therapy [68].

Conclusions

Given the importance of eye disease in systemic inflammatory disorders, a close cooperation between the rheumatologist and ophthalmologist should be warranted for an accurate ocular assessment and a subsequent improvement of visual outcome. Eye involvement may outbreak at disease onset and in the disease course with potentially blinding manifestations that may complicate the clinical scenery and substantially challenge clinicians. Several papers in the medical literature indicate a successful employment of anti-IL-1 agents in these sight-threatening conditions [14, 19, 21, 22, 26, 28]. More specifically, ANA and CAN increase the availability of biological options and should be considered in the management of IL-1-driven ocular diseases.

A trustworthy literature supporting an inflammatory component in the pathogenesis of DED [49, 50] has given birth to new opportunities for treatment of this complex ocular affection [7, 8]. Evidence for a phlogistic background and good results of IL-1-blocking agents have also been proved in other eye diseases including diabetic retinopathy, ADM, retinopathy of prematurity, and even corneal graft rejection [12, 36, 63]. Notably, topical therapy with anti-IL-1 drugs other than ANA, such as isunakinra [8], the allosteric modulator of IL-1R 101.10 [38], and gene therapy [4, 5] might represent interesting approaches which however require further confirmations. Of course, all the discussed therapeutic findings provide a strong biologic rationale for targeting IL-1 in inflammatory ocular diseases and may herald a new era in the treatment of these complex disorders.

Compliance with ethical standards

Disclosures None.

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