Ocular Manifestations in Rheumatoid Arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is an inflammatory rheumatic disease that generally damages synovial-line joints. Extra-articular manifestations of RA have been reported in cases of multiorgan involvement. These manifestations can occur in the hematologic and cardiovascular system, lungs, kidneys, and eyes. Various ocular manifestations of RA have been previously reported including keratoconjunctivitis sicca, conjunctivitis, uveitis, scleritis, retinal vascular occlusion, optic neuritis, and amaurosis fugax. It is important to recognize these ocular issues as manifestations of RA since they can sometimes be a response marker for the onset of an immune reactivation. Urgent management of ocular complications is essential to manage sight-threatening complications and prevent further damage to the eyes.

Keywords: Rheumatoid arthritis; connective tissue disease; autoimmune disease; ocular manifestations; eye involvement (Siriraj Med J 2022; 74: 340-349)

List of abbreviations

AION; anterior ischemic optic neuropathy
C; complement
CCP; cyclic citrullinated peptide
CD; cluster of differentiation
DMARDs; disease-modifying antirheumatic drugs
FDA; Food and Drug Administration
HLA; human leukocyte antigen
Ig; immunoglobulin
IL; interleukin
JIA; juvenile idiopathic arthritis
KCS; keratoconjunctivitis sicca
MMP; matrix metalloproteinases
MTX; methotrexate
NSAIDs; non-steroidal anti-inflammatory drugs
PUK; peripheral ulcerative keratitis
RA; rheumatoid arthritis
RF; rheumatoid factor
SMIs; small molecule inhibitors
SS; Sjögren's syndrome
TNF-α; tumor necrosis factor-alpha

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Rheumatoid arthritis (RA)

Introduction of ocular manifestation of rheumatoid arthritis

Origin/history of the ocular manifestation of rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic progressive autoimmune disease characterized by polyarticular synovitis. Ocular complications, which are caused by inflammatory mediators such as immune complex depositions and upregulation of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin (IL) 6, are commonly associated with dry eye, peripheral ulcerative keratitis (PUK), and scleritis.[1-3]

Epidemiology

RA is reported to be the most common systemic autoimmune disease. It affects roughly 1% of the general population.[4] Previously, extra-articular manifestations of RA were believed to occur in the late stages of the disease, following joint inflammation[5], but we now know that extra-articular complications can present at any stage of the disease.[3] Extra-articular manifestations often present as hematologic and cardiovascular complications, while ocular complications are less common.[3]

Pathophysiology

TNF-α, IL-1, and IL-6, as proinflammatory cytokines, are believed to be involved in the inflammatory pathway.[3] Prada J et al. investigated specific gene probes for TNF-α and IL-6 from paraffin corneal sections from seven patients who had corneal ulcerations/perforations with RA. The results revealed TNF-α expression in 71% and IL-6 expression in 100% of the analysed tissue samples.[6] Unfortunately, there was no control group in their study. The authors concluded that collagenolytic corneal damage was caused by the production of metalloproteinases as a result of the upregulation of the proinflammatory cytokines. RA patients who presented with necrotizing scleritis and/or PUK were involved in one of our studies. Conjunctival and/or scleral biopsy samples revealed microangiopathy with fibrinoid necrosis, vessel invasion by neutrophils, and/or vascular immunodeposits with immunoglobulin (Ig) A, IgG, IgM, complement (C) 3 and C4 in all patients with PUK and in 83% of patients with necrotizing scleritis.[7] Moreover, RA patients who experienced dry eye were found to have high levels of IL-17 in their tears.[8] A prospective case-control study among 72 RA patients revealed that there was no correlation between joint activity and the severity of keratoconjunctivitis sicca (KCS) symptoms.[9]

Ocular manifestation of RA (Table 1)

Definition/criteria for diagnosis

Secondary Sjögren's syndrome (SS) and KCS

RA is one of the most common autoimmune disorders associated with KCS.[10] Lymphocytic infiltration and destruction of acini in the lacrimal glands results in secondary SS.[10] This lymphocyte infiltration from pathological sections of lacrimal glands obtained from patients with primary SS and secondary SS cannot be distinguished. The severity of dry eye symptoms and corneal fluorescein dye staining were similar in both primary SS and secondary SS. These features suggest autoimmune mechanisms as a cause of dry eye, which is fairly common in many systemic autoimmune diseases.[10]

Pathophysiology

Lymphocyte and plasma cell infiltration is generally found in the tubuloacinar glands of lacrimal gland lobules.[11-13]

Symptoms and signs

The most common clinical presentation of secondary SS is dry eye. In addition, patients may also experience redness, light sensitivity, ocular burning sensation, foreign body sensation, and painful superficial keratitis. Punctate erosion, which can be detected through fluorescein, rose bengal, or lissamine green staining, is also common. Moreover, some patients can present with visual deficiencies, corneal epitheliopathy, filament keratopathy, and plaque formation. Diagnosis of secondary SS can also be confirmed through objective measures such as a decrease in lacrimal secretion (hyposecretion) through Schirmer's test and a decrease in lacrimal stability, measured by a decrease in tear break-up time.[14,15]

Episcleritis

Episcleritis is the inflammation of episcleral tissue over the sclera. The frequency of episcleritis in RA patients was reported to be 0.17-3.7%.[16]

Pathophysiology

Increased inflammation associated with RA can lead to the infiltration of white blood cells to the episcleral tissue and result in episcleritis. This causes the anterior ciliary arteries to become congested and more prominent. In addition, the dysregulation of levels of cytokines such as transforming growth factor b in tear fluid and the subsequent loss in tear integrity are believed to be related to episcleritis.[14]

TABLE 1. Comparison of mean number of decayed teeth by CFUs within groups.

Ocular manifestations	Frequency among RA individuals	References
Keratoconjunctivitis sicca	18-90%	14
Episcleritis	1-5%	14
Scleritis	1-6%	14
Anterior uveitis	14-42%	14
Peripheral ulcerative keratitis	1-2%	44
Retinal vasculitis	18% (subclinical)	36
Choroiditis	rare	
Optic neuropathy	rare	

Abbreviations: RA; rheumatoid arthritis

Symptoms and signs

Episcleritis patients generally present with red eyes as a result of vasodilation of superficial radial episcleral vessels, which can be sectoral, diffuse, or nodular. Bilateral involvement was found in 40% of episcleritis cases.[16] The disease itself is painless and visual loss has not been reported. In order to differentiate between episcleritis and scleritis, 10% phenylephrine drops can be instilled to assess if the characteristic constricting and blanching of episcleral vessels associated with episcleritis occurs.[14]

Scleritis

The most common systemic association with scleritis that has been reported is RA.[17,18] About one-fifth to one-fourth of patients with scleritis have RA and conversely, 0.2-6.3% of RA patients suffer from scleritis.[19] Most RA patients develop articular manifestations preceding the onset of scleritis. Necrotizing scleritis, which is the most severe form of scleritis, is caused by vascular occlusion of the affected area, shown in Fig 1. Associated uveitis and peripheral ulcerative keratitis may be associated with scleral inflammation. Complicated cataract and secondary glaucoma are frequently found in patients with scleritis, especially in those patients with severely inflamed eyes.[17] On the other hand, patients can also develop anterior scleritis without inflammation, known as scleromalacia perforans (Fig 2). Thinning of the sclera and visible uveal tissue gradually develops as a late complication of the inflammatory processes; however spontaneous perforation is rare. Posterior scleritis can also be associated with RA. In these cases, subretinal fluid, macular edema, papillitis,

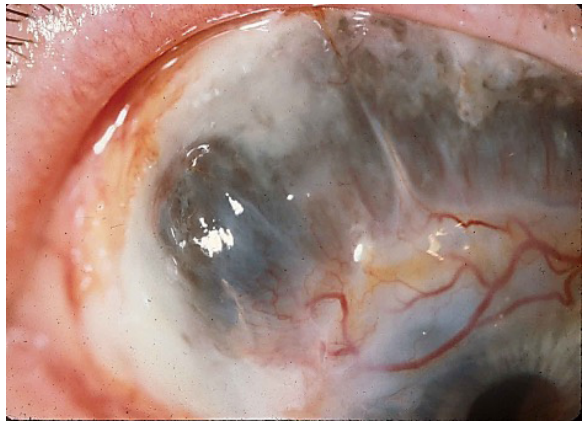

Fig 1. Necrotizing scleritis with associated peripheral ulcerative keratitis in rheumatoid arthritis patient.

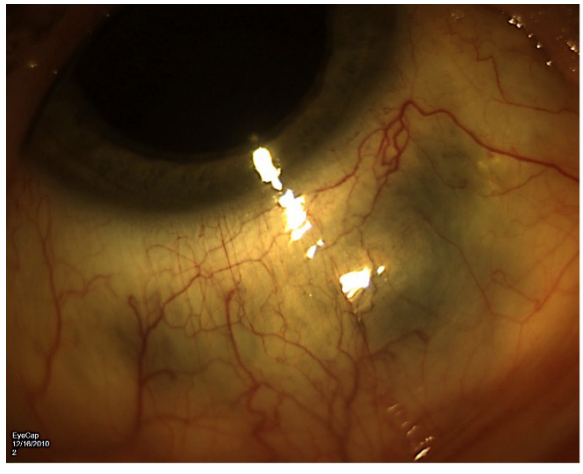

Fig 2. Scleral thinning with exposure of the choroid covered by healthy conjunctiva without inflammation, which is also known as scleromalacia perforans.

or uveal inflammation can result in the deterioration of vision (Fig 3). RA-associated scleritis is typically classified as a condition of intermediate severity.[20]

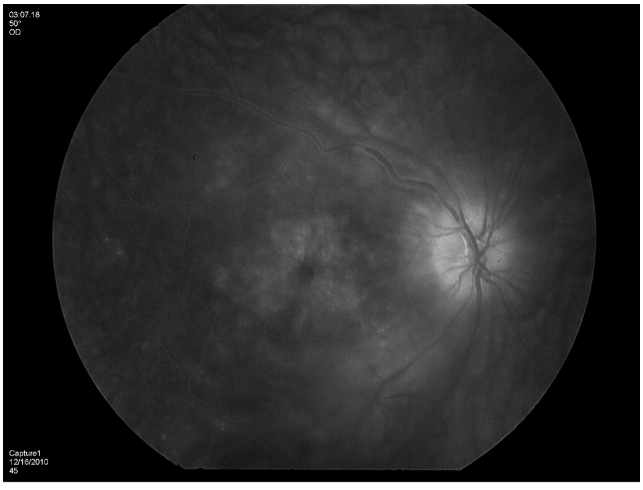

Fig 3. Fundus fluorescein angiogram of rheumatoid arthritis patient who had posterior uveitis with papillitis, retinal vasculitis and cystoid macular edema in the right eye.

Pathophysiology

Histopathological examination of scleral tissue of patients with scleritis has shown fibrinoid necrosis and vascular infiltration, specifically infiltration of macrophages and T-lymphocytes. These findings are similar to what is found in patients with occlusive retinal vasculitis.[21,22] Furthermore, collagenase matrix metalloproteinase-3 (MMP-3), MMP-8, and MMP-9 are speculated to be responsible for collagen breakdown, in combination with the imbalance of MMP and tissue inhibitors of MMPs.[14,23]

Symptoms and signs

Severe eye pain is the main symptom of scleritis. Bilateral involvement was found in half of cases.[24] Redness (deep violaceous hue) with scleral edema and dilation of the superficial and deep episcleral vascular plexuses are important signs of scleritis. Tearing, photophobia, and decreased visual acuity can also be found.[14]

Classification regarding anatomical location

The location of inflammation compared to the insertion of the rectus muscles is used to classify scleritis to either anterior scleritis and posterior scleritis. Anterior scleritis is more commonly found compared to posterior scleritis.[15,16] The diagnosis of posterior scleritis is more challenging. Ocular examination in the early stages of inflammation may sometimes show no abnormalities, while more severe cases may reveal optic disc swelling, retinal fold, retinal exudates, subretinal fluid and macular edema.[15] Ocular pain is an important feature that should alert the physician to assess if scleritis is present. Blurred vision is commonly associated with scleritis, as a result of refractive shift from thickened posterior sclera or from the inflammatory processes itself. Patients may experience metamorphopsia from macular fold and macular edema.[25] B-scan ultrasonography is the most useful diagnostic tool, which confirms the diagnosis of posterior scleritis by showing scleral thickening and demonstrating any scleral nodules, if present.[26] (Fig 4)

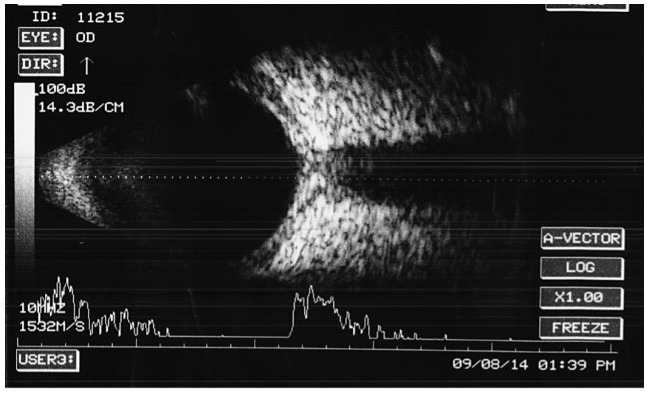

Fig 4. B-scan ultrasonography of the right eye shows chorioretinal thickening with classicT-sign, which represent subtenon fluid in patient with posterior scleritis.

Classification regarding the pattern of scleral inflammation

Scleritis can be classified into diffuse scleritis, nodular scleritis and necrotizing scleritis with or without inflammation. Diffuse anterior scleritis is the most common type of RA associated scleritis, followed by nodular anterior, necrotizing, and posterior scleritis.[27] Diffuse scleritis is more benign than other types of scleral inflammation.[28] Necrotizing scleritis with inflammation is a type of inflammation that increases the probability of other ocular complications such as marginal keratitis, anterior uveitis, and secondary ocular hypertension, and disease associations include connective tissue diseases and vasculitic diseases with infectious diseases, rosacea, and foreign body.[16] Scleromalacia perforans is characterized by the bluish-grey hue of the sclera without any sign of inflammation. It was believed to be a result of scleral thinning.[25]

Peripheral ulcerative keratitis

PUK is relatively common in patients with connective tissue diseases, especially among RA patients.[17] PUK can lead to corneal melt syndrome and ocular perforation, and may be associated with scleritis.[17] Corneal perforation is the most severe ocular complication in RA patients.[24] We

reported the mortality rate of RA patients' concurrence with PUK and/or necrotizing scleritis was approximately 50% at 10 years without immunosuppressive medication. The major cause of death in that study was rheumatoid vasculitis.[29] When PUK is found in RA patients, urgent multidisciplinary management is required.[24]

Pathophysiology

Both cellular and humoral immunity are involved in the inflammation process. T- and B-lymphocytes play an important role in increasing antibody production and immune-complex deposition around the peripheral cornea.[30,31] Inflammatory cells, specifically neutrophils and macrophages, are recruited to the cornea by C activation.[24] Collagenases and other proteases, secreted from those inflammatory cells, cause corneal melting and eventually perforation.[32] Abnormal MMP-2 production and the presence of MMP-9[33,34], and possibly other MMPs have been thought to be related to PUK progression.

Symptoms and signs

Symptoms and signs of PUK include ocular pain and redness, photophobia, tearing, visual deterioration from corneal astigmatism or corneal opacity, peripheral corneal thinning, and ulceration[15] (Fig 5).

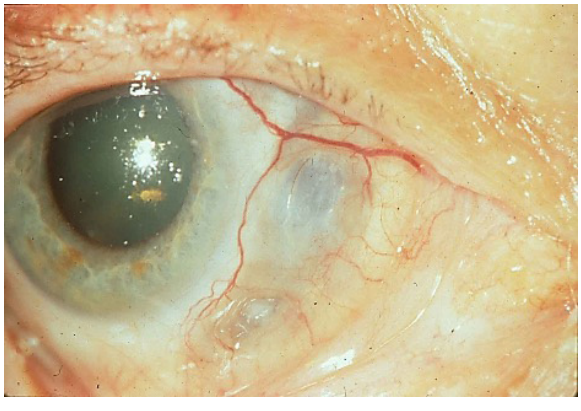

Fig 5. Anterior segment photograph showing an extensive area of peripheral corneal thinning with abnormal feeding vessel in a patient with peripheral ulcerative keratitis associated with rheumatoid arthritis.

Retinal vasculitis

Retinal vasculitis, which describes inflammation of retinal blood vessels can result in poor visual outcome[35] and is associated with several connective tissue diseases, including RA.[36]

Pathophysiology

Rheumatoid vasculitis is believed to be related to longstanding rheumatoid factor (RF) positive cases.[37] Circulating immune complex, co-stimulatory molecule (CD28) on naive T cells, and proinflammatory cytokines are involved in the inflammatory processes.[38] Intraocular inflammation, more specifically retinal vasculitis (despite its rare presentation), PUK and necrotizing scleritis, is considered as a clinical manifestation of rheumatoid vasculitis.[36,39]

Symptoms and signs

Most RA patients with retinal vasculitis are asymptomatic and show no clinical signs of retinal vasculitis. However subclinical retinal vasculitis with retinal vascular leakage on fundus fluorescein angiogram has been reported in 18% of RA patients.[40]

Optic neuritis and anterior ischemic optic neuropathy (AION)

Optic neuritis and AION occur at a lower frequency compared to PUK, corneal melt, and scleritis.[10] Optic disc swelling can occur secondary to posterior scleritis.[17]

Risk factors

Predisposing genetic factors such as the human leukocyte antigen (HLA)-DR4 allele, and inappropriate immune mechanisms leading to immune complex deposition and microvasculitis in the joint play a pivotal role in the pathogenesis and joint destruction of RA.[7] High titers of RF, circulating immune complexes, cryoglobulinemia and hypocomplementemia are strongly associated with rheumatoid systemic vasculitis.[41] These laboratory parameters also have been abnormal in a high percentage of patients with RA who developed necrotizing scleritis and/or PUK, observed in our study.[7] Patients who were both anticyclic citrullinated peptide (anti-CCP) and RF positive tend to have more severe ocular disease.[42-44]

Treatment

Indications for treatment

Most RA patients have dry eye symptoms, which is generally mild to moderate in severity. Treatment for these patients comprise of lubricating eye drops, and in some instances, topical cyclosporine eye drops.[24] The use of autologous serum tear drops is typically reserved for more severe cases of dry eye.[45] Systemic medications such as doxycycline can inhibit MMP and induce T cell apoptosis, which is also useful in decreasing the inflammatory cascade associated with dry eye syndrome.[46,47] For the more severe cases of dry eye, such as dry eye with corneal epitheliopathy, scleritis, and PUK, the previously mentioned therapy is generally inadequate

to control the disease[10] (Fig 5). Almost every type of scleritis eventually requires systemic therapy such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids.[28] Immunomodulatory therapy is indicated in PUK or scleritis patients who fail to respond to oral corticosteroid therapy. Therapy failure is defined as having persistent inflammation, disease progression, intolerability to corticosteroid side effects, or unable to taper prednisolone to physiologic doses.[27] The treatment modalities for ocular manifestations in RA is summarized in Table 2.

Medical treatment

Non-steroidal anti-inflammatory medications

Oral NSAIDs are considered useful in mild forms of scleritis.[25] They can be used as a first-line therapy for patients with non-necrotizing scleritis.[48] Necrotizing scleritis, which is the more severe form of scleritis, and posterior scleritis, where the inflammatory site located at the back of the eye, require systemic corticosteroid therapy, and eventually immunomodulatory therapy.[25]

Corticosteroids

Initial treatment that is effective at controlling active inflammation is high doses of systemic corticosteroids. For the more severe cases such as necrotizing scleritis or PUK with impending corneal perforation, methylprednisolone infusion is recommended. During maintenance therapy, slow taper of the medication is required. Relapsed inflammation can often occur during the tapering of medication.[25,49] Topical steroids can be used as an adjunctive treatment for scleritis with anterior uveitis.[25]

Immunosuppressant medications

About ¼ of scleritis patients require immunomodulatory therapy to control their inflammation.[19] In RA associated scleritis, the indication for immunosuppressants is broad.[7]

Antimetabolite

Methotrexate (MTX) has proved to be highly beneficial.[7] MTX has less potential toxicity compared to cytotoxic agents and is used as a first-line medication in the chemotherapeutic management of PUK and necrotizing scleritis in most patients with RA. Azathioprine is a second-line medication for chemotherapeutic management in RA.[7]

Calcineurin inhibitor

Cyclosporine is a second line drug, which may be successful in select cases.[31]

Cytotoxic agent

Chlorambucil has been used as a treatment option for RA, but its efficacy related to extra-articular manifestation is rarely reported. Cyclophosphamide has been the most effective, but[7] is associated with higher toxicity.

Biologic agents

Biologic agents are usually reserved for the treatment of RA that is refractory to conventional therapy. They have a favorable safety profile as compared to cytotoxic agents but their use must be closely monitored to avoid the reactivation of latent infections such as mycobacterium tuberculosis and to avoid the risk of opportunistic infections.[44,50]

TNF inhibitors

TNF inhibitors that are approved by the U.S. Food and Drug Administration (FDA) for the treatment of RA are etanercept (Enbrel®), infliximab (Remicade®), adalimumab (Humira®)[3], certolizumab pegol (Cimzia®) and golimumab (Simponi®).[51] TNF inhibitors can decrease inflammation and corneal destruction by decreasing the products of MMP, such as MMP-9, which halts the destruction of corneal epithelial basement membrane and the degradation of extracellular matrix of the corneal stroma.[34,52,53] MTX may have synergistic effects when combined with TNF inhibitors.[54] Etanercept and adalimumab were also reportedly successful in select cases.[55,56] Infliximab is the more favorable treatment option, especially in uveitis, because of its successful outcomes.[57,58] On the other hand, some reports suggested that etanercept may induce intractable scleritis or is ineffective in treating scleritis.[59,60] Certolizumab pegol, a newer TNF-α inhibitor, has been used to treat extra-articular manifestations of RA, but very few reports have been published on this medication.[61] This medication differs from the older TNF-α inhibitors in that it has a longer half-life with less toxicity.[62] The use of golimumab in several case reports and case series demonstrate successful control of recalcitrant uveitis associated with juvenile idiopathic arthritis (JIA), Adamantiades-Behçet's disease, idiopathic retinal vasculitis, spondyloarthropathies, and HLA-B27 positivity.[63-67]

IL-1 inhibitor

Anakinra (Kineret®) is approved by the FDA.[3] In scleritis, both TNF-α and IL-1 released by the local inflammatory cell infiltrate have been associated with scleral destruction.[68] An observation by C. Botsios et al. demonstrates the efficacy of anakinra in RA associated diffuse scleritis.[69]

TABLE 2. Treatment modalities for ocular complications in rheumatoid arthritis.

Medications	Route of administrations	Indications	Evidence
Artificial tears	ED	KCS	
Autologous serum	ED	KCS	
Topical cyclosporine	ED	KCS	
Doxycycline	Oral	KCS	
NSAIDs	ED/ oral	Episcleritis/ scleritis (mild form)	
Corticosteroids	ED/ oral/ IV	Episcleritis/ scleritis/ PUK/ uveitis	
Immunosuppressant			
Antimetabolite			
Methotrexate	Oral/ SC	Scleritis/ PUK/ uveitis	First line
Azathioprine	Oral	Scleritis/ PUK/ uveitis	Second line
Mycophenolate mofetil	Oral	Scleritis/ PUK/ uveitis	-
Calcineurin inhibitor			
Cyclosporine	Oral	Scleritis/ PUK/ uveitis	Second line
Cytotoxic agents			
Cyclophosphamide	Oral/ IV	Scleritis/ PUK/ uveitis	Recommended in severe and/ or refractory cases
Chlorambucil	Oral	Uveitis	-
Biologic agents			
TNF inhibitors			
Infliximab	IV	Scleritis/ PUK/ uveitis	RCT
Adalimumab	SC	Scleritis/ PUK/ uveitis	FDA-approved
Certolizumab pegol	SC	Uveitis	Case reports
Golimumab	SC	Uveitis	Case reports
Etanercept	SC	Not recommended (less effective)	Phase II/III
IL-inhibitors			
Anakinra	SC	Scleritis	Case reports
Tocilizumab	SC/ IV	Scleritis/ PUK/ uveitis	Case reports
Gevokizumab	SC	Scleritis	Phase I/II
B-cell depletion			
Rituximab	IV	Scleritis/ PUK/ uveitis	Phase I/II
Cytotoxic T-lymphocyte antigen 4			
Abatacept	SC/ IV	Scleritis/ uveitis	Case reports
Small molecules inhibitors			
Janus kinase			
Tofacitinib	Oral	Scleritis/ uveitis	Phase II
Baricitinib	Oral	Uveitis	Case reports
Filgotinib	Oral	NA	NA
Peficitinib	Oral	NA	NA
Decernotinib	Oral	NA	NA
Other new medications			
ACTH gel	SC	Scleritis	Phase II
Sirolimus	Subconjunctival	Scleritis	Case reports

Abbreviations: ED; eye drops, KCS; keratoconjunctivitis sicca, NSAIDs; non-steroidal anti-inflammatory drugs, IV; intravenous, PUK; peripheral ulcerative keratitis, SC; subcutaneous, TNF; tumor necrosis factor, RCT; randomized controlled trial, FDA; food and drug administration, IL; interleukin, NA; not applicable, ACTH; adrenocorticotropic hormone

IL-6 inhibitor

Tocilizumab (Actemraâ) is approved for the treatment of RA and JIA.[70] Successful suppression of PUK in RA patient with tocilizumab has been reported.[71]

B-cell depletion

Rituximab (Rituxanâ) is a chimeric monoclonal antibody against cluster of differentiation (CD) 20 aimed at depleting B cells. It is reported as a successful treatment for many connective tissue diseases, including RA. T-cell activation in scleritis and PUK might be associated with the existence of B lymphocytes surrounding blood vessels, resulting in immediate action of rituximab.[72,73]

Cytotoxic T-lymphocyte antigen 4 (CTLA 4)

Abatacept (Orenciaâ) is a recent yet widely utilized therapeutic option in RA.[74] Its efficacy to treat extra-articular manifestations is under investigation. One patient developed PUK while on abatacept, and the treatment was switched to tofacitinib citrate (Xeljanzâ) combined with corneal gluing within one week, which led to a successful treatment of the PUK.[75] Several reports demonstrated its efficacy to control or improve refractory JIA related uveitis.[76-79]

Surgical treatment

Surgical indication for scleritis and PUK is corneoscleral melting with impending perforation or perforation, both of which require immediate surgical intervention. Surgery can also be used as an adjunctive treatment to decrease or halt the progression of active inflammation in some instances.[25] Surgical interventions include cyanoacrylate adhesive, tectonic corneal graft, conjunctival flap, and scleral grafting. Conjunctival resection may also be done to enhance the healing process of PUK by decreasing the number of inflammatory cells and cytokines surrounding the cornea and thus, promoting corneal epithelialization.[7,80] A combination treatment of immunomodulatory medication and adjuvant surgical intervention can generally preserve the eyeball in most of the RA patients, but visual outcome is sometimes unsatisfied.[7]

Future direction

Recently, there has been development of small molecule inhibitors (SMIs) for RA as a new generation of targeted synthetic disease-modifying antirheumatic drugs (DMARDs). These medications can block pro-inflammatory pathways such as Janus kinase, mitogen-activated protein kinase, and spleen tyrosine kinase.[81] The therapeutic treatment of SMIs for ocular manifestations related to RA is yet to be investigated.[44]

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Conflict of interest

S Boonsopon, S Dhanireddy and A Manhapra report no conflict of interest. C. Stephen Foster reports no conflict of interest, but declares consultancies with Aldeyra Therapeutics, Allakos, Bausch & Lomb Surgical, Inc, Eyegate Pharma, Genentech, Novartis, pSivida; grants or grants pending with Aciont, Alcon, Aldeyra Therapeutics, Bausch & Lomb, Clearside Biomedica, Dompé pharmaceutical, Eyegate Pharma, Mallinckrodt pharmaceuticals, Novartis Pharmaceuticals, pSivida, Santen; payment for lectures including service on speaking bureaus: Alcon, Allergan, Mallinckrodt pharmaceuticals; stock or stock options: Eyegate Pharma.

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