Journal of
Clinical & Translational Ophthalmology

MDPI

Review

Updates on Systemic Immunomodulation in Peripheral Ulcerative Keratitis

Arash Maleki [1,2], Tate Valerio [1,3], Yasmin Massoudi [1,3], Maria L. Ruggeri [1,3], C. Stephen Foster [1,3,4] and Stephen D. Anesi [1,3,*]

[1] The Ocular Immunology and Uveitis Foundation, Waltham, MA 02451, USA; arash.maleki01@gmail.com (A.M.); ymassoudi@mersi.com (Y.M.)
[2] Department of Ophthalmology, University of Florida, Gainesville, FL 32611, USA
[3] Massachusetts Eye Research and Surgery Institution, Waltham, MA 02451, USA
[4] Department of Ophthalmology, Harvard Medical School, Cambridge, MA 02138, USA
* Correspondence: sanesi@mersi.com

Abstract: Peripheral ulcerative keratitis (PUK) is an inflammatory process causing thinning of the cornea, epithelial defect, and inflammatory infiltrates and is caused by several etiologies. This sight-threatening condition can indicate the presence of potentially fatal underlying systemic conditions, and, accordingly, warrants thorough investigation upon clinical presentation and immediate intervention in order to mitigate disease progression. This review aims to provide an update on the current diagnostic and management landscape for PUK, specifically with immunomodulatory methods in cases of noninfectious etiologies. A literature search was conducted to develop a nuanced, evidence-based perspective in which we present our preferred approaches. There are currently a number of viable options, following which a "stepladder" method is typically employed, where treatment methods are escalated as a result of inadequate clinical response to lower-level interventions. This method balances efficacy with the potential side effects of immunomodulatory medications. Ultimately, carefully monitored treatment regimens are needed to mitigate visual impairment in patients with PUK, and efforts must be made to achieve steroid-free remission to avoid the known side effects of long-term corticosteroid use.

Keywords: peripheral ulcerative keratitis; keratopathy; ulceration; immunomodulatory therapy; biologic response modifiers; diagnostic testing

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Citation: Maleki, A.; Valerio, T.; Massoudi, Y.; Ruggeri, M.L.; Foster, C.S.; Anesi, S.D. Updates on Systemic Immunomodulation in Peripheral Ulcerative Keratitis. *J. Clin. Transl. Ophthalmol.* **2024**, *2*, 131–139. https://doi.org/10.3390/jcto2040011

Academic Editor: Sotiria Palioura

Received: 12 June 2024
Revised: 29 August 2024
Accepted: 20 October 2024
Published: 23 October 2024

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1. Introduction

Peripheral ulcerative keratitis (PUK) is typically characterized by a clinical triad consisting of the rapid progression of a crescent-shaped peripheral corneal thinning, an epithelial defect, and an inflammatory corneal infiltrate [1]. PUK could be a presentation of an underlying infectious and noninfectious ocular or systemic condition; however, systemic vasculitides and collagen vascular diseases with autoimmune origins are frequently associated with PUK. The presence of these systemic conditions often complicates both diagnosis and management [2]. Research indicates that both humoral and cellular immunity play roles in the pathogenesis of PUK [3,4].

PUK holds significance as it can indicatethe presence of a potentially life-threatening systemic disease which might initially present in an ophthalmological setting. Additionally, it has the potential to cause severe vision impairment if ineffectively managed, necessitating careful attention [1]. In this review, we aim to offer an update on pertinent information regarding systemic immunomodulation in managing PUK.

2. Epidemiology

Epidemiological studies estimate the annual incidence of PUK to range from 0.2 to 3 cases per million population [5,6]. While there is typically a predilection for females [6],

there are some reports indicating equal incidence between males and females [5]. In the United States and the UK, the majority of cases are linked to systemic autoimmunity. Almost half of all noninfectious cases of PUK are associated with a connective tissue disorder, of which rheumatoid arthritis is the most common. In RA, PUK affects both eyes in nearly half of all cases in the later stages of the disease [1].

3. Pathophysiology

The diverse causes of PUK indicate that numerous pathways can result in peripheral corneal inflammation and keratolysis. An initial event likely entails the formation of antigen–antibody immune complexes at the terminal ends of limbal vessels, triggering a secondary, multicellular immune cascade marked by complement activation, anti-corneal antibodies, collagenases, proteases, and the activation of adaptive immunity [7]. PUK is strongly associated with, and occasionally triggered by, prior ocular surgery and systemic infections resulting from immune system stress and overactivation. This suggests that sensitization of the immune system, either through corneal antigens or molecular mimicry, may play a role.

4. Etiology

PUK can arise from a range of disorders, encompassing both ocular and systemic infectious and noninfectious conditions. Ocular causes of PUK can be categorized as infectious, traumatic, neurological, related to eyelid abnormalities, malignancy-associated, and autoimmune. Systemic causes of PUK may include infectious, autoimmune, dermatological or collagen vascular diseases, or malignancies [8]. The diverse ocular and systemic autoimmune etiologies of PUK are outlined in Table 1. Sainz de la Maza and colleagues found that all 24 included patients with PUK possessed at least one potentially lethal systemic disease, and found that these patients had worse ocular and systemic outcomes compared to other scleritis-associated peripheral keratopathies [6]. These findings underline the critical importance of a comprehensive investigation into the underlying etiology of patients with a clinical presentation consistent with PUK.

Table 1. Ocular and systemic autoimmune etiologies of peripheral ulcerative keratitis (PUK).

Autoimmune Etiologies
Systemic Etiologies
Granulomatosis with polyangiitis
Polyarteritis nodosa
Microscopic polyangiitis
Churg–Strauss syndrome
Relapsing polychondritis
Bechet's disease
Rheumatoid Arthritis
Sarcoidosis
Temporal arteritis
Sjogren syndrome
Takayasu arteritis
Systemic lupus erythematosus
Inflammatory bowel disease
Stevens Johnson syndrome
Autoimmune hepatitis
Allograft rejection
Ocular Etiologies
Cicatricial pemphigoid
Mooren's ulcer

Additionally, it should be noted that Mooren's ulcer (MU) is a diagnosis of exclusion in unilateral or bilateral PUK [9]. True PUK presents with conjunctival involvement that is less prominent and typically a consequence of underlying systemic conditions affecting the

cornea. With MU, conjunctival changes can be more directly involved, sometimes with the conjunctiva actively participating in the disease process.

5. Clinical Presentation and Evaluation

Patients with PUK typically experience symptoms such as redness, photophobia, foreign body sensation, and pain. Decreased vision may also be reported. Scleral involvement, including scleritis, may occur in conjunction with PUK. Initially, PUK tends to be unilateral or asymmetrically bilateral, but follow-up examinations reveal bilateral involvement in as many as 40–60% of patients [5,10].

The signature finding, peripheral crescentic ulceration, is marked by an epithelial defect, corneal thinning, and limbal infiltration with overhanging edges. Initially, the ulcer affects the superficial superior third of the cornea and may later advance to corneal perforation [11].

Pinpointing the precise cause of PUK is crucial for effective treatment. While a detailed history and thorough clinical assessment often enable identification of the cause in most cases, situations may arise where no identifiable cause is evident (idiopathic PUK), necessitating a battery of laboratories tests and investigations to uncover the underlying etiology.

Routine investigations such as a complete blood hemogram with erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), blood urea nitrogen (BUN), fasting blood sugar (FBS), and urinalysis (U/A) are recommended for all cases of PUK. Immunological assessments, including antineutrophil cytoplasmic antibodies (c-ANCA, p-ANCA) titers, antinuclear antibodies (ANA), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-)CCP antibodies, and angiotensin-converting enzyme (ACE) levels, are essential for diagnosing conditions such as granulomatosis with polyangiitis (GPA), systemic lupus erythematosus (SLE), sarcoidosis, and RA [12]. Complement factor levels, including C3, C4, and CH50, contribute to the diagnosis of certain immunological causes and systemic vasculitides. Imaging modalities such as chest X-ray and contrast-enhanced computed tomography of the chest are essential for diagnosing conditions like tuberculosis (TB), sarcoidosis, GPA, and SLE. Computed tomography (CT) of sinuses and X-rays or magnetic resonance imaging (MRI) of the sacroiliac joint can be ordered to evaluate for granulomatosis with polyangiitis and HLA-B27-positive sacroiliitis. Syphilis can be identified through the venereal disease research laboratory (VDRL) test, the fluorescent treponema antibody absorption (FTA-ABS) test, and the treponema pallidum particle agglutination (TPPA) test. It is important to note that in ocular conditions, including PUK, both nonspecific and specific syphilis laboratory tests should be ordered. In cases where viral infections are suspected, hepatitis B, hepatitis C, and HIV antibodies should be evaluated [9]. Suspected TB can also be initially evaluated with either the purified protein derivative (PPD) skin test or QuantiFERON-TB Gold blood tests. The stool test may be helpful in PUK secondary to parasitic infections such as helminth infections.

In rare cases where the diagnosis is unclear, conjunctival or corneal biopsy can be performed to rule out unusual infectious or neoplastic causes of symptoms.

6. Management of Inflammatory PUK

6.1. Initial Medical Treatement

PUK, frequently stemming from systemic diseases, often necessitates early collaboration between ophthalmologists and rheumatologists. Depending on the systemic manifestations, involvement of other consultants and specialists such as nephrologists, dermatologists, pulmonologists, and infectious disease specialists may also be warranted. The primary objective is to promote corneal epithelial healing and arrest keratolysis by suppressing ocular inflammation. The initial treatment typically revolves around topical, local, and systemic corticosteroids. Prednisone is generally administered at a dosage of 1–1.5 mg/kg per day if infection suspicion is low. In cases of severe disease, intravenous methylprednisolone pulse therapy, implemented at 500–1000 mg daily for 1–3 consecutive days, may be administered. Preservative-free artificial tears are employed to address the

ocular surface issues and flush out inflammatory mediators. Topical corticosteroids are frequently beneficial; in mild cases, they can resolve the acute process as monotherapy [13]. Broad-spectrum antibiotics to prevent bacterial superinfection should be considered as a local adjunctive therapy alongside topical corticosteroids. Oral intake of vitamin C and MMP inhibitors like doxycycline may help to decelerate the process of keratolysis. [14,15].

Early procedures, including conjunctival resection or amniotic membrane placement, have also been reported to yield favorable outcomes. Other treatments that have shown anecdotal success include topical cyclosporine, autologous serum tears, topical medroxyprogesterone, and topical collagenase inhibitors [1]. Some authors argue that the use of autologous serum drops is contra-indicated in PUK if an underlying autoimmune cause is suspected because of the possible presence of pro-inflammatory agents in the serum. They propose using cord blood serum drops instead to circumvent this possibility. Additionally, Medroxyprogesterone 1% binds to glucocorticoid receptors, through which it can exert anti-inflammatory features. Additionally, it can promote collagen synthesis in the cornea by inhibiting neutrophil-related collagenases.

6.2. Immunomodulatory Therapy

Long-term immunomodulatory therapy (IMT) is essential to prevent recurrences and manage the underlying process effectively. Foster et al. [8] highlighted the significance of IMT in patients with RA presenting with necrotizing scleritis and PUK. They observed that the mortality rate among patients receiving glucocorticoid therapy alone was 54%, whereas it was 5% among those receiving IMT. Over time, with advancements in IMT and surgical techniques, mortality rates decreased [16]. In a cohort from 1987 to 2002, Timlin et al. [17] demonstrated that almost all patients who succumbed either discontinued IMT or experienced recurrence despite being on IMT [17]. A study from 2020 showed that patients without IMT had a mean estimated survival of 10.7 years, whereas those receiving IMT had a significantly longer mean estimated survival of 24.7 years among all patients with PUK [17].

It is crucial to emphasize that the escalation of IMT should occur even if PUK is the sole indication of disease activity and the other aspects of the underlying issue are fully under control. Additionally, the clinician should consider early initiation of IMT for individuals with undifferentiated PUK suspected to be of an autoimmune origin. These agents decrease disease mortality and ocular morbidity [4,18]. Since the response to IMT is invariably delayed, these agents should be commenced concurrently with an appropriate systemic corticosteroid therapy. The selection of the agent typically varies based on the underlying systemic diagnosis; however, as a general rule in choosing an agent, IMT follows a stepwise approach. Less potent medications with a safer side effect profile are implemented first. If the initial treatment proves ineffective on the highest possible dose, the next step involves employing a more potent medication with potentially more side effects. Considering the risk of potential serious adverse effects, careful monitoring and frequent follow-up visits are necessary to identify any adverse effects related to the drug or dosage. For female patients with child-bearing potential, risks to pregnancy should be discussed prior to initiating IMT. Immunosuppression can also increase the risk of life-threatening opportunistic infections. These risks should be thoroughly discussed with the patient before initiating IMT. IMT agents are classified into conventional (antimetabolite and T lymphocyte inhibitors), biologic response modifiers, and cytotoxic agents.

6.2.1. Conventional IMT

Methotrexate

Methotrexate is the most widely utilized IMT agent as the first line of treatment for less severe PUK especially associated with RA [19]. It primarily targets rapidly dividing cells, including T- and B-lymphocytes. Its dosing is convenient (once a week), and it is associated with less systemic toxicity compared to most other IMT agents. For protecting normal cells

in the body, vitamin B9 (folic acid) is used concurrently with methotrexate. Methotrexate can be toxic to the liver and close monitoring of liver function tests is strongly recommended.

Mycophenolate Mofetil

Mycophenolate mofetil is another effective antimetabolite with steroid-sparing properties and manageable side effects when administered at a dose of 1–3 g in two divided daily doses. Hand tremor is a distinctive side effect of mycophenolate mofetil, in addition to the general adverse effects seen with immunosuppressive therapy (IMT) agents. Additionally, mycophenolate mofetil has been associated with colitis; thus, it is recommended to take it on an empty stomach. Given these risks and the side effect profile, the dosage should be increased gradually in the beginning of the course of treatment.

Azathioprine

Azathioprine, a conventional IMT agent, is a safe alternative as well but exhibits lower efficacy. It typically takes at least 3–4 weeks after therapy initiation to induce a response. Before commencing treatment with azathioprine, it is essential to evaluate the level of the liver enzyme thiopurine methyl transferase (TPMT), as azathioprine is metabolized by this enzyme.

Calcineurin Inhibitors

Calcineurin inhibitors (CNIs) are a type of drug that alter immune cell activity to manage inflammatory conditions and support organ transplants. They function by inhibiting calcineurin, a protein involved in the inflammatory process. By suppressing the immune system, CNIs prevent the proliferation of T-cells. Cyclosporine A (CsA) stands as the preferred choice among IMT drugs within the CNI category. Its mechanism involves the inhibition of antigen-triggered signal transduction in T lymphocytes [20]. However, prolonged high-dose treatment with cyclosporine has been cautioned against due to its potential nephrotoxicity and systemic arterial hypertension [21]. Oral formulations are typically used in ophthalmology. It is crucial to note that topical cyclosporine A can serve as a supplementary treatment in PUK, as there exists an additive effect when combining CsA with other antimetabolites such as methotrexate, azathioprine, and mycophenolate mofetil [2,22]. Tacrilimus, as a calcineurin inhibitor with a deferent mechanism of action, has also been used successfully in treatment of patients with inflammatory PUK [9].

6.2.2. Biologic Response Modifier Agents

These agents include tumor necrosis alpha inhibitors (TNF-α inhibitors), anti-interleukin (IL) agents (targeting interleukins such as IL-1 and IL-6), B-cell receptor inhibitors (targeting ligands CD20 and CD22), anti-co-activation signaling (CTLA-4 antibodies), intravenous immunoglobulin (IVIg), and Janus kinase (JAK) inhibitors. These agents can be employed as monotherapy or in combination with conventional IMT [23].

TNF-α Inhibitors

Infliximab [24] and adalimumab [23,25] have been employed in cases of refractory PUK that have not responded to conventional treatments. Golimumab and certolizumab are other TNF-α inhibitor agents which have been employed in the treatment of underlying conditions in patients with PUK [26]. Among TNF-α inhibitor agents, etanercept is less effective and it is not recommended for patients with ocular inflammatory diseases, including PUK [27].

B Lymphocyte Inhibitors (Anti-CD20 Agents)

Rituximab is the most known agent in this class of medications. It stands as the most effective agent for maintaining remission in antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitides, such as GPA [28], microscopic polyangiitis [28], and RA [29]. A multicenter trial was conducted to compare anti-TNF-alpha agents versus

rituximab in patients with refractory PUK. Both treatments were found to be equally effective in addressing refractory PUK across various rheumatic conditions [30,31].

IL-6 Inhibitors

Tocilizumab is the best-known agent in this category of medications. The literature on using tocilizumab in PUK is notably sparse. There is no agreement on the impact of tocilizumab on PUK. Cohen et al. [32] documented that rare instances of PUK may arise in patients with longstanding RA following a transition to tocilizumab; however, Huang et al. [33] reported the potential efficacy of tocilizumab in managing PUK, advocating for vigilant patient monitoring.

Other Biologic Response Modifier Agents

While various biological agents such as the IL-1 receptor antagonist (anakinra), T cell-blocking agents targeting the Fc portion protein of the extracellular domain of CTLA-4 (abatacept), IL-17 inhibitors (secukinumab and ixekizumab), Janus kinase (JAK) inhibitors, and IVIg have been utilized in treating the autoimmune diseases causing PUK, their effectiveness specifically for PUK as an isolated condition remains unstudied [34].

6.3. Cytotoxic Medications

Cyclophosphamide

Cyclophosphamide, administered orally (up to 2 mg/kg daily) [35] or intravenously (up 1000 mg/m^2 every 3–4 weeks) [36], is another favored choice for enhancing immunosuppression in severe PUK cases. Due to its significant cytotoxicity, blood cell counts should be monitored at least every 2–3 weeks. Moreover, cyclophosphamide can lead to hemorrhagic cystitis and bladder cancer. Due to these potential side effects, adequate hydration with a daily intake of more than 3 L of fluids and regular urine analysis, every 1–2 weeks, is strongly recommended.

Table 2 summarizes immunomodulatory therapy agents in patients with PUK.

Table 2. Common systemic immunomodulatory therapy (IMT) agents in peripheral ulcerative keratitis (PUK).

Immunomodulatory Therapy Classes	Agents
Conventional Immunomodulatory Therapy	Metotrexate Mycophenolate Mofetil Azathioprine Cyclosporine A
Biologic Response Modifiers	Infliximab Adalimumab Rituximab
Cytotoxic Agents	Cyclophosphamide

6.4. Future Horizon for IMT in PUK

In recent years, advances in basic science have provided deeper insights into the mechanisms of the pathogenesis of PUK. The role of inflammasomes, such as NLRP3 and its cascades in the causation of PUK, has been particularly elucidated [9]. Additionally, increased expression of the GPR91 succinate receptor, which increases NF-κB activity, has also been associated with the pathogenesis of PUK [37]. These molecules could potentially serve as therapeutic targets for IMT in PUK in the future.

6.5. Surgical Management

Surgery for PUK should be postponed until sufficient immunosuppression has been attained, as there is a high risk of graft melts and PUK recurrence, except for urgent

surgeries secondary to PUK complications such as perforation. In such cases, high-dose systemic corticosteroids are warranted perioperatively [1,9].

Systemic immunosuppression helps manage the underlying inflammation in PUK, lowering the incidence of graft melts and rejection rates, thus improving the outcomes of surgery. Surgical options are selected based on factors such as the size of perforation or thinning and the extent of ocular disease. In cases involving corneal thinning, potential surgical options include amniotic membrane transplantation (AMT) and conjunctival resection/recession [9].

7. Treatment Protocols for PUK in Specific Systemic Conditions

7.1. GPA and Polyarteritis Nodosa (PAN)

These two life-threatening and sight-threatening conditions should be initially treated aggressively with systemic corticosteroids and cyclophosphamide. Rituximab [28] and cyclophosphamide [38], either as monotherapy or combined with other agents, have demonstrated significant success in the long-term treatment of inflammation in PUK associated with GPA.

7.2. RA

Systemic corticosteroid, when combined with conventional IMT, particularly methotrexate, are regarded as the standard treatment for the acute phase of active PUK [19]. However, more severe and aggressive cases of PUK associated with RA should be treated with rituximab or cyclophosphamide [30,35,36].

7.3. Mooren's Ulcer

The distinction between PUK and MU is important for guiding appropriate treatment, especially regarding the need for systemic versus localized therapies. The current treatment approach for MU follows a "stepladder approach". This approach begins with initial treatment using topical corticosteroids and topical cyclosporine 0.05 to 2%, progressing to limbal conjunctival resection or excision in cases with no response [9]. Subsequently, systemic immunosuppression is implemented, starting with conventional immunomodulatory therapy (IMT), before progressing to biologic response modifiers, and eventually considering cytotoxic medications. It is worth noting that the stepladder approach with immunomodulatory therapy (IMT) is implemented in all types of PUK cases with unknown etiology. In MU secondary to hepatitis C virus, treatment with interferon α2b, as a biologic agent, is recommended. This therapy has been demonstrated to aid in the resolution of corneal ulceration [39].

8. Strategy

The stepladder approach is a therapeutic strategy for managing PUK. Corticosteroids, administered through various routes, serve as the primary treatment in acute cases, with systemic corticosteroids reserved for more severe presentations. For long-term management, immunomodulatory therapy should be considered. Conventional immunomodulatory agents are typically the second line of treatment; however, in cases that are severe or resistant, biologic response modifiers (biologics) can be used as an alternative second-line therapy. In extreme situations, cytotoxic agents like cyclophosphamide may be employed as a last resort to prevent corneal melting or perforation in PUK patients.

9. Conclusions

PUK is a sight-threatening corneal disorder that raises concerns among both ophthalmologists and rheumatologists, as it may indicate an impending serious and life-threatening medical condition. Recurrences are common in cases of PUK, particularly among those treated with insufficient immunosuppression. Specific protocols are available for PUK with known underlying systemic conditions. In cases of PUK with an unknown systemic underlying etiology, a stepladder IMT approach is implemented. This involves starting

with conventional IMT, advancing to biologic therapies, and ultimately considering cytotoxic medications. However, due to the delayed onset of action of these agents, a course of systemic corticosteroids is strongly recommended as a bridge to IMT. Given the side effect profiles of IMT agents, a close monitoring of the complete blood count, liver function tests, kidney function tests, and urine tests are strongly recommended. Additionally, since cyclophosphamide can lead to potential side effects of hemorrhagic cystitis and bladder cancer, regular urine analysis is advised. Considering the serious ophthalmic and systemic adverse effects associated with corticosteroid use via any route of administration, the treatment goal is achieving steroid-free remission.

Author Contributions: A.M.: conceptualization, investigation, writing—original draft, writing—review and editing, supervision, T.V.: investigation, writing—review and editing, Y.M.: investigation, writing—review and editing, M.L.R.: writing—review and editing, C.S.F.: conceptualization, writing—review and editing, supervision, S.D.A.: conceptualization, writing—review and editing, supervision. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

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