· Review ·

Research progress on the pathogenesis and clinical treatment of recurrent aphthous ulcer

Liyang Jiang[1#], Huanhuan Wang[1#], Huayan Sun[1], Fenghua Xu[1*], Rui Xiao[2*]

[1]Department of Pharmacy, Medical Supplies Center of PLA General Hospital, Beijing 100853, China.
[2]Department of Stomatology, The First Medical Center of PLA General Hospital, Beijing 100853, China.

Abstract

Recurrent aphthous ulcer (RAU) is the most common oral mucosal disease with the highest incidence rate worldwide, accounting for 20%–50% of the population. RAU has a large effect on the daily diet, language communication, and quality of life of patients. With the rapid development of biotechnology in recent years, research on the pathogenesis of RAU has made breakthrough progress in the past 5 years. This review systematically summarizes the latest achievements of understanding RAU in the field of cellular and molecular biology in recent years. This review focuses on the new discoveries at the levels of immune cell subset dysfunction, cytokine network imbalance, abnormal proteomics of epigenetic regulation, microorganisms, and signaling pathways. This article also discusses in detail the efficacy characteristics and applicable symptoms of innovative drugs used in clinical practice in the past 5 years. These drugs include the new Class 1.1 innovativetraditional Chinese medicine (TCM) Catechu Shangqing pill, the targeted preparation apremilast, the natural product cannabidiol gel, and a new drug delivery carrier. Studies have shown that the breakthrough of basic research is promoting transformation of the clinical treatment mode of RAU from traditional symptomatic intervention to precision and individualization. The clinical implementation of biomarker detection, targeted therapy, immune regulation, and other technologies provides a new direction for the diagnosis and treatment of RAU. This review aims to provide researchers and clinicians in the field of stomatology with cutting-edge developments in the pathogenesis and treatment of RAU, and to help further improve research in this field.

Keywords: recurrent aphthous ulcer, pathogenesis, clinical medication

Introduction

Recurrent aphthous ulcer (RAU), commonly known as recurrent oral ulcer, is the most common chronic inflammatory oral mucosal disease [1–6]. The typical features of RAU are periodic attacks and self-healing.

#These authors contributed equally to this work.
F.X. and R.X. were co-corresponding authors.
***Correspondence:**
Fenghua Xu; Email: xufh@301hospital.com.cn
Rui Xiao; Email: xiao_rui0809@163.com

The clinical manifestations of RAU are round or oval superficial ulcers in the oral mucosa, accompanied by typical symptoms of red, yellow, concave, and painful [7-10]. Globally, the prevalence of RAU is between 10% and 20%. The prevalence of RAU in some specific populations (e. g., people with immune dysfunction) can be up to 50%, and its prevalence in women is higher than that in men. Adolescents and young adults aged 10–30 years are a high-risk group [11, 12].

Although the incidence of RAU remains high, its etiology and pathogenesis are not fully understood. Traditionally, the occurrence of RAU is thought to be related to genetic factors, immune status, infection, nutritional deficiency, mental stress, and other factors [13,14]. In the past 5 years, with the development of high-throughput technologies, such as genomics, proteomics, and transcriptomics, as well as an improvement in the understanding of the immune system, new breakthroughs have been made in the study of the pathogenesis of RAU. Notable developments have been in the fields of immune cell dysfunction, cytokine network imbalance, and epigenetic regulation, which provide a new perspective for analyzing the pathogenesis of RAU.

Furthermore, based on the research results of the pathogenesis of RAU, its clinical treatment is constantly innovating. In the past 5 years, a variety of innovative drugs with independent intellectual property rights have been successfully approved, including the new traditional Chinese medicine class 1.1 drug Catechu Shangqing pill, the targeted drug apremilast, and the natural product cannabidiol gel. These drugs have not only achieved a breakthrough in efficacy, but also represent the transformation of RAU treatment from traditional empirical medicine to precision medicine.

This article systematically reviews the latest research progress of RAU in the field of pathogenesis and clinical medication in recent years, focusing on innovative discoveries in cell biology and molecular biology, as well as the transformation path from basic research results to clinical practice. Using an in-depth analysis of the latest literature, this review provides innovative information of the diagnosis and treatment of RAU for dental researchers and clinicians, and will promote further development of research and application in this field.

New progress in basic research on the pathogenesis of RAU

Mechanism of abnormal function of immune cell subsets

Pedersen et al. quantitatively studied peripheral blood T lymphocyte subsets (helper T [Th] cells and suppressor T [Ts] cells) in 20 patients with RAU in the ulcer stage and inactive stage. The T lymphocyte subsets were compared with those of matched control donors without a history of RAU. There was a higher number of Ts cells in patients with RAU than in controls. Therefore, the ratio of Th cells to Ts cells in the two stages of patients with RAU was lower than that in controls. At these two stages, there was no significant difference in the number of Th cells between the patients and the controls. This study supports the hypothesis that RAU is an immunodeficiency disease [15].

The role of Th17 cells in the pathogenesis of RAU has gradually become a research hotspot. In 2023, studies showed that the cytokines secreted by Th17 cells are essential for maintaining oral immune homeostasis. When epithelial cells are stimulated by antigens, Th17 cells proliferate and differentiate release inflammatory factors, recruit other lymphocytes to clear infection, and then maintain the integrity of the epithelial barrier. However, excessive activation of the Th17/interleukin

(IL)-17 axis may lead to autoimmune damage [16].

Ryder et al. investigated whether there are signs of immunodeficiency or activation of peripheral blood mononuclear cells in patients with RAU by three-color immunofluorescence staining flow cytometry, which has not been previously applied in such patients. The subjects included 13 patients with active RAU, 14 patients with inactive RAU, and 18 healthy volunteers without a history of RAU as controls. The most significant finding was that the proportion of T cell receptor γδ + cells (median percentage: 8.5%) in patients with active RAU was significantly higher than that in controls (median percentage: 2.8%; $p < 0.001$) and in patients with inactive RAU (median percentage: 5.0%; $p < 0.01$). These results indicate immune stimulation during exacerbation of RAU [17].

Imbalance mechanism of the cytokine network

Al-Samadi et al. found that IL-17C was highly expressed in epithelial cells of RAU lesions. This high IL-17C expression appears to stimulate oral keratinocytes to produce pro-inflammatory cytokines through IL-17RA/IL-17RE, indicating that human oral epithelial cells may be important inflammatory cells in RAU. These findings provide a new perspective on the role of IL-17 in the pathogenesis of RAU and indicate the importance of IL-17-related pathways in the inflammatory response of RAU [18].

Xiang et al. studied the relationship between IL-17A rs2275913 and IL-17F rs763780 single-nucleotide polymorphisms and the incidence and severity of RAU in the Han population. After excluding the effect of age, body mass index, sex, smoking status, and drinking status, the rs2275913 polymorphism of the *IL-17* gene was associated with the risk of RAU. The risk of RAU in the AA genotype was 2.759 times higher than that in the GG genotype, and the risk of RAU in A allele carriers was 1.783 times higher than that in G allele carriers. The polymorphism of rs763780 was also associated with the risk of RAU. The detection rates of the TC genotype, CC genotype, and C allele in patients with RAU were higher than those of the TT genotype. The risk of the TC genotype was 1.895 times that of the TT genotype. The risk of the CC genotype was 4.080 times that of the TT genotype. The risk of C allele carriers was 1.969 times that of T allele carriers. Additionally, serum IL-17 concentrations in patients with RAU were higher than those in controls. Furthermore, IL-17 concentrations were associated with the polymorphisms of the two above-mentioned IL-17 gene loci [19].

As a key pro-inflammatory cytokine, tumor necrosis factor (TNF) -α plays a role in the pathogenesis of RAU. Surboyo et al. evaluated TNF-α levels in saliva, serum, and RAU lesions by a comprehensive search of multiple databases, such as PubMed and Scopus. They found that TNF-α levels in healthy people were lower than those in patients with RAU. Although there were differences in samples and detection types between databases, significant differences in TNF-α levels between the two groups were detected. This finding indicated that TNF-α was closely related to the pathogenesis of RAU, but the specific mechanism still needs to be investigated [20].

Wu et al. used Revman 5.3 software in a meta-analysis to evaluate the association between cytokine gene polymorphisms, such as IL-1β (−511C/T) and IL-1β (+3954C/T), and RAU. They showed that the T allele in IL-1β (−511C/T) increased the probability of recurrent aphthous stomatitis in the European population, and the C allele in IL-1β (+3954C/T) was associated with the risk of recurrent aphthous stomatitis in Americans. These findings indicate that IL-1β gene polymorphism

is associated with the risk of recurrent aphthous stomatitis [21].

Epigenetic regulation mechanism

The role of epigenetic regulation in the pathogenesis of RAU has been a research hotspot in recent years. MicroRNA (miRNA), which is an important post-transcriptional regulatory molecule, plays a key role in immune regulation and the inflammatory response of RAU. Manoj et al. studied three groups of key and functional miRNA–protein regulatory pairs that were screened out through the combined analysis of proteomics and transcriptomics. These pairs were miR-8058-lactate dehydrogenase A, miR-4802-5p-serine protease inhibitor A1, and miR-4802-5p-superoxide dismutase 3. The miRNA miR-8058 promotes the progression of RAU by targeting the expression of lactate dehydrogenase A, aggravating oxidative stress, and releasing inflammatory factors. Additionally, miR-4802-5p can directly target serine protease inhibitor A1, weaken its anti-inflammatory and protease activity, and indirectly promote upgrading of the inflammatory response of RAU to promote disease progression. Furthermore, miR-4802-5p can target superoxide dismutase 3 and enhance the antioxidant capacity of the body by regulating the expression of this key antioxidant enzyme, thereby inhibiting the development of RAU. These findings further reveal the major role of oxidative stress and the inflammatory response in the pathogenesis of RAU [12].

DNA methylation is another important epigenetic regulation mechanism. Yuan et al. found that there was hypermethylation in the promoter region of the IL-4 gene in patients with RAU, especially the methylation rates of CpG (−1556), CpG (−1483), and CpG (−1479), and the other 10 CpG sites were higher than those in healthy controls. IL-4 gene promoter hypermethylation was significantly negatively correlated with IL-4 mRNA expression levels ($r = -0.494$, $p < 0.05$). This finding suggested that DNA methylation is involved in the pathogenesis of RAU by inhibiting IL-4 gene transcription. Additionally, their study also showed that smoking behavior and vitamin B12 and folic acid levels were significantly correlated with the overall methylation rate of the IL-4 gene promoter. This finding indicated that environmental factors may be involved in the pathogenesis of RAU by affecting DNA methylation [22].

New discovery in proteomics

Lewkowicz et al. found that excessive activation of the complement system is an important finding in the pathogenesis of RAU. Studies have shown that serum complement C3 and C4 concentrations in patients with RAU are reduced, while those of complement activation products (e.g., C3a and C5a) are increased, indicating that the complement system in patients with RAU is over-activated. Excessive activation of the complement system may directly damage oral mucosal epithelial cells by forming a membrane attack complex or recruit inflammatory cells by releasing allergic toxins to aggravate local inflammatory responses [23].

There is also abnormal expression of immunoglobulin and complement-related proteins in patients with RUA. Studies have shown that serum immunoglobulin (Ig) M concentrations in patients with RAU are reduced, while IgE concentrations are increased. A decrease in IgM concentrations may affect the efficiency of the first immune response, and an increase in IgE concentrations may indicate the possibility of an allergic reaction or parasitic infection. This abnormal immunoglobulin expression may be involved in the immunopathological process of RAU [24].

Relationship between the microbiome and RAU

Shuai et al. studied 130 patients with RAU who were treated in a hospital from June 2020 to May 2021. They were divided into the ulcer group and the healing group according to the stage of development of RAU. Sixty-five healthy people who underwent a physical examination during the same period were included as the control group. The percentages of gram-positive cocci, gram-negative cocci, gram-positive bacilli, gram-negative bacilli and cocci, straight bacilli, fusiform bacteria, filamentous bacteria, *Campylobacter*, and spirochetes in the three groups were detected and compared. They found that there were differences in the percentages of gram-negative cocci, cocci, straight bacilli and fusiform bacteria between the three groups. This finding suggested that changes in microbial flora may be related to the pathogenesis and prognosis of RAU [25].

Existing meta-analysis evidence indicates a significant association between Helicobacter pylori infection and RAU, with a pooled OR of 1.83 (95% CI: 1.41-2.37, P=0.001). Subgroup analyses suggest that detection methods are a key source of heterogeneity: PCR and urea breath test (UBT) both confirm a significant correlation, while ELISA shows no statistically significant difference. This implies that the effect of H. pylori on RAS may vary by detection method and sample source, and further large sample and standardized clinical studies are needed to clarify its exact role [26].

Abnormal activation of signaling pathways

Zhu et al. searched the HERB and Diseases databases for the chemical constituents and target genes of the compound medicinal materials of Kouchuang adhesive powder and the target genes related to oral ulcers. The candidate target genes were found by intersection processing, and then g：Profiler was used to enrich and analyze these genes to identify the main signaling pathways. Additionally, the effect of Kouchuang adhesion powder on the activity of oral epithelial cells was evaluated by *in vitro* experiments. Furthermore, the therapeutic effect and molecular mechanism of an acetic acid-induced oral ulcer rat model were observed in *in vivo* experiments. A network pharmacology analysis showed that KOJS may affect cell proliferation, apoptosis, migration and the immune inflammatory response mainly by regulating nuclear factor-κB (NF-κB) and other signaling pathways. The rat experiments showed that this drug reduced mucosal injury of rats with oral ulcers induced by acetic acid, improved pathological changes, and promoted the proliferation and recovery of oral mucosal epithelial cells. Additionally, in this model, the disorder of inflammatory factors in rats induced by acetic acid was improved, and activation of the nuclear transcription factor-κB signaling pathway was inhibited [27].

The PI3K-Akt signaling pathway plays a key role in cell survival, proliferation, and metabolism. Zhai et al. found that the core prescription of the Chinese medicine specialist Li Diangui in the treatment of RAU may play a therapeutic role by regulating the PI3K-Akt signaling pathway. The activation of this pathway may promote the repair and regeneration of oral mucosal epithelial cells and inhibit the inflammatory response [28].

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway is indispensable in cytokine-mediated immune responses. Zhao et al. showed that cytokines, such as IL-6 and IL-17, can activate the JAK-STAT pathway, leading to the activation of transcription factors such as STAT3, thereby regulating the expression of inflammation-re-

lated genes. In patients with RAU, this pathway may be over-activated, resulting in an uncontrolled inflammatory response [29].

Clinical medication of RAU

Breakthrough of innovative drugs of traditional Chinese medicine

In the past 5 years, innovative drugs of traditional Chinese medicine have made important breakthroughs in the field of RAU treatment. The Ercha Shangqing pill is a class 1.1 innovative drug of traditional Chinese medicine developed by Hubei Qijin Pharmaceutical Co., Ltd. This medicine was approved by the State Drug Administration in January 2024 and became the first class 1.1 innovative drug with independent intellectual property rights for the treatment of mild RAU with upper energizer excess heat syndrome.

The therapeutic mechanism of Ercha Shangqing pills for light RAU upper Jiao excess heat syndrome is not only in line with the traditional Chinese medicine theory, but also supported by modern pharmacological research. This drug shows "clearing heat and purging fire, detoxifying and astringing sores" as the core treatment principle, and closely follows the root cause of upper energizer excess heat in RAU. Through the synergistic effect of the active ingredients in the prescription, this drug clears away the heat toxin accumulated in the upper energizer and dissipates the heat of the mouth and tongue. At the same time, Ercha Shangqing pills converge the ulcer wound, detumescence, and pain relief, and fundamentally alleviate the related symptoms. From the perspective of modern pharmacology, this drug exerts anti-inflammatory and analgesic effects by inhibiting the release of inflammatory factors, such as IL-6 and TNF-α, blocking pain signal transmission, improving local blood circulation of ulcers, promoting the proliferation and repair of mucosal epithelial cells to accelerate wound healing, and moderately regulating the body's immune function to reduce the probability of recurrence. Furthermore, Ercha Shangqing pills have an inhibitory effect on common oral pathogens, reduce wound infection, and remove toxic metabolites in the body, and finally achieve the synergistic therapeutic effect of "local symptomatic relief plus systemic conditioning" [30].

The results of phase III clinical trials of Catechu Shangqing pills are exciting. In a clinical trial of 360 patients, the target ulcer healing rate of the Catechu Shangqing pill group reached 70.89%, while that of the placebo group was only 36.75% ($p < 0.0001$). Additionally, the Catechu Shangqing pill group was superior to the placebo group for all key indicators, such as the ulcer healing rate, ulcer healing time, and target ulcer healing time. These data indicate the important effects of Catechu Shangqing pills [31].

The successful listing of Jiaoercha Shangqing pills is of great importance. First, this is the only new class 1.1 drug for the treatment of mild RAU with upper energizer excess heat syndrome. Second, this drug is delivered by oral administration, directly acting on the lesion site, avoiding the first-pass effect of the liver, increasing the local drug concentration, and reducing systemic adverse reactions. Finally, as an innovative drug of traditional Chinese medicine, Catechu Shangqing pills have the unique advantages of traditional Chinese medicine in the treatment of RAU. These pills provide a new choice for the treatment of RAU with integrated traditional Chinese and Western medicine.

Clinical application of targeting drugs

The pathogenesis revealed by basic research provides

a clear target for targeted therapy. Although TNF-α inhibitors have not been approved for RAU, studies to investigate their application prospects have been performed. Based on the key role of TNF-α in the pathogenesis of RAU, anti-TNF-α therapy may be effective for patients with severe RAU. Similarly, IL-17 inhibitors and IL-23 inhibitors are also being investigated, especially for RAU subtypes associated with the IL-17/IL-23 axis.

The successful application of phosphodiesterase 4 (PDE4) inhibitors is a model of clinical transformation of targeted therapy. Apremilast, which is a PDE4 inhibitor, is a model of clinical transformation of RAU targeted therapy. The core target of apremilast is PDE4, which increases intracellular cyclic adenosine monophosphate levels by specifically inhibiting PDE4 activity. This inhibition accurately regulates the production and release of inflammatory factors and intervenes in the inflammatory response process of RAU at the molecular level. The clinical indications have covered RAU, and apremilast has also been approved for autoimmune inflammation-related diseases, such as plaque psoriasis and psoriatic arthritis. This targeted therapy model based on a clear molecular mechanism is effective. This therapy can effectively reduce the recurrence of RAU ulcers and relieve symptoms, with controllable adverse reactions and good safety. The clinical success and expansion of indications of apremilast also provide an important reference for the development, exploration of mechanisms, and clinical transformation of targeted drugs for RAU and other autoimmune inflammatory diseases [32].

As emerging targeted drugs, JAK inhibitors have also shown potential in RAU treatment. Based on the key role of JAK inhibitors in the JAK-STAT signaling pathway in cytokine-mediated immune responses, JAK inhibitors may play a therapeutic role by blocking the signal transduction of various pro-inflammatory cytokines. At present, a variety of JAK inhibitors have shown good efficacy in autoimmune diseases, and their application in RAU is promising [33–35].

Clinical investigation of chemical preparations of natural products

Cannabidiol (CBD) gel is a biological agent that has emerged in the treatment of RAU in recent years. CBD is a non-psychoactive component in cannabis plants, and it has a variety of pharmacological effects, such as anti-inflammatory, anti-oxidant, and immune regulation. Studies have shown that CBD promotes oral ulcer healing by inhibiting cytosine/uridine monophosphate kinase 2-mediated NLRP3 inflammasome activation and pyroptosis. A study showed that CBD oral spray showed efficacy in mouse tongue acid-induced or wound-induced oral ulcer models, and it could inhibit inflammation, relieve pain, and accelerate lesion healing. A mechanism study showed that the expression of genes related to the NLRP3 inflammasome pathway was downregulated after CBD treatment, the expression of lysed gasdermin D was decreased, and the percentage of cells that underwent pyroptosis was decreased. CBD can also reduce the expression of cytosine/uridine monophosphate kinase 2, thereby inhibiting the production of oxidized mitochondrial DNA and inhibiting the activation of inflammasomes [36]. Kongkadee et al. studied the inhibitory effects of cannabis extract and CBD on TNF-α and IL-1β in lipopolysaccharide-induced mouse macrophages and the wound healing activity of human gingival fibroblasts *in vitro*. They showed that cannabis extract and CBD reduced the release of TNF-α and IL-1β and promoted wound healing of human gingival fibroblasts, These findings indicate the potential benefits of CBD in the treatment of oral inflammation and ulcers [37].

Innovation of new drug delivery systems

In the past 5 years, the innovation of drug delivery systems has led to new breakthroughs in RAU treatment. Traditional oral or topical drugs often have problems, such as low local drug concentrations, a short action time, and systemic adverse reactions. The development of new drug delivery systems has greatly improved the therapeutic effect by improving the targeting and bioavailability of drugs.

Microneedle patch technology is an innovative delivery system that has attracted much attention in recent years. A patent study in 2021 reported a soluble drug-loaded microneedle patch based on three-dimensional printing technology. The patch uses a biocompatible polymer as a microneedle matrix, composite growth factors, and antibacterial drugs, and a layered structure is constructed by centrifugal perfusion. The microneedle patch has the advantages of good biocompatibility, it is minimally invasive, and it is painless. Microneedle patch technology can pierce the ulcer surface and dissolve immediately, and effectively release the loaded therapeutic drugs into the deep layer of the ulcer surface. This technique achieves the dual purpose of inhibiting the formation of the bacterial membrane and promoting ulcer healing [38].

The advantage of the microneedle patch lies in its unique mode of administration. Traditional topical drugs are difficult to penetrate into the deep layer of ulcers, while microneedle patches can directly deliver drugs to the lesion site and increase local drug concentration. Additionally, the dissolution characteristics of microneedles avoid the pain of removal and improve patients' compliance. Furthermore, through the hierarchical design, controlled release of drugs can be achieved, and the action time can be prolonged [39].

Progress of precision medicine in RAU treatment

Based on an in-depth study of the pathogenesis of RAU, its treatment is changing from traditional empirical medicine to precision medicine. Genetic testing has begun to be applied to individualized treatment of RAU. Studies have shown that IL-17A and IL-17F gene polymorphisms are associated with the risk of RAU, and patients with specific genotypes may respond differently to immunomodulatory therapy. Therefore, predicting the patient's treatment response using genetic testing can provide a reference for clinicians to choose the appropriate treatment plan.

The assessment of immune function is another important aspect of precision medicine. By detecting T cell subsets, cytokine levels, immunoglobulins, and other indicators, doctors can fully understand the immune status of patients and develop individualized immune regulation programs. In patients with hyperfunction of Th17 cells, targeted therapy targeting the IL-17 pathway may be an option. Additionally, in patients with low Treg cell function, treatment strategies that enhance Treg cell function can be used.

The combination of traditional Chinese medicine syndrome differentiation and modern molecular biology has opened up a new method for the precise treatment of RAU. A network pharmacological study in 2024 showed the mechanism of the core prescription of the Chinese medicine specialist Li Diangui for treating RAU. He found that this prescription mainly played a therapeutic role through the PI3K-Akt signaling pathway and the ACE-RACE signaling pathway. This traditional Chinese medicine syndrome differentiation and treatment based on molecular mechanisms not only improves the therapeutic effect on RAU, but also provides a foundation for the standardization and inter-

nationalization of traditional Chinese medicine.

Summary

In the past 5 years, important progress has been made in the pathogenesis and clinical treatment of RAU. In the field of basic research, the in-depth determination of the mechanisms of immune cell subset dysfunction, cytokine network imbalance, epigenetic regulation abnormalities, proteomics changes, and microbiome disorders provides a comprehensive theoretical basis for understanding the complex pathogenesis of RAU. In particular, the imbalance of regulatory T cells and Th17 cells, abnormal activation of the IL-17/IL-23 axis, and regulation of key miRNAs have not only improved the understanding of the pathogenesis of RAU, but also suggested a direction for the development of new treatment strategies.

In clinical treatment, a variety of innovative drugs and treatment methods for RAU have emerged in the past 5 years. The development of Catechu Shangqing pill, which is a new class 1.1 drug of traditional Chinese medicine, represents a major breakthrough in the field of RAU treatment. The targeted drug apremilast shows good therapeutic prospects by inhibiting PDE4. Furthermore, natural product preparations, such as CBD gel, show unique advantages for treating RAU. Finally, new drug delivery systems, such as microneedle patches and nanocarriers, have greatly improved the targeting and bioavailability of drugs. These innovations not only enrich the treatment options of RAU, but also reflect the trend from traditional empirical medicine to precision medicine.

Substantial progress has been made in the transformation from basic research to clinical application. Biomarker detection has become an important means of diagnosing and monitoring RAU. Precision medicine based on gene polymorphism and immune function assessment is gradually being realized. New strategies, such as targeted therapy and immunomodulatory therapy, have shown good results in clinical practice. The formulation of individualized treatment plans is more scientific and accurate than without individualization. This transformation has not only improved the diagnosis and treatment of RAU, but also provided an important reference for the research and treatment of other oral mucosal diseases.

However, the research and treatment of RAU still face many challenges. The complexity of the pathogenesis of RAU causes difficulty in making breakthroughs in the treatment of a single target. Additionally, the heterogeneity between different patients requires more accurate individualized treatment. Moreover, although the existing treatment methods are effective, they still cannot completely prevent the recurrence of RAU. Therefore, the long-term safety and efficacy of new drugs for RAU still need more clinical verification.

Looking forward to the future, the research and treatment of RAU should develop in the following directions. (1) Further study of the heterogeneity of RAU and establishment of a precise diagnosis and treatment system on the basis of molecular typing are required. (2) The development of more pathogenesis-based targeted drugs, especially biological agents targeting key signaling pathways and cytokines, is necessary. (3) Artificial intelligence and big data should be applied in the diagnosis and treatment of RAU, and intelligent diagnosis and treatment decisions should be realized. (4) Research of integrated traditional Chinese and Western medicine should be further pursued to apply the advantages of traditional Chinese medicine to the treatment of RAU.

In summary, the progress of research on the pathogen-

esis of RAU and its clinical treatment in recent years is encouraging. With the improvement of basic research and the continuous innovation of clinical technology, we believe that RAU, which has been present for thousands of years, will eventually be overcome and the quality of life of patients will be considerably improved.

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Author contributions

Liyang Jiang and Huanhuan Wang contributed equally to this work. Liyang Jiang and Huanhuan Wang conducted the literature review, and drafted the manuscript. Huayan Sun contributed to literature collection and manuscript editing. Fenghua Xu and Rui Xiao conceived and designed the study, supervised the project, critically revised the manuscript for important intellectual content, and finalized the manuscript. All authors reviewed and approved the final version of the manuscript.

Conflict of interest

All authors declare no conflicts of interest.

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