JANUS KINASE INHIBITORS FOR RELAPSING POLYCHONDRITIS TREATMENT: A HYPOTHESIS

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Abstract
Relapsing polychondritis (RP) is a rare autoimmune disease marked by recurrent episodes of inflammation impacting cartilaginous structures. The underlying mechanism has not been fully elucidated; however, comprehensive genetic and histopathological evaluations have revealed the involvement of specific genes, cell-mediated immunity, and humoral immunity in the pathogenesis of RP. The spectrum of symptoms associated with this condition ranges from mild manifestations to severe, life-threatening presentations. Treatment options vary depending on the disease severity. Non-steroidal anti-inflammatory drugs, colchicine, dapsone, and systemic corticosteroids are commonly utilized as first-line therapeutic options. Furthermore, cyclophosphamide, methotrexate, azathioprine, cyclosporine, and biological disease-modifying anti-rheumatic drugs are employed as second-line treatment. Nevertheless, there is insufficient data regarding the use of Janus kinase inhibitors (JAKi) in RP patients as a treatment option. This hypothesis suggests that JAKi may be a viable treatment option for relieving symptoms in these patients.

Keywords: Autoimmune disease, Hypothesis, Janus kinase inhibitors, Relapsing polychondritis


INTRODUCTION
Relapsing polychondritis (RP) manifests as an autoimmune inflammatory disorder typified by recurrent episodes directed towards cartilaginous structures and tissues abundant in proteoglycans across various anatomical sites in the organism. The principal structures afflicted by RP predominantly involve cartilaginous tissues, spanning the auricular, nasal, respiratory, and articular regions. It is imperative to note that RP can also affect non-cartilaginous tissues such as the skin and heart [1]. Up to 35% of RP patients exhibit concurrent or associated comorbidities, including connective tissue diseases (rheumatoid arthritis, Sjögren syndrome, etc.), spondyloarthritis (ankylosing spondylitis, psoriatic arthritis), vasculitis (antineutrophil cytoplasmic antibody-associated vasculitides, polyarteritis nodosa, Behçet disease), hematological disorders (myelodysplastic syndromes and lymphoma) and autoimmune thyroid diseases [2-4].

The clinical manifestations of RP encompass a spectrum ranging from mild, intermittent auricular, and nasal chondritis to severe presentations with life-threatening implications, including tracheobronchial and cardiovascular involvement (Figure 1).

The well-known clinical symptom of RP is usually auricular chondritis [5]. Notwithstanding the potential for
an insidious onset, auricular chondritis typically presents acutely. Nasal chondritis constitutes a prevalent manifestation observed in 53% of patients throughout the disease [5,6]. In these patients, "saddle nose" deformity can be observed as a consequence of the progressive destruction resulting from recurrent inflammation [5,7]. Laryngeal and tracheobronchial involvement has been documented in up to 10% of RP patients. This involvement can be life-threatening by causing respiratory tract infection [2,5,7]. Musculoskeletal involvement stands as the second most prevalent manifestation. Arthritis commonly manifests as the initial symptom in 30% of cases, and it subsequently develops over time in 50-85% of patients [5,6]. Cardiovascular involvement which consists of valvular and vascular manifestations, arrhythmias and conduction defects, pericardial and myocardial involvement, is relatively rarer than ear/nose and musculoskeletal system involvement [8]. Ocular symptoms have been documented in up to approximately 60% of RP patients [1,9]. Neurological symptoms have also been delineated in these patients, and the implicated etiological mechanism is postulated to involve concurrent vasculitis [10]. Renal disease is relatively rare. Cutaneous manifestations may ultimately arise in up to 35% of patients as the disease progresses [5].

The underlying mechanism is still elucidated; however, a predominant hypothesis posits that autoimmune responses targeting type II collagen constitute a pivotal factor in the pathogenesis under consideration [1]. Certain specific genes, namely HLA-DR4, HLA-DQB1*05:02, HLA-B*67:01, and HLA-DRB1*16:02, have been identified as significantly linked to RP manifestations [4,5]. Furthermore, the pathogenesis is intricately influenced by both humoral and cell-mediated immune responses. The examination of gene expression in Peripheral Blood Mononuclear Cells (PBMCs) uncovered indications of regulatory T cell (Treg) exhaustion or anergy in individuals with RP, concomitant with aberrations in T cell functionality linked to heightened activation of innate immune cells [4,11]. Ultimately, Treg cells are thought to have a fundamental role in the cell-mediated immunity of patients with RP. In histopathological evaluations, CD4+ Th and natural killer T (NKT) cells, and CD68+ monocytes/macrophages, plasma cells, and neutrophils have been determined in specimens from cartilage tissue and skin. Moreover, there is empirical evidence indicating eosinophil infiltration within conjunctival, nasal cartilage, and skin biopsy specimens [4,5,11,12]. Within humoral responses, the release of Th cell-associated cytokines, IFNγ, and interleukin-10 (IL-10) exhibits disparate levels contingent upon the states of inflammation status. Consequently, a reduction in IL-10 levels, coupled with elevated levels of interleukin-1 beta (IL-1β) and interleukin-6 (IL-6), has been noted during inflammatory states. Conversely, heightened IL-10 levels and diminished concentrations of IL-1β and IL-6 have been reported during periods of steady-state [4,11]. The transient shift in gene expressions from anti-inflammatory to pro-inflammatory attributes within immune cells over short intervals may be implicated in the relapsing nature of the disease course [11].

**Treatment**

Patients with RP can be categorized into two subgroups as 'mild' and 'severe' according to the course of the disease. Mild manifestations include chondritis affecting the ears and nose, along with arthritis. Furthermore, severe manifestations consist of laryngotracheal and cardiovascular involvement, renal and neurologic disease, as well as instances of severe or recurrent arthritis [2,5]. Non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, and dapsone can be used in patients with mild symptoms [2,5,13]. Generally, systemic corticosteroids (oral and intravenous) are utilized as first-line treatment for severe and life-threatening symptoms. As a second-line therapeutic approach for patients experiencing a severe disease course, medications such as cyclophosphamide, methotrexate, azathioprine, and cyclosporine have been employed [2,5,7]. In the literature, biological disease-modifying anti-rheumatic drugs (bDMARDs), comprising TNF inhibitors (including etanercept, infliximab, and adalimumab), tocilizumab, anakinra, rituximab, and abatacept, have been used in patients demonstrating refractoriness to conventional therapeutic modalities. The dosage of these bDMARDs is analogous to that employed in patients diagnosed with rheumatoid arthritis [2,14-16]. Current information regarding the efficacy of certain treatment modalities for RP, including leflunomide, intravenous immunoglobulins, anti-CD4 monoclonal antibody, plasmapheresis, and Janus kinase inhibitor (JAK inhibitor), remains limited [2,15,16].

**JAK inhibitors for the treatment of autoimmune rheumatic disease**

The four Janus kinase proteins, comprising JAK1–3 and TYK2, along with the Signal Transducers and Activators of the Transcription (STAT) signaling pathway, have played a regulatory role in the cellular response to interferons, cytokines, and growth factors by affecting molecular signaling to the nucleus and stimulating the gene expressions [17]. Janus kinase inhibitors (JAKi), administered orally, attenuate
hyperactivation of the JAK/STAT signaling pathway by selectively or non-selectively inhibiting JAK and TYK2 proteins [18]. Consequently, JAKi modulate the production of IFN-α, IFN-γ, and various cytokines, including IL-2, IL-4, IL-6, IL-10, IL-12, and IL-23. These interferons and cytokines play a pivotal role in the pathogenesis of numerous autoimmune diseases [17,19]. In the literature, patients diagnosed with rheumatoid arthritis, primary Sjögren’s syndrome, systemic lupus erythematosus, systemic sclerosis, dermatomyositis, and vasculitis have been documented to experience improvement following the administration of JAKi [17]. Nevertheless, the available data regarding the use of JAKi in the management of RP remains insufficient.

**JAK inhibitors for the treatment of RP**

In the literature, a case report documented a patient exhibiting progressive nasal chondritis accompanied by a saddle nose deformity, arthritis, scleritis, laryngeal and tracheal involvement, fever, and elevated acute phase reactants. The patient, who declined treatment with any parenteral agents, provided informed consent for the off-label use of oral tofacitinib, a decision made by the authors. After a year, the patient achieved clinical remission and discontinued corticosteroid use, with concurrent improvement observed in laryngeal wall thickening as evidenced by computed tomography scanning [20].

**HYPOTHESIS**

JAKi may be as effective as biological agents like TNF inhibitors in relieving symptoms in RP patients. Additionally, oral administration is easier than parenteral administration. Therefore, JAKi may be preferred over bDMARDs due to its advantage of simple administration. However, some safety concerns have arisen following the results of the ORAL Surveillance study [21]. Consequently, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have issued essential recommendations to be observed prior to the initiation of these pharmacological medications [22]. Accordingly, the utilization of JAKi should not be considered in elderly patients, those with a history of smoking, and those with risk factors for cardiovascular disease or malignancy. In those patients, these agents can be used if there are no suitable alternatives [22]. As a result, the efficacy and safety profile of JAKi in patients with RP should be elucidated through rigorous and well-designed studies.

**STUDY DESIGN**

This hypothesis necessitates to be tested with observational and interventional studies [23,24]. Different research designs and methodologies can be selected for pharmaceutical research studies. Initially, case reports and case series can provide valuable insights into demonstrating the impact of JAKi on the manifestations of RP [25]. Observational studies can give us more information than case reports. However, the most appropriate way to demonstrate the efficacy of a drug is through randomized controlled trials. Clinical research phases are specifically designed based on a protocol formulated by the researcher. The evaluation of the efficacy and safety of pharmaceutical agents typically entails multicenter, double concealed, randomized placebo-controlled, phase 3 trials [26]. The study should be conducted by the guidelines of the International Conference on Harmonization, the relevant regulations, and guidelines overseeing the conduct of clinical trials, as well as the principles outlined in the Declaration of Helsinki. After deciding on the study protocol, appropriate inclusion and exclusion criteria need to be defined to characterize the eligible study population [27,28]. Randomization can be stratified by the type of involvement, disease course, and/or disease activity. RP patients, especially those with cardiovascular involvement, should be specifically analyzed to evaluate the safety profile of JAKi. The Relapsing Polychondritis Disease Activity Index (RPDAI) should be used to monitor the clinical progression of RP patients [2].

**CONCLUSION**

This hypothesis posits that JAKi may offer utility in alleviating the manifestations of RP and in controlling disease activity. Despite the theoretical merit of these agents in such patients, the existing data on this matter is insufficient. Consequently, longitudinal and randomized controlled studies are imperative to substantiate the efficacy and safety of JAKi in patients with RP.

**References**


Figure 1. Clinical symptoms and signs of Relapsing Polychondritis
РЕЦИДИВТИК ПОЛИХОНДРИТТІ ЕМДЕУГЕ АРНАЛҒАН ЯНУС КИНАЗА ИНГИБИТОРЛАРЫ: ГИПОТЕЗА

Тұйындымен

Рецидивтік полиходндриит (РП) – шеміршек құрылымдарына әсер ететін қайталанатын қабыну әрізодтарының сипатталатын сирек кезделетін аутоиммундық ауру болып табылады. Негізінен механизмың толқының зертханалығына жақсы тәуелді, ауруның мәндемелігінен әр фазадағы жерде жасушалық иммунитеттің және гуморалдық иммунитеттің қатысушы сыйығы таңдайды. Бұл жағдайлмен байланысты белгілердің спектрі қезіл көрінішерден ауыр, өмірге қауіп тәндеретін көрініштерге дейін өзгереді. Емдеу нұсқалары аурудың ауырлықтарына байланысты өзгереді. Емдеу нұсқалары аурудың ауырлығына байланысты өзгереді. Бірінші қатардағы терапия ретінде, эдетте, стероидтік емес қабынұға қарсы препараттар, колхицин, дапсон және жұылелік кортикостероидтар қолданылады. Сонымен қатар, циклофосфамид, метотрексат, азатиоприн, циклоспорин және ауруды өзгеретін биологиялық антиревматикалық препараттар екінші қатардағы ем ретінде қолданылады. Дегенмен, емдеу нұсқасы ретінде РП бар емделушілерде Янус-киназа ингибиторларын (JAKi) пайдалану тұралы деректер жеткіліксіз. Бұл гипотеза JAKi өсү науқақтарда симптомдарды жекілдету үшін өмірші емдеу нұсқасы болуы мүмкін деп болындайы."

Тұйынды сөздер: аутоиммун дисуру, гипотеза, Янус киназа ингибиторлары, қайталанатын полиходндриит.


ИНГИБИТОРЫ ЯНУС-КИНАЗЫ ДЛЯ ЛЕЧЕНИЯ РЕЦИДИВНОГО ПОЛИХОНДРИТА: ГИПОТЕЗА

Резюме

Рецидивирующий полиходндрит (РП) – редкое аутоиммунное заболевание, характеризующееся рецидивирующими эпизодами воспаления, поражающими хрящевые структуры. Основной механизм до конца не выяснен; однако комплексные генетические и гистопатологические оценки выявили участие специфических генов, клеточного иммунитета и гуморального иммунитета в патогенезе РП. Спектр симптомов, связанных с этим состоянием, варьируется от легких проявлений до тяжелых, опасных для жизни проявлений. Варианты лечения варьируются в зависимости от тяжести заболевания. В качестве терапии первой линии обычно используются недостаточные противовоспалительные препараты, колхицин, дапсон и системные кортикостероиды. Кроме того, в качестве лечения второй линии используются циклофосфамид, метотрексат, азатиоприн, циклоспорин и биологические противоревматические препараты, модифицирующие заболевание. Тем не менее, данных об использовании ингибиторов Янус-киназы (JAKi) у пациентов с РП в качестве варианта лечения недостаточно. Эта гипотеза предполагает, что JAKи может быть жизнеспособным вариантом лечения для облегчения симптомов у этих пациентов.

Ключевые слова: аутоиммунное заболевание, гипотеза, ингибиторы Янус-киназы, рецидивирующий полиходндрит.


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