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Potential of Janus Kinase (JAK) Inhibitors for Allergic Conditions Complicating Rheumatoid Arthritis (RA): Suppressing the Multiple Immunopathogenic Pathway

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Abstract

Eosinophilic Pneumonia (EP) is a well-known form of antibiotic-resistant pneumonia with increased eosinophils, and Chronic EP (CEP) has a subacute course with respiratory symptoms lasting several months and progressive dyspnea. Although Glucocorticoid (GC) therapy shows a marked response in the early stages of CEP, there is no sufficient evidence for the optimal duration of GC administration and many patients are forced to continue GC maintenance therapy. Hence, adverse events associated with long-term administration such as osteoporosis and infections are problematic.

Rheumatoid Arthritis (RA) is a systemic autoimmune polyarthritis that recent strategic therapies using Disease Modifying Anti-Rheumatic Drugs (DMARDs), such as Methotrexate (MTX), and biologics have been promoted to induce disease remission, while GC is not recommended due to concerns about adverse events. The development of targeted synthetic DMARD, Janus Kinase (JAK) inhibitors, has also promoted the treatment strategy of RA. JAKs are members of the intracellular, nonreceptor protein tyrosine kinase family, which includes four JAKs (JAK1-3 and TYK2). Among them, a JAK1/2 inhibitor baricitinib, not only slow the progression of joint damages by inhibiting T helper type 1 (Th1) cytokines, but also demonstrates regulatory effects on Th2 cytokines such as IL-4, IL-5, and IL-13.

Recent reports have shown the association between RA and allergic diseases such as asthma and Atopic Dermatitis (AD), indeed, we also experienced a case of RA complicated CEP that the patient was weaned from long-standing GC by taking baricitinib.

Though values of GCs on various inflammatory and autoimmune diseases, adverse events associated with long-term administration negatively affect patients' quality of life and prognosis.

Based on the own experience, we discuss the possibility of tailor-made therapies that are effective for both the underlying disease and complications, utilizing the unique immunosuppressive effects of JAK inhibitors.

Keywords: Eosinophilic pneumonia; Rheumatoid arthritis; Janus kinase inhibitor; JAK/STAT pathway; Glucocorticoid withdrawal

Introduction

Eosinophilic Pneumonia (EP) is a well-known form of antibiotic-resistant pneumonia, characterized by increased eosinophils both in peripheral blood and Bronchoalveolar Lavage Fluid (BALF). Along with infiltrating eosinophils, chemical mediators produced by activated macrophages also injure lung tissues [1,2]. Various factors, infectious and noninfectious, contribute to eosinophil infiltration of the lungs, and most infections are caused by parasitic, but noninfectious causes include certain drugs, toxins, environmental factors, and malignancies [1-4].

EP is classified into Acute Eosinophilic Pneumonia (AEP) and Chronic Eosinophilic Pneumonia (CEP) according to its clinical course and clinical characteristics. AEP requires an attention to rapidly progressive respiratory symptoms,

Sometimes causes acute lung injury or Acute Respiratory Distress Syndrome (ARDS) [5]. CEP, on the other hand, has a subacute course with respiratory symptoms lasting several months and progressive dyspnea with wheezing. About half of CEP patients have atopic diseases such as bronchial asthma, and allergic reactions are thought to be involved in its development. Many EP patients, but not all, blood test shows increased eosinophils in the peripheral blood and chest X-rays shows infiltrations in the middle and upper lungs bilaterally. For definitive diagnosis, chest Computed Tomography (CT) is considered highly useful [1,3].

Literature Review

Although Glucocorticoids (GC) are used in the treatment of the two conditions of EP, there are significant differences in outcomes. In patients with AEP, respiratory symptoms may rapidly resolve within an hour of GC administration, and most patients have a dramatic response with resolution of lung infiltration within a month. Hence, GC can often be discontinued within a few weeks. GC therapy also shows a marked initial response in patients with CEP, however, there is no sufficient evidence for the optimal duration of GC administration, which currently requires at least 3 months, often 6-9 months, or longer. Further, approximately half of CEP patients relapse after withdrawal of GC, forcing continuation of maintenance therapy [3,5]. Anti-IL-5 agents are among the drugs with potential efficacy in CEP [6]. IL-5 is produced by T-helper type 2 (Th2) cells and plays an important role in the proliferation and maturation of eosinophil precursor cells, but dysregulated production leads to eosinophilic inflammation [7]. Mepolizumab, an anti-IL-5 agent, is effective in severe asthma and Eosinophilic Granulomatosis with Polyangiitis (EGPA) [8]. Similarly, omalizumab, an anti-IgE antibody, has been used against CEP as well as severe asthma, while its effectiveness is mainly limited to cases with high IgE levels [9].

Rheumatoid Arthritis (RA) is a systemic autoimmune disease characterized by inflammatory synovitis and progressive joint destruction. A treat-to-target (T2T) strategy, in which low disease activity or remission is the main therapeutic target, has been recommended [10,11]. In recent years, several drugs with different pharmacological actions can be administered alone or in combination, contributing to the promotion of the T2T strategy. Since its discovery in 1948, GC has been the most frequently used drug for RA, valued for the anti-inflammatory and immunosuppressive effects [12]. However, today, with growing concerns about adverse events such as osteoporosis and infections, long-term administration of GCs is no longer supported [13,14].

Thus, Methotrexate (MTX), a conventional synthetic Disease Modifying Anti-Rheumatic Drug (csDMARD), is the current anchor drug for RA. In cases with patients who response inadequately to MTX, the addition of another csDMARD, a biological DMARD (bDMARD) or a targeted synthetic DMARD (tsDMARD) is recommended [10,11]. To add, no clear differences in clinical efficacy are reported between bDMARDs and tsDMARDs in the current RA treatment [15].

The development of tsDMARD, such as Janus Kinase (JAK) inhibitors, has supported great changes in the treatment strategy of RA. JAKs are members of the intracellular, nonreceptor protein tyrosine kinase family, which includes four JAKs (JAK1-3 and TYK2)[16]. The activated JAK/STAT (Signal Transducer and Activator of Transcription) pathway has been shown to play an important role in intracellular signaling and can dramatically reduce the disease activity of RA by inhibiting multiple inflammatory cytokines. Depending on the selectivity of the JAK isoforms, each JAK inhibitors exhibit different efficacy and safety profiles; JAK1 appears to be the primary driver, inhibition of JAK2 and 3 dependent pathways may also contribute to clinical efficacy in RA. Especially, inhibition of JAK2 may contribute to the efficacy of non-selective JAK inhibitor *via* modulation of platelets, which play a supporting role to synovitis [17].

Baricitinib, JAK1/2 inhibitor, not only inhibits cytokine signaling such as Interleukin (IL)-6, IL-12, IL-20, IL-22, IL-23, and IFN-γ, but also demonstrates regulatory effects on T helper type 2 (Th2) cytokines such as IL-4, IL-5, and IL-13 [18]. Compared to MTX, baricitinib can slow the progression of structural damage even in RA patients with moderate to high disease activity [19].

Indeed, treatment with JAK inhibitor is reported to reduce the concomitant dose of GCs and improve prognosis in the management of systemic immune-mediated inflammatory diseases [17].

Ideally, disease activities in both RA and CEP should be controlled with minimal oral GC or, if possible, GC-free. However, the reality in clinical practice remains divergent from this ideal: concomitant use of GCs increases the risk of severe infections particularly in elderly RA patients treated with bDMARDs, and GC monotherapy for patients with RA also increases mortality rate as compared with appropriate DMARDs therapy [20-22]. It is not surprising that an anti-IL-5 agent mepolizumab and an anti-IgE antibody omalizumab cannot be expected to be effective for RA, but there have been reports of a development of RA in CPE patients receiving mepolizumab [23], and of a RA-like polyarthralgia after initiating omalizumab [24]. Could the suppression of Th2-driven pathology, by anti-IL-5 agents or anti-IgE antibodies, have unintentionally caused arthritic symptoms, a common feature caused by Th1 cytokines? Though the classical Th1/Th2 effector paradigm has partially changed by establishing Th17 subpopulation, we should always be aware of a seesaw-like balance between Th1 and Th2 that may determine the development of autoimmune and atopic diseases [25]. Recently, a case series of dual biologic therapy for rheumatic diseases and asthma has been reported [26], however, the use of mepolizumab or omalizumab in patients with RA seems challenging to be cautious of the risks.

Discussion

We recently experienced a case of GC-dependent CEP; a 42-year-old Japanese woman with 20 years of RA. Initially, she successfully achieved remission for CEP using GC though continuous use of low dose GC resulted in progressive RA-derived joint destruction. Since the next introduced bDMARDs had to be discontinued due to severe infectious complications, then, baricitinib was administered. As results, a GC-free remission was finally achieved by dual suppression of the Th1/Th2 pathway; subsiding of arthritis and respiratory symptoms [27].

The number of complications of RA with EP is by no means high, though a review of previous reports shows that 8 out of 10 patients had longstanding RA when they presented with acute eosinophilic pulmonary infiltrates [28]. In addition, recent systematic review and meta-analysis found that patients with asthma had a significantly higher risk of RA compared with individuals without asthma; the hazard ratio of 1.42 (95% CI, 1.18 - 1.70) [29]. In a similar line with described above, the proportion of patients with autoimmune diseases with Atopic Dermatitis (AD) is significantly higher than that of AD patients without underlying disease, and patients with AD have been considered a high-risk population for later development of autoimmune diseases [30]. Furthermore, a UK retrospective cohort study of patients with these allergic diseases, e.g., allergic rhinitis/conjunctivitis, atopic eczema and asthma, found more patients complicated with autoimmune diseases, including RA, than controls [31]. Among JAK isoforms, inhibition of JAK2 has been reported to be effective in bronchial asthma and Atopic Dermatitis (AD), because differentiation and proliferation of eosinophils are inhibited by suppressing IL-5 signaling [32-34]. Further, actions of JAK inhibitor *via* group 2 Innate Lymphoid Cells (ILC2) have been shown to contribute to the treatment

of bronchial asthma [34]. Therefore, JAK inhibitor appears to be a candidate drug with the potential to reduce GC doses in both patients with RA and diseases in atopic conditions.

Among JAK inhibitors other than baricitinib, a pan-JAK inhibitor tofacitinib (inhibiting JAK1, JAK2 and JAK3), has also been reported to be effective in asthma in animal models and human clinical trials [34]. While the inhibitory effect on JAK2 is somewhat weaker than baricitinib, tofacitinib improves respiratory symptoms in asthma by inhibiting broad JAKs, suggesting that its targets may be cytokines other than the IL-5 mentioned above, namely IL4, IL13 and Thymic Stromal Lymphopoietin (TSLP) [32].

In today's clinical practice, where the division of labor in medicine has become the norm, rheumatologists are not necessarily skilled in the treatment of respiratory diseases, nor do respiratory physicians prefer to treat RA. However, to at least decrease the risk of infectious complications, rheumatologists and infection control physicians should share their knowledge of the latest therapeutic agents to reduce or withdrawal GC.

We recently experienced a case of RA complicated CEP in which the patient was weaned from long-standing GC by taking a JAK inhibitor. This experience has reaffirmed for us the broad efficacy of a certain JAK inhibitor for different types of diseases, especially if we focus on T cell regulatory mechanisms and the Th1/2 and/or Th17 pathways. Indeed in immunopathogenesis of AD, Th2 category diseases similar to CEP, Th2 cytokines are also known to play a pivotal role, especially in the acute phase, with varying degrees of Th1 and Th17 cytokine activation in the chronic phase [34]. Although GCs are very effective in various inflammatory and autoimmune diseases, adverse events associated with long-term administration negatively affect patients' quality of life and prognosis [35]. JAK inhibitor also has the risk of drug related adverse events such as the development of herpes zoster, and its risk of both malignancies and cardiovascular events should also continue to be carefully monitored [36,37].

Conclusion

Despite the need for such risk managements, the mechanism by which JAK inhibitor suppress multiple immunologic pathogens is an attractive possibility, indicating tailor-made therapies for individual patients' condition having RA and allergic complications such as Chronic Eosinophilic Pneumonia (CEP), asthma, or Atopic Dermatitis (AD).

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