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Difficult-to-treat rheumatoid arthritis treated with Abatacept combined with Baricitinib: A case report

Abatacept plus Baricitinib in RA

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Abstract

BACKGROUND

Sporadic cases of rheumatoid arthritis (RA) due to unsatisfactory responses to abatacept (ABT) have been reported; however, the rescue therapy has not been finalized. Here, we present a case with difficult-to-treat rheumatoid arthritis (D2T RA) that was resistant to either a single ABT or a JAK inhibitor (tofacitinib, TOF), but improved with a combination of ABT and JAK inhibitor (baricitinib, BAT).

CASE SUMMARY

A 46-year-old Chinese woman who had RA for ten years that was resistant to tocilizumab (TCZ), etanercept (ETN), adalimumab (ADA), and ABT. According to the European League Against Rheumatism (EULAR) definition, the patient was diagnosed with difficult-to-treat (D2T) RA. It was then improved with a combination of ABT and a Janus kinase (JAK) inhibitor (baricitinib, BAT).

CONCLUSION

ABT combined with BAT may be an acceptable strategy for treating D2T RA.

Key Words: Difficult-to-treat rheumatoid arthritis; Abatacept; Baricitinib; Combination therapy; Case report

Qi J, Jiang H, Wu T, Zhang Y, Huang W, Li Y, Wang J, Zhang J, Ying Z. A Case of Difficult-to-Treat Rheumatoid Arthritis (RA) Treated with Abatacept Combined with Baricitinib. *World J Clin Cases* 2023; In press

Core Tip: Although the combined use of ABT and JAK inhibitors is not recommended in RA treatment guidelines, inflammatory cytokines have been found to compensate for the inhibitory effect of ABT on co-stimulatory signals, activate T-lymphocytes through the JAK/STAT pathway, and promote the inflammatory response. In the treatment of

this patient, BAT, as a JAK inhibitor, combined with ABT can be used as a rescue treatment for D2TRA, especially for patients with poor responses to single ABT treatment.

INTRODUCTION

New disease-modifying anti-rheumatic drugs (DMARDs) have drastically improved rheumatoid arthritis (RA) patients' quality of life[1]. However, 5%-20% of patients continue to show symptoms and clinical signs of autoimmune inflammatory activity despite the continuous treatment with various conventional synthetic, targeted synthetic, and biological DMARDs (cs, ts, and bDMARDs), Such patients are considered as difficult-to-treat RA (D2T RA) population[2,3], according to the European League Against Rheumatism (EULAR) definition of difficult-to-treat (D2T) RA (see Table 1 for a complete definition) [4]. D2T RA patients were found to have lower physical function and quality of life, along with substantial fatigue and discomfort than non-D2T RA patients, implying a larger illness load, more significant impairment effects, and early mortality [5]. The current treatment of D2T RA involves a repeated trial process of switching to another b/csDMARD after the first fails, as there are no specific management guidelines for these patients [6]. Therefore, establishing new treatment modalities for this population has become a top priority.

Compared to other b/tsDMARDs, abatacept (ABT) , a novel T-cell costimulation modulator, created compelling clinical benefits and security in patients who did not respond to anti-tumor necrosis factor (TNF)-α or methotrexate treatment [7,8]. However, ABT is not effective in all patients[9]. The poor response to ABT in D2T RA patients may be linked to inflammatory cytokines; however, the exact pathogenesis remains unknown. According to recent reports, combination therapy with other DMARDs is a more effective management option for patients who do not significantly respond to ABT [9]. Janus kinase (JAK) inhibitors are currently the routine therapy for RA patients on whom csDMARDs are ineffective, and are widely used as an alternative to biologics in patients with no risk factors for venous thromboembolism (VTE). Combination

therapy has been demonstrated to be clinically and radiologically superior to monotherapy [10]. Although the use of ABT and JAK inhibitors in combination is not suggested in the RA treatment guidelines, it is considered a preliminary experiment because various biologics have been attempted in the past with no notable outcomes. Herein, we present a report of a patient who did not respond to multiple bDMARDs (tocilizumab [TCZ], etanercept [ETN], adalimumab [ADA], and ABT) and was successfully treated with a combination therapy of ABT and baricitinib (BAT).

CASE PRESENTATION

Chief complaints

A 46-year-old woman presented with arthralgia for half a month.

History of present illness

Two years ago, following knee arthroplasty, she experienced profound weariness and stiffness in the morning, with swelling and soreness of several peripheral joints. Quickly, she had trouble moving, and was unable to crouch or rise without assistance. Subsequently, she was admitted to Zhejiang Provincial People's Hospital on October 1, 2020.

History of past illness

The 46-year-old Hangzhou woman developed RA when she was 36 years old. After more than one year of treatment, the disease was nearly controlled.

Personal and family history

The patient had a joint replacement two years ago without a family history.

Physical examination

A body temperature of 37.2°C, a blood pressure of 117/85 mmHg, a heart rate of 83 beats/min, and a respiratory rate of 19 times/min were noted. Swollen and painful

joints on both sides of the knuckles, proximal interphalangeal joints, wrist joints and left knee joints.

Laboratory examinations

On presentation to the clinician, the patient had elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels of 118 mm/h (normal range; 0-26 mm/h) and 63.8 mg/L (normal range; 0-8 mg/L), respectively. The levels of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibody increased to 1590.0 IU/mL (normal range; 0-20 IU/mL) and 1351.6 U/mL (normal range; 0-25 U/mL), respectively. Serum immune complex levels, anti-neutrophil cytoplasmic antibody, anti-SS-A, and anti-SS-B titers were also significantly increased. Clinical symptoms and serological tests were used to diagnose RA. The disease activity score of 28 joints with erythrocyte sedimentation rate (DAS28-ESR) was 6.05 (DAS28-ESR ≤ 2.6, remission; 2.6 < DAS28-ESR ≤ 3.2, mild activity; 3.2 < DAS28-ESR ≤ 5.1, moderate activity, and DAS28-ESR > 5.1, severe activity).

Imaging examinations

Ultrasonic studies revealed a thickened synovial membrane, suprapatellar bursa effusion, and degenerative changes in the left knee joint (Figure 1 A-B).

FINAL DIAGNOSIS

Subsequently, the patient was treated with ABT for 3 mo. Although the joint swelling and tenderness improved slightly, the DAS28-ESR decreased from 5.1 to 4.12, and ESR and CRP dropped to 89 mm/h and 64.5 mg/L, respectively, the disease was still in remission. The ultrasound test revealed the development of synovitis and pannus in the articular cavity of the left knee, and blood flow in the articular cavity was more abundant than before (Figure 1 C-D). Difficulty in walking, squatting, and upright standing were still present. Comorbidities such as ankylosing spondylitis, psoriatic arthritis, osteoarthritis, lupus, and arthritis caused by other causes were excluded based

on laboratory data, joint ultrasonography, and clinical picture. According to the EULAR definition of D2T RA, it was diagnosed as D2T RA.

TREATMENT

Thereafter, BAT was introduced, considering that the combination of these medications may be successful if the patients do not have any contraindications, such as TB infection or viral hepatitis. After one month, the patient's DAS28-ESR score was 4.08, and ESR and CRP level were 76 mm/h and 10.8 mg/L, respectively. All three indicators constantly remained below this level for the next 3 mo. Furthermore, when compared to the prior time, the ultrasound test revealed that the development of synovitis and pannus in the left knee joint cavity had improved, and blood flow signals were significantly reduced (2021-10 [Figure 2, B] and 2022-1 [Figure 2, C] joint CDFI comparison). During treatment, no significant side effects were observed.

OUTCOME AND FOLLOW-UP

The patient's ESR and CRP levels were within the normal thresholds (26 mm/h and 3.5 mg/L, respectively) after 3 mo, and DAS28-ESR was 3.26, indicating low-level activity. Moreover, the patients' autonomous walking, squatting, and standing abilities were significantly improved compared to before combination therapy. Entire clinical process and pharmacological dose of the patient is depicted in Figure 2. With the addition of BAT, the patient received effective and continuous treatment for the first time.

DISCUSSION

The pathophysiology of D2T RA is complex, and it is currently categorized into two groups: (1) multidrug resistance caused by autoimmune disorders and environmental factors in RA patients, such as smoking, pharmacogenetics, or drug immunogenicity; and (2) difficulties with intensive treatment, including comorbidities, poor medication compliance, financial constraints, and reluctance to intensify treatment [11]. Furthermore, from an immunogenetics standpoint, T-lymphocyte pathways play a significant role in

inducing and perpetuating chronic relapsing arthritis of D2TRA [12]. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) was first identified as an inhibitory signal that is delivered to stop the immune response and has the potential to adversely limit T-lymphocyte activation in various ways [13]. In several research investigations, the prevalence of D2TRA ranged from 5% to 20% of patients with RA [14]. Compared to RA patients, D2T RA patients have more impairment and die sooner. As a result, high-quality evidence is needed to guide D2 TRA patients' management and assist in the formulation of a structured and tailored treatment approach.

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) was first identified as an inhibitory signal delivered to stop immune response and has the potential to adversely limit T-lymphocyte activation in a variety of ways [15]. ABT is a soluble, recombinant, completely humanized fusion protein made up of CTLA-4's extracellular domain and IgG1's Fc region. Interacts with co-stimulatory molecules CD80 and CD86 on antigen-presenting cells and inhibits T-lymphocyte activation by interfering with CD28 signaling. ABT has been demonstrated to be beneficial in combating a multitude of autoinflammatory disorders, including RA [16,17]. However, several clinical studies have proved that the single CTLA-4 therapy has a limited ability to block T-lymphocyte activation [18,19]. Inflammatory cytokines (IL-6, IL-17, IL-18, and IL-1), which compensate for the loss of costimulatory signals in an inflammatory environment, can enhance the activation of allogeneic T-lymphocytes in a CD28-independent way. By signaling inflammatory cytokines, the JAK/STAT system plays a vital role in CTLA-4 failure [20].

JAK inhibitors interact with the ATP-binding sites such as JAK1, JAK2, JAK3, and TYK2 to suppress kinase phosphorylation and the JAK/STAT signaling pathway. However, it increases the risk of upper respiratory infections, herpes zoster, hematological abnormalities, and gastrointestinal problems [21]. Four JAK inhibitors are currently approved for RA[22]. As one of them, BAT can effectively inhibit JAK1 and JAK2, and moderately inhibit TYK2. Studies have shown that BAT with safety profiles may be more suitable for RA patients who are resistant to multiple bDMARDs and have a higher ACR response rate than TOF (which mainly inhibits JAK1 and JAK3) [23,24]. It is

known that IL-6 signaling is mediated by JAK1 and JAK2, and IL-17 and IL-18 signaling are mainly mediated by JAK2 [25–28]. In the treatment of this patient, BAT may have inhibited the signaling of inflammatory cytokines by inhibiting the JAK/STAT pathway, cooperated with the inhibitory effect of ABT on costimulatory signals, and blocked the inflammatory response. With a more comprehensive exploration of the inflammatory molecules that antagonize CTLA4-Ig and the mechanisms underlying the synergism between BAT and CTLA4- Ig, it will be helpful to identify next-generation JAK inhibitors that will interact with other immunosuppressants more selectively and develop safer and more effectivet D2T RA managemens.

We report a case of D2T RA in which the effect was not significant after the replacement of multiple DMARDs, especially ABT, and the combination of ABT and JAK inhibitors was effective. Inflammatory cytokines can compensate for the inhibitory effect of ABT on costimulatory signals, activate T lymphocytes through the JAK/STAT pathway, and promote the inflammatory response. When considering the etiology and treatment of D2T RA patients, especially when the ABT response is not significant, this case can be used as a valuable reference.

CONCLUSION

Inflammatory cytokines can compensate for the inhibitory effect of ABT on co-stimulatory signals, activate T-lymphocytes through the JAK/STAT pathway, and promote the inflammatory response. In the treatment of this patient, BAT, as a JAK inhibitor, combined with ABT can be used as a rescue treatment for D2TRA, especially for patients with poor responses to single ABT treatment.

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