Janus kinase 1/2 inhibition with Baricitinib for treatment of anti-signal recognition particle necrotizing autoimmune myositis: a case report

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Abstract

Following recent success in dermatomyositis treatments, Baricitinib, a selective Janus Kinase 1/2 (JAK1/JAK2) inhibitor, has been the subject of speculation as a potential new remedy for IIM. In this case report, our patient was presented with a typical clinical symptoms of necrotizing autoimmune myositis (NAM), a subset under an umbrella of idiopathic inflammatory myopathy (IIM), and was treated according to European neuromuscular center's (ENMC) protocol but to no avail. It was then decided that Baricitinib would be administrated as a rescue treatment. In that order, this has become the very first documented use of Baricitinib against the IIM other than dermatomyositis. Despite the unfortunate adverse events of disseminated tuberculosis, Baricitinib has indeed shown a positive outcome for the patient, suggesting a possibility for future developments and treatments of NAM.

Keywords: baricitinib, necrotizing autoimmune myositis, anti-SRP autoimmune myopathy,

Over the years, treatment for idiopathic inflammatory myopathy (IIM) has improved significantly increasing the possibility of better outcomes for the patient. In the case of an anti-signal recognition particle necrotizing autoimmune myositis (anti-SRP NAM) a European neuromuscular center's (ENMC) consensus was frequently used for clinical decision guidance for the initial treatments. We have observed the suggestion of rituximab prescription, along with methotrexate, for severe cases despite limited statistical information. Nevertheless, most patients still suffered from morbidity and mortality, indicating that new effective treatments are still being sought.[1,2]

Following recent success in dermatomyositis treatment,[2,3] Baricitinib, a selective JAK1/JAK2 inhibitor, has been the subject of speculation as a potential new remedy for IIM.[4] This medication holds more potential for curative effects than conventional counterparts.[3] However, as efficacy studies are still in their early stages,[5] specific data for NAM is limited.

This case report illustrates the outcome of using Baricitinib as a rescue therapy, which has demonstrated a lot of potential, but ultimately ensued with severe adverse effects.

Case Report

Our patient was a 52-year-old Asian female with dyslipidemia, who had first been prescribed simvastatin 10 milligrams (mg) per day for 10 months prior to the events. On the 3rd and 7th month follow-ups, her condition nor the laboratory investigation exhibited any sign of abnormalities. She had no complaints about muscle pain, weakness and her laboratory result was no sign of transaminitis or decrement of renal functions. She then presented to the hospital with severe pain and weakness in the calf and deltoid areas and also raynauld phenomenon at fingertip of her 2nd-4th digits of both hands for two weeks. At first, her motor power grading as medical research council (MRC) scale was 2/5 points. Creatinine kinase (CK) level was elevated at 12,016 units/l. The investigation for occult

malignancy, parasitic infections was unremarkable. Myositis profile and muscle biopsy result was positive for anti-SRP necrotizing autoimmune myositis. The physical examination then prescribed medication as ENMC protocol with methylprednisolone, followed by oral prednisolone. One week later, her symptoms had not improved. Immunoglobulin (IVIG) and methotrexate were introduced. Despite the medication, her condition continued to deteriorate with quadriplegia and respiratory failure.

Concerned about her worsening condition, the physician then theorized the approach to adjourn the progression of the disease. Baricitinib, a selective JAK1/JAK2 inhibitor, is known to inhibit various intracellular signaling including those of interleukin 6, an important proinflammatory cytokine in the proposed pathophysiology of seropositive NAM pathogenesis,[6] and this was raised as a possibility to improve the condition of the patient. Previously, Baricitinib was a food and drug administration (FDA) approved medication for rheumatoid arthritis and alopecia areata but recently has become widely known for usage in severe coronavirus disease 2019 (COVID-19) pneumonia patients and, more importantly, a proof of concept usage against dermatomyositis,[2] another disease under the same umbrella of IIM with NAM.

The physician then confers with the patient and the relatives for the potential benefits and possible adverse reaction. All parties agreed to introduce Baricitinib as an off-label rescue therapy. The medication was started at 4 mg daily with daily neurologic assessment. Initially, the patient showed signs of improvement. with increment of motor power as MRC scale up to III/V on all extremities. Nonetheless, the CK level remained high and expressed no decrement.

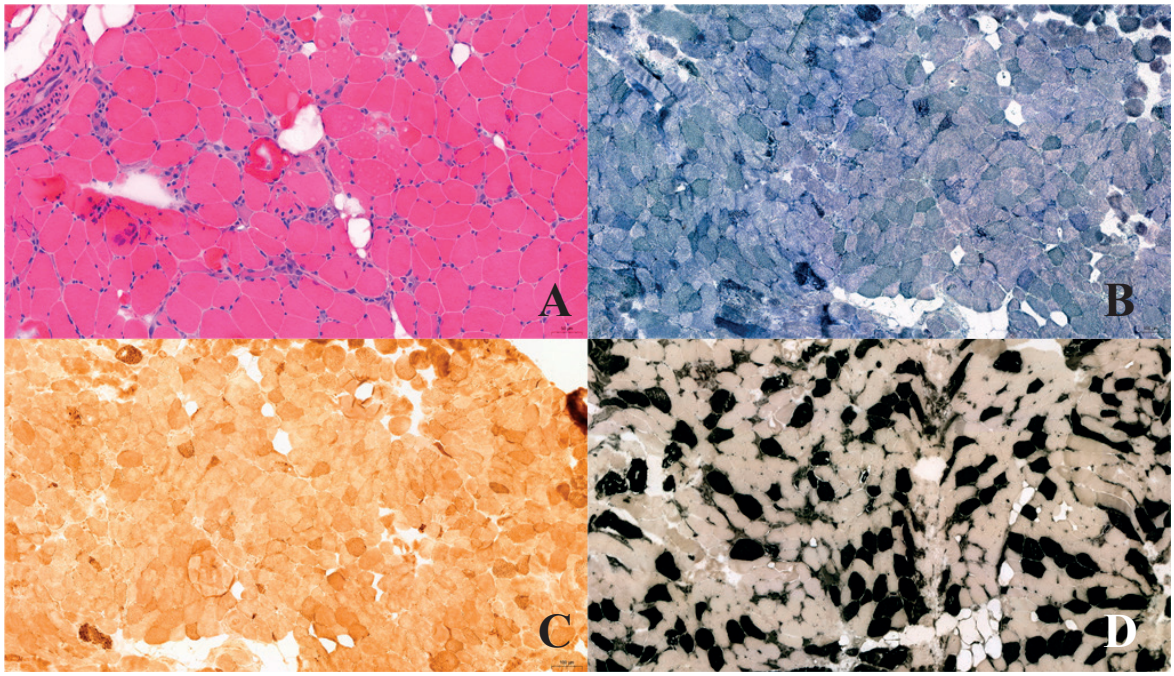

Figure 1: Muscle pathology from the patients, **A)** Regenerating and necrotic fiber in a diffuse distribution in an H&E staining, **B)** Necrotic fibers was prominent on oxidative stains, **C)** Myophagocytosis features in non-specific esterase, **D)** ATPase staining shows muscle fiber size fluctuation due to atrophic changes

During the following week, the patient developed a fever and productive cough. Cellulitis and an erythematous scaly patch appeared. Initial chest radiography showed no abnormality. Based on the aforementioned symptoms, a hospital-acquired infection was suspected, so a septic workup and antibiotic treatment was initiated. After a two-week course of antibiotics, symptoms had still not subsided. Furthermore, skin lesions appeared to be spreading. A skin biopsy revealed disseminated mycobacterium tuberculosis infection. The patient was then treated accordingly and hospitalized for three months before discharge with residual severe weakness (grade 2/5 MRC scale).

On follow-ups after 6 months' post-discharge, the patients still exhibit weakness of thigh and calf muscle with a slight amount of muscle recovery up to 3/5 until 18 months' post-discharge, in which it is appears to be at a plateau with motor strength up to 4/5 in both lower limbs.

Discussion

This is the first in-detailed documented usage of JAK1/JAK2 inhibitor against IIM other than dermatomyositis. Although the physician managed the case according to ENMC protocol,[5] the patient still demonstrates signs of rapid

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deterioration, which could have lead to her demise. It was then decided to introduce Baricitinib as a compassionate drug to adjourn the progression of the disease since it was directly inhibiting the inflammatory process, the key pathogenesis of the disease. Initially, the patient exhibits sign of improvement, likely due to inhibition of intracellular inflammatory cytokine signaling pathway, similar to the usage in severe cases of COVID-19 pneumonia.[7] Nevertheless, the favorable result of the medication had its shortcoming due to a serious opportunistic infection, which were stated in multiple reports with various extents.[8,9] However, for the relatively short duration of this medication, its potency remains noteworthy and a comprehensive study should be implemented.

We also suggest that chest radiographic evaluation as well as tuberculin skin test (TST) are inadequate for ruling out occult tuberculosis, especially for tuberculosis endemic areas. An extensive investigation should be considered beforehand.

Nevertheless, this report also has some minor shortcomings, since there is no instrument that could accurately measure the muscle unit and their strength, all motor power score documentation, including its degradation and improvement particularly in an ambiguous term, has to be relied on the neurologist's accord which may differ even among neurologists.

Conclusion

Despite the unfortunate series of events, for a period of time, Baricitinib was shown to halt and even improve the rapidly declining conditions precipitated by the disease. Assuming that a vigilant and thorough antecedent investigation for a possible occult infection was performed, Baricitinib was considered relatively safe to be administered and exhibited a relatively positive outcome in concordance to previous study of usage against other type of inflammatory myopathy, suggesting a possibility for the future developments and treatments of NAM.

Statement of Ethics

The subjects have given their written informed consent to publish their case.

- Study approval statement: This study protocol was reviewed by The Human Research Ethics Committee of Thammasat University no.1 (Faculty of Medicine) And stated that the ethics approval was not required.
- Consent to publish statement: A written informed consent was obtained from the participant for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Data Availability Statement

All data of this study are available from the corresponding author, upon reasonable request.

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