



ARTIST
RUBY ZHENG

CRITICAL REVIEW

**Pacritinib: A novel
therapeutic agent for treating myelofibrosis**

ABSTRACT

Selective inhibitors are an important advancement in clinical medicine, providing a method to target proteins within signal transduction pathways. One such inhibitor, pacritinib, targets Janus Kinase 2 (JAK2) to treat patients with myelofibrosis (MF). In MF patients diagnosed with a specific point mutation (JAK2V61F), the JAK/STAT pathway is over-activated, leading to an increase in cell proliferation rates. Pacritinib restores normal JAK/STAT activity by targeting aberrant activity of JAK2V61F mutant proteins and inhibiting cell proliferation in bone marrow tissue. In recent studies, pacritinib has shown better results at treating MF than the best available therapy. Though pacritinib is a potentially effective treatment option, it does not address all aspects of MF and should be supplemented with other treatments.

INTRODUCTION

Myelofibrosis (MF) is a rare bone marrow cancer that develops from genetic mutations in the hematopoietic stem cell population.¹ Around 50–60% of MF cases have a Janus Kinase 2 (JAK2) mutation, suggesting a correlation between the pathogenesis of MF and JAK2 mutants.² The point mutation JAK2V61F, which is a conversion of valine to phenylalanine at position 617, is found in most MF patients.² However, the etiology of JAK2 mutations that lead to myeloproliferative neoplasms remains unclear.¹ These neoplasms continue to grow as scar tissue forms in the bone marrow. Scarring can disrupt normal blood cell production and cause anemia. In its early stages, MF is difficult to detect. However, as the bone marrow undergoes fibrosis, patients manifest symptoms such as weakness, bone pain, shortness of breath, and frequent infections.³ MF is diagnosed by the presence of bone marrow fibrosis in bone samples.³ Other methods of diagnosing MF include a complete blood count and palpating to detect enlargement of the spleen.³

The following review will discuss the mechanisms behind the pathophysiology of MF, current treatments, and promising novel treatments targeting the JAK2/STAT pathway. In particular, recent studies report that the novel agent pacritinib has increased efficacy in treating MF over other therapeutic modalities.

PATHOPHYSIOLOGY

JAK2 is a tyrosine kinase that propagates and amplifies signals in a cell. It does so by catalyzing the transfer of a phosphate group from adenosine triphosphate donors to tyrosine residue receivers on proteins.⁴ JAK2 mutations have been implicated in MF and other myeloproliferative neoplasms. The most prevalent mutation, JAK2V617F, causes JAK2 to become constitutively active, escaping auto-inhibition and causing uncontrolled signal transduction.^{4,5} The activated JAK2 proteins phosphorylate the signal transducer and activator of transcription (STAT) proteins.⁶ Phosphorylation activates the STAT proteins, leading to their active transport into the nucleus where they enhance the transcription of target genes.⁶

The JAK/STAT pathway responds to growth factors, increasing the expression of genes that induce cell growth, differentiation, and apoptosis.⁶ This pathway is constitutively inhibited; the target genes are expressed in the cell only when the pathway is activated. The dysregulation of this pathway by mutations such as JAK2V61F can lead to the formation of myeloproliferative tissue, which can later become tumorigenic and lead to enlargement of the spleen (splenomegaly).⁶ Neoplasm growth is usually a slow process in MF. Consequently, symptoms are not observed by the patient until the scar tissue becomes prominent in the region and begins affecting blood cell production.

CURRENT TREATMENTS

The drug that is currently used to treat MF with splenomegaly is ruxolitinib, a potent and selective JAK1/2 inhibitor. By inhibiting the JAK/STAT pathway, ruxolitinib downregulates target genes that promote cell growth and proliferation. A study conducted in 2012 compared the efficacy of ruxolitinib treatment for MF to best available treatments, which include anti-neoplastic agents and glucocorticoids. To compare treatments, they monitored the reduction in spleen size and MF-related symptoms.⁷ Ruxolitinib reduced spleen length by 56% on average, whereas the best available treatment group demonstrated a 4% increase in length at 48 weeks.⁷ The patients in the ruxolitinib group also reported a decrease in MF symptoms over time.⁷ Although ruxolitinib was superior to the best available treatment in reducing spleen size, both treatments had similar survival rates. Ruxolitinib is currently approved by the Food and Drug Administration and Health Canada to treat MF, and is the first MF agent to be commercially available.^{8,9}

Another MF treatment is allogeneic hematopoietic cell transplantation (HCT).¹⁰ This procedure has potential to be a long-term solution for MF, with minimal chance of relapse. In one study, 36 of 56 MF patients who received allogeneic HCT and achieved both engraftment and chimerism survived between 0.5 to 11.6 (median, 2.8) years post-treatment.¹⁰ Most of these patients enrolled in this trial after conventional treatments proved ineffective.¹⁰ The

paper noted that infections were implicated in most of the non-relapse deaths that occurred within 6 months of treatment: pneumonia and other infections caused 13 out of 20 deaths. Thus, effective infection-prevention strategies need to be developed for stem cell transplant treatment. Although HCT is associated with risks, researchers believe that this avenue shows promise for long-term survival of MF patients.

MF is a complex disease. One treatment cannot be used as a standardized protocol for cases with varying severity and prognostic factors. Therefore, different treatments are administered in an orderly fashion to find the most effective candidate.

FUTURE DIRECTIONS

In 2018, Mascarenhas et al. published a study comparing the efficacy of pacritinib, a JAK2 inhibitor, to the best available treatments, including ruxolitinib.¹¹ The results indicated that pacritinib is more effective at reducing spleen length and the total symptom score in MF patients. Furthermore, the side effects of pacritinib were minimal and did not generally cause discomfort. Though these results are promising, they may not be generalizable to all MF patients, given the small sample size of 33 patients. In a phase 3 trial, pacritinib was more effective at treating symptoms than current MF treatment, but the survival rates were not significantly different between groups.¹² Moreover, phase 1 and 2 trials indicated that pacritinib treatment may incur lower risk of producing treatment-emergent conditions, such as thrombocytopenia and anemia, than other JAK2 inhibitors.¹³

Treatment with pacritinib has no associated significant cardiac or hematologic treatment-emergent events.¹³ Furthermore, this novel treatment may offer increased efficacy and decreased side-effects in comparison to ruxolitinib in certain patient populations.¹³ The reduced risk of adverse effects could increase patient compliance and the likelihood of treatment continuity.

One common aspect of MF is anemia, which requires the patient to undergo red blood cell transfusions.¹¹ The study by Mascarenhas et al. indicated that patients treated with pacritinib required fewer transfusions than those who were treated with ruxolitinib. This decrease in transfusion burden is a clinically significant outcome, because anemia is the root cause for some other symptoms.¹¹ By mitigating the severity of anemia in MF patients, pacritinib may also decrease the development of other complications.

Since MF patients become increasingly susceptible to infections as they undergo treatment, further research needs to be conducted on infection risk-reduction strategies. The weakened immune systems of MF patients undergoing treatment prevents a robust response against infectious agents, leading to serious adverse outcomes including tissue damage and death.¹⁴ Pacritinib may also lead to adverse immunological changes because it targets the same

pathway as ruxolitinib, which has been linked to inhibition of dendritic cell function and the downregulation of regulatory T cells.¹⁴ Consequently, serious complications can arise, including tuberculosis, an increase in hepatitis B titres, and the reactivation of the herpes simplex virus.¹⁴ Thus, it is important to research the effects of pacritinib on the immune system to develop preventative measures against infections.

Currently, MF treatments target the JAK/STAT pathway. Though this pathway is an important target in treating the disease, there are other mechanisms that contribute to MF pathophysiology. Peripheral mechanisms contribute to the symptomatology of MF, and targeting them could lead to better patient outcomes and increased quality of life.¹⁴ However, focusing on treating the cause of the symptom can be more effective in improving long-term quality of life, than simply finding a short-term solution that alleviates the symptoms. Thus, drugs that target the peripheral mechanisms behind bone marrow dysmorphia need to be developed.¹⁴

It is evident that research focusing on the cause of the symptoms and the peripheral pathways of MF is required. Pacritinib is only a promising solution for one dysregulated pathway in MF. Further research needs to be conducted to validate these findings in order for pacritinib to be approved by healthcare authorities. The development of new and more selective JAK1/2 inhibitors can be a possible solution to MF, but in some cases, these inhibitors require supplementation with more potent treatments. The use of JAK inhibitors to treat MF seems to provide a short-term solution to the problem, but tolerance to JAK inhibitors can render these drugs less effective. Therefore, it is important to create a combined treatment plan that addresses the treatment challenges of MF in a systematic way.

CONCLUSION

The prevalence of rare blood cancers is increasing in Canada, and research into anticancer treatments is rapidly gaining importance.³ MF is a debilitating disease that continues to affect thousands around the world, and specific JAK inhibitors show great promise in battling myeloproliferative conditions. The next challenge for researchers is to develop sufficient evidence for a treatment protocol for MF that can improve prognosis while increasing treatment access.

REVIEWED BY DR. CHRIS HILLIS

Dr. Chris Hillis is an Assistant Professor in the Department of Oncology at McMaster and a malignant hematologist at the Juravinski Cancer Centre.

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