JAK inhibitors producing significant response in myelofibrosis patients

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Two janus kinase (JAK) inhibitors are substantially improving treatment of myelofibrosis in patients, say Mayo Clinic researchers who are presenting results of several clinical trials at the 52nd annual meeting of the American Society of Hematology (ASH) Dec. 4 in Orlando.

Their findings suggest that both drugs, CYT387 and TG101348, effectively reduce spleen size and alleviate constitutional symptoms, major symptoms of this disorder, but that each have unique benefits.

According to Ayalew Tefferi, M.D., a Mayo Clinic hematologist and principal investigator for both clinical trials, results were both "surprising and pleasant" for CYT387, the first drug of its class to alleviate anemia in a substantial proportion of patients. TG101348 was also the first in its class to result in a measurable decline in JAK2 mutation burden and to substantially reduce high white blood cell and platelet counts, he says.

"These drugs represent smarter, targeted treatments that appear to make a substantial difference in treatment of this disorder," says Animesh Pardanani, Ph.D. (mayoresearch.mayo.edu/staff/pardanani_a.cfm), the lead investigator on both studies. One of the two studies being presented at ASH is longer-term follow-up on the use of TG101348 in 59 patients with myelofibrosis who are being treated at Mayo Clinic, Stanford University Medical Center, MD Anderson Cancer Center, Dana-Farber Cancer Institute, University of Michigan and University of California, San Diego.

The study concludes that after 12 cycles of treatment, 95 percent of patients had some reduction in the size of their spleen. Within that group, 26 percent had a 100 percent reduction. The study also found that of the 48 patients who had a JAK2 mutation, 23 (48 percent) had a reduction in mutation burden. Patients who completed 12 cycles of therapy had the most reduction. Thirteen patients (72 percent) had a median 50 percent decrease. That response has lasted more than a year, says Dr. Pardanani.

The researchers also found that 56 percent of patients treated with 12 cycles of TG101348 achieved normal white blood cell counts.

"TG101348 represents the first proof of principle that a selective JAK2 inhibitor can shut down a signaling pathway and reduce the burden of neoplastic blood cells," Dr. Pardanani says. "It also offers significant clinical benefit in that it decreases spleen size, controls excess blood cell counts in more than half of patients, and improves symptoms such as fatigue and night sweats."

In the second study being presented at ASH, 32 of 36 enrolled patients had completed at least one cycle of CYT387 therapy in a phase I/II clinical trial. Within this group of patients, 41 percent achieved an improvement in anemia, as defined by the International Working Group criteria. And 97 percent had some degree of spleen-size reduction (at least a 50 percent reduction in 37 percent of those patients).

"CYT387 not only works to reduce spleen size and to help with other symptoms, but it is the first in its class to show a significant response rate in anemia in myelofibrosis patients," Dr. Tefferi says.

"These drugs represent a very important step in the right direction in treatment of myelofibrosis," Dr. Pardanani says. "The initial responses have been very promising, but more work needs to be done to define

their individual role in the treatment of this disease."

"We are still learning how to use these agents, such as understanding the precise doses and schedule of administering them," he adds. "We are also trying to see how to combine them with other classes of drugs that we know can be effective in myelofibrosis."

The research team is currently conducting more studies to validate these results, and move the drugs further toward studies that are required for consideration of Food and Drug Administration approval.

Provided by Mayo Clinic