New drugs

Ruxolitinib

Approved indication: myelofibrosis
Jakavi (Novartis)
5 mg, 15 mg and 20 mg tablets
Australian Medicines Handbook section 14.2.3

Myelofibrosis can present as a primary disease or develop from polycythaemia vera or essential thrombocythaemia. It is characterised by fibrosis of the bone marrow, progressive anaemia and hepatosplenomegaly from overproduction of abnormal, immature blood cells. Survival of patients after diagnosis ranges from 2 to 11 years. Apart from stem cell transplant, current treatment is usually supportive and directed at symptoms.

Myelofibrosis is associated with overactivation of the Janus kinase pathway. In many patients, this is associated with a mutation in the Janus kinase 2 gene (V617F mutation). Overactivity of the pathway results in increased signalling of a number of cytokines and growth factors involved in haematopoiesis and immune functions.

Ruxolitinib is a selective inhibitor of Janus kinase 1 and 2. Its safety and efficacy has been assessed in two phase III trials – COMFORT-I and COMFORT-II.[1,2] COMFORT-I compared ruxolitinib to placebo for 24 weeks whereas COMFORT-II compared it to best available therapy (usually hydroxyurea or glucocorticoids) for 48 weeks. Approximately half of the patients in the trials had primary myelofibrosis, a third had post-polycythaemia vera myelofibrosis and the rest had post-essential thrombocythaemia myelofibrosis.

In both studies, more patients receiving ruxolitinib (15–25 mg twice daily) had at least a 35% reduction in spleen size compared to patients receiving the control treatments (see Table). Spleen size increased in patients who did not receive ruxolitinib. In COMFORT-I, more patients taking ruxolitinib reported a 50% or more improvement in disease-associated symptoms (such as night sweats, itching and abdominal discomfort) than those taking placebo (45.9% vs 5.3%). Similarly in COMFORT-II, more patients taking ruxolitinib reported an improved quality of life and better functioning than those taking best available treatment. In both trials, patients with the V617F mutation seemed to have a better response to ruxolitinib than those without the mutation.

After a median follow-up of 12–14 months, there appeared to be a survival advantage for ruxolitinib over placebo in COMFORT-I (8.4% vs 15.6% of patients had died). However, this was not the case for ruxolitinib over best available treatment in COMFORT-II (7.6% vs 5.6% of patients had died).

Haematological effects with ruxolitinib are common. Anaemia (81.7%), thrombocytopenia (67.4%) and neutropenia (15.3%) were the most frequently reported in the trials. These were generally managed by dose interruption or adjustment but some patients required a blood or platelet transfusion. Three cases of bleeding were fatal in patients receiving ruxolitinib, but only one was attributed to the treatment. The dose should be reduced if platelets fall below 100 x 10^9/L and interrupted if they fall below 50 x 10^9/L.

Overall, infections were common with ruxolitinib and control treatments (38.1% vs 41.7% in COMFORT-I and 63.7% vs 42.5% in COMFORT-II) and were fatal in some cases. Urinary tract infections, herpes zoster, tuberculosis and progressive multifocal leukoencephalopathy[3] have been reported. Ruxolitinib should not be started until serious infections have resolved and patients should be monitored for signs and symptoms of infection.

Diarrhoea[1,2], headache, dizziness, fever and bruising frequently occurred with ruxolitinib, as

Table **The efficacy of ruxolitinib for myelofibrosis in the COMFORT trials** [1,2]

Proportion of patients with 35% reduction in spleen volume	COMFORT-I		COMFORT-II	
	ruxolitinib	placebo	ruxolitinib	best available therapy
at 24 weeks	41.9% (65/155)	0.7% (1/154)	32% (46/144)	0% (0/72)
at 48 weeks	–	–	28% (41/144)	0% (0/72)

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

did hypercholesterolaemia. Elevations in alanine aminotransferase and aspartate aminotransferase were very common during treatment so monitoring of liver function should be considered.

Ruxolitinib is a pregnancy category C drug and is not recommended in pregnancy or lactation. Animal studies found that it crosses the placenta and is excreted in breast milk.

Following oral administration, ruxolitinib is rapidly absorbed with maximum plasma concentrations reached after an hour. The drug is mainly metabolised by cytochrome P450 (CYP) 3A4 and metabolites are excreted in the urine (74%) and faeces (22%). Its elimination half-life is approximately three hours.

Blood counts should be measured before starting ruxolitinib as the initial dose is determined by the patient's platelet count. Blood monitoring every 2–4 weeks is required to initially titrate the dose (maximum is 25 mg twice daily). A lower starting dose should be used in hepatic impairment, moderate to severe renal impairment (creatinine clearance <60 mL/minute) and in people taking concomitant strong CYP3A4 inhibitors (such as boceprevir, clarithromycin and ketoconazole).

After stopping treatment, myelofibrosis symptoms return to baseline after seven days. Serious withdrawal symptoms have been reported and tapering the dose has been recommended.[4]

Ruxolitinib reduces spleen volume and disease-associated symptoms in patients with myelofibrosis and offers another option for symptom control. However, its long-term efficacy and tolerability are still to be determined.

[X] manufacturer did not supply data

REFERENCES *†

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4. Tefferi A, Pardanani A. Serious adverse events during ruxolitinib treatment discontinuation in patients with myelofibrosis. Mayo Clin Proc 2011;86:1188-91.

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The Transparency score ([T]) is explained in 'New drugs: T-score for transparency', Aust Prescr 2011;34:26–7.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).