IRISH MEDICINES BOARD

Lenalidomide (Revlimid) – risk of serious hepatic adverse reactions
Routine monitoring of liver function now recommended

Lenalidomide (Revlimid) is authorised in combination with dexamethasone for treatment of multiple myeloma in patients who have received at least one previous treatment. Lenalidomide is an immunomodulatory agent similar to thalidomide and has antineoplastic, antiangiogenic, and proerythropoietic properties.

Suspected adverse hepatic reactions have been reported in <1% of patients treated. Of these reactions, abnormal liver investigation results and clinical signs and symptoms of hepatic disorders are the most common (58.7%). The spectrum of hepatic reactions reported includes hepatic failure, fibrosis, and cirrhosis (17.2%); cholestasis and jaundice of hepatic origin (13.8%). The remaining reports (10%) describe non-infectious hepatitis, liver-related coagulation and bleeding disorders, and neoplasms. A fatal outcome was reported in 5% of cases.

In many of the cases, including most with a fatal outcome, there were confounding risk factors for liver disease such as history of hepatic and renal disorders including viral hepatitis; progression of myeloma; myeloma involvement of the liver; prior chemotherapy; infection or sepsis; and concomitant medications known to cause liver injury, particularly antibiotics.

Among nine liver biopsies performed in patients with hepatic reactions, six showed histological evidence of drug-induced liver injury. In addition, there have also been a substantial number of cases where liver function has improved on discontinuation of lenalidomide, some cases of positive rechallenge, and some cases of negative rechallenge at a lower dose.

Review of the available evidence suggests that lenalidomide may be associated with drug-induced liver injury. The results of liver biopsies and cases in which there has been a positive dechallenge or a positive rechallenge provide the most convincing evidence of a causal association. The most common hepatic reactions observed in patients treated with lenalidomide are abnormalities of liver enzymes presenting as hepatocellular injury, and/or with a cholestatic pattern. Elevations of liver enzymes frequently occur soon after initiation of treatment with lenalidomide; the median time to onset appears to be 41 days, but reactions have been reported from one day to more than three years after the start of treatment. Early elevations in liver enzymes are usually moderate and may normalise without progression to major liver toxicity. Serious liver injury due to lenalidomide has been reported in relatively small numbers of patients and appears to be idiosyncratic. Predisposing factors that may increase the risk of serious liver injury with lenalidomide include elevated baseline liver enzymes, increased age, concomitant treatment with known hepatotoxic medicines, and pre-existing viral liver disease.

Advice to Healthcare Professionals

- Routine monitoring of liver function with the same frequency as haematological monitoring* (see details below) is recommended for patients receiving lenalidomide. This is particularly important in patients with a history of, or concurrent, viral liver infection, or when lenalidomide is given at the same time as other medications known to be associated with liver injury.
- Healthcare professionals should consider the possibility of lenalidomide-induced liver injury in patients presenting with otherwise unexplained deterioration of liver function.
- Impairment of liver function generally resolves when lenalidomide treatment is stopped. Once abnormal liver function parameters return to baseline, resumption of treatment with lenalidomide at a lower dose may be considered.
- Lenalidomide is excreted mainly by the kidneys, and therefore it is important to adjust the dose in patients with renal impairment to avoid high plasma levels which may increase the risk of hepatotoxicity as well as haematological side effects.

* *Haematological monitoring recommendations for lenalidomide are as follows: A complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and haematocrit should be performed at baseline, every week for the first 8 weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias.*

Key message

- Elevations in liver enzymes may occur soon after initiation of treatment with lenalidomide. Serious liver injuries (potentially fatal) such as toxic hepatitis, hepatic failure and cholestatic hepatitis have also been reported with the overall rate of hepatic reactions estimated as occurring in <1% of patients treated.
- Routine monitoring of hepatic function is recommended for all patients receiving lenalidomide, particularly in patients with a history of, or concurrent, viral liver infection or in patients receiving other medications known to be associated with liver injury.
- Healthcare professionals should consider the possibility of lenalidomide-induced liver injury in patients presenting with otherwise unexplained deterioration of liver function.
- The dose should be adjusted in patients with renal impairment to avoid high plasma levels which may increase the risk of severe hepatotoxicity as well as haematological side-effects.