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DISEASE MANAGEMENT OF CHRONIC IMMUNE THROMBOCYTOPENIA IN ADULTS: LONG TERM EXPERIENCE WITH TPO-R AGONISTS

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Immune thrombocytopenia (ITP) is an acquired autoimmune disorder characterized by a low platelet count (less than 100 × 109/L; normal range 150–400 × 109 /L). In patients who are refractory to traditional therapy, or who require high doses of steroids in order to maintain a high count, there has been an unmet need for new, non-immunosuppressive agents. Following on from the previously controversial understanding of a reduced production of platelets in ITP, new developments have focused on increasing the production of platelets. Recently, two thrombopoietin-receptor agonists, romiplostim and eltrombopag have been licensed for the treatment of chronic ITP. The current indications for thrombopoietin-receptor agonists are for splenectomized adult patients with chronic ITP who are refractory to other treatments and adult non-splenectomized patients in whom splenectomy is contraindicated. This reviews concentrates on the clinical efficacy and safety profile of TPO-R agonists in the treatment of ITP. Eltrombopag is an orally administered small-molecule nonpeptide TPO-R agonist. It has been shown to effectively increase platelet counts and reduce bleeding symptoms in patients with chronic ITP with overall response rate of 60– 80%. Eltrombopag is well tolerated and has a good safety profile. It is recommended for splenectomized patients with ITP who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). It may also be considered as second-line treatment for adult non-splenectomized patients who refused surgery or in whom surgery is contraindicated.

In the EXTEND study, 13 of 301 patients (4.5%) had prolonged remission (median 50 weeks) without ITP therapy following discontinuation of eltrombopag . In this study the median time from diagnosis of ITP was 24 months (range 6–73 months) and the median duration of eltrombopag therapy was 237 days (range 14–1014 days). Therefore, in some patients with chronic ITP, it may be possible to gradually taper and eventually discontinue eltrombopag. If the disease relapses, eltrombopag can be restarted at the previous effective dose. According to data from the REPEAT study, such patients will still be responsive to eltrombopag.

In view of the relatively predictable response eltrombopag may be used in the preparation of patients with chronic ITP for elective surgery. Patients can start taking eltrombopag at home 2 weeks before the scheduled surgery, thus avoiding pre-surgical admission for IVIG infusion, which is current common practice. Eltrombopag is not recommended for use in children and adolescents below the age of 18 years due to insufficient data on safety and efficacy. Even though no increased incidence of thromboembolic events, myelofibrosis, or irreversible hepatic damage was reported in follow up over 4 years, patients on eltrombopag should still be monitored closely for such adverse events.

Overall, both of the agents have shown very promising early results, with a good side-effect profile and excellent responses. A global and rigorous pharmaco-vigilance system needs to be maintained to fully evaluate the real and potential adverse events with their long-term use. Although the long-term studies, with follow up of over 5 years for Romiplostim and over 3 years for Eltrombopag have not highlighted any new or unexpected safety issues. While these agents have been licensed for use in patients with chronic and refractory ITP, further safety and efficacy data and analysis of their use within either persistent or newly diagnosed ITP may allow us to use these agents earlier on in the disease course, with the potential to induce tolerance and to further reduce the use of steroids and other immune supressive agents.