What's New in the Management of Chronic Primary Immune Thrombocytopenia in Adults and the Use of Thrombopoietin Receptor Agonists

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Introduction

Primary immune thrombocytopenia (ITP) is an autoimmune disorder typified by a platelet count below the normal range ($<100 \times 10^9/l$). Clinical manifestations are related to the severity of thrombocytopenia and include purpura and bleeding episodes. In the past, 'acute ITP' described a self-limited form of disease (e.g. secondary to viral illness) and 'chronic ITP' thrombocytopenia lasting for more than 6 months. In the absence of reliable predictive clinical or laboratory parameters of disease duration, the term 'newly diagnosed ITP' is now adopted for all cases at diagnosis. The term 'persistent ITP' was introduced for patients with disease between 3 and 12 months from diagnosis. This category includes patients not achieving remission or maintaining their response after having stopped treatment. The term 'chronic ITP' is used for patients with ITP lasting for more than 12 months [1].

The natural history of ITP is variable and unpredictable. For patients who are otherwise in good health, treatment is not required if the platelet count is close to or above $20 \times 10^9/l$. The mortality rate is $<1\%$, and the morbidity associated with treatment can be worse than the disease. Thus, platelet count and risk for bleeding events should be considered together before treatment is initiated.

Management of ITP

Two thirds of patients with ITP experience some increase in the number of platelets after receiving corticosteroids, intravenous immune globulin (IVIG) or Rh₀(D) IVIG (anti-D Ig), but many relapse. Patients who fail to respond or who relapse face the options of undergoing treatment with second-line drug therapy or splenectomy; however, there is no clear evidence base to support the best approach. In some patients, identifying and treating *Helicobacter pylori* infection may be all that is necessary. Splenectomy has been shown to provide long-term efficacy, but this is still only successful in around 60% of cases. Second-line drug therapies include high-dose dexamethasone or methylprednisolone, high-dose IVIG or anti-D Ig, vinca alkaloids and danazol, the immunosuppressants cyclophosphamide, azathioprine and cyclosporine or mycophenolate mofetil, and the anti-CD20 monoclonal antibody rituximab [2].

ITP is a disease of increased platelet destruction, but recent evidence suggests that suboptimal platelet production by suppression of megakaryocyte function also occurs. Therefore, treatment aimed at increasing platelet production has become a potential treatment option.

Thrombopoietin Receptor Agonists

Megakaryopoiesis and platelet production are governed by signaling through the Mpl receptor and its ligand thrombopoietin (TPO), which has a pivotal role in platelet production. Two recombinant TPO molecules were developed, recombinant human TPO and pegylated human recombinant megakaryocyte growth and development factor (PEG-rHuMGDF). However, early trials were halted in 1998 with reports that patients receiving PEG-rHuMGDF (which has significant sequence homology with endogenous TPO) developed severe thrombocytopenia stemming from antibodies against PEG-rHuMGDF that cross-reacted with endogenous TPO, neutralizing its biologic activity.

Despite these concerns, the success of these first-generation growth factors in stimulating platelet production led to the development of a second generation with no sequence homology with native TPO. Clinical trials with these – the TPO peptide mimetic AMG 531 (Nplate or Romiplostim; Amgen, Thousand Oaks, Calif., USA) and the nonpeptide mimetic eltrombopag (Revolade or Promacta; GlaxoSmithKline, Research Triangle Park, N.C., USA) resulted in dose-dependent increases in platelets in healthy subjects, and in significant increases in platelets in patients with chronic ITP [3].

Extensive clinical studies have shown platelet responses in approximately 80% of cases, which is much more than is achieved by traditional alternatives, and these re-

sponses are maintained while the drugs continue to be administered. They are effective in splenectomized as much as in nonsplenectomized patients [4], and recent phase III studies have confirmed the efficacy and safety following long-term usage [5, 6].

Both are well tolerated without the autoantibody formation seen in the initial studies. Increases in marrow reticulin have been reported, but this appears to be a reversible phenomenon and is not associated with formation of collagen fibrosis. There appears to be no increased incidence of thrombotic events compared with cases receiving placebo; however, thrombotic events have been reported in patients with other risk factors for cardiovascular disease, and a recent report has shown increases in venous and arterial thromboembolism in any patient with ITP, suggesting it is a prothrombotic condition [7].

Regarding patients with relapsed and refractory ITP there is no clear consensus on treatment. Treatment should be based on clinical state rather than platelet count, but what that second-line treatment should be, and in what order it should be implemented, is by no means agreed. A recent consensus publication has presented an evidence-based approach to treatment, providing options in a logical fashion so that the place of newer agents such as the TPO receptor agonists can be understood and incorporated into routine clinical use [8]. Clinical trials are also being conducted on hepatitis C virus-infected individuals, myelodysplasia and postchemotherapy.

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