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Idiopathic thrombocytopenic purpura in adults: the treatment paradigm

Idiopathic thrombocytopenic purpura (ITP) in adults is an acquired autoimmune disease characterized by increased platelet destruction, impaired megakaryocytes maturation with reduced platelets production, possible bleeding. The incidence is nearly 50 new cases per million people per year with a female prevalence particularly in younger.[1] ITP exhibits a heterogeneous biologic and clinical behavior, frequently has an insidious onset with different severity of thrombocytopenia, chronic course and higher lifetime risk of fatality due to bleeding, mainly intracranial.[2]

Treatment is generally reserved only to symptomatic patients, i.e. those who show clinical signs of bleeding or have platelet count 20-30×10^9/L or less and is based on two main therapeutic approaches, i.e. steroids and splenectomy. Prednisone 0.5-1.5 mg/d up to platelet recovery with subsequent tapering and discontinuation is the standard induction therapy for adult patients with symptomatic ITP. Nearly 70-80% respond but, unfortunately, in most cases, prednisone tapering or withdrawal is followed by a fall in platelet count and the need for further treatments.[3] The use of high dose dexamethasone instead of prednisone appears promising,[4-5] but results need to be confirmed in randomized studies. Intravenous immunoglobulin (IVIG) may be added to steroids particularly in those cases with very low platelets count and higher risk of fatal bleeding. Again the effect if IVIG is only transient and further administration result necessary. Splenectomy is the standard salvage treatment; however, after splenectomy, 40% of cases either do not respond or relapse,[6] and patients have a higher lifelong risk to develop bacterial infections.[6] Laparoscopic splenectomy should be considered the best surgical approach because of lower incidence of morbidity and mortality if compared with open surgery (0.2% *vs.* 1.7%).[7]

For patients refractory to steroid and/or splenectomy a variety of other immune-suppressive, cytotoxic agents as cyclosporine-A, azathioprine, cyclophosphamide or hormonal agents such as danazol, or dapsone may be active in some patients and their long-term administration may carry toxic effects.

In these last years two new therapeutic approaches, Rituximab-mediated B-cell depletion and increased platelets production stimulation with second-generation thrombopoietic receptor (TPO-R) agonists, have shown remarkable results in ITP treatment, offering valid alternatives

to conventional standard of care treatment.

Rituximab acts selectively on B-cells, causing B-cell depletion; this effect has been followed in order to inhibit the pathologic effect of B-cell in the pathophysiology of ITP (i.e. production of autoantibodies specific for GPIIb/IIIa and Ib/IX, cytokines secretion, APC-activity, interaction with T-cells). Rituximab, therefore, can be consider a curative agent since it acts on ITP pathologic immune pathway. Different reports highlighted the activity of rituximab as a salvage treatment for ITP patients[8-18] with 50-70% overall response and 30-50% complete response rate. Recently, in his systematic review, Arnold and co-workers reported short- and mid-term responses in 62.5% of patients.[16] Among responsive patients, 89.5% maintained the response during the whole follow-up period (median follow-up: 9.5 months, range: 2-25), with a median response duration of 10.5 months (range: 3-20). Rituximab appears to be safe and potentially long-term curative option in 30-40% of patients. At the 50th meeting of the American Society of Hematology in San Francisco, the results of first Italian multicenter randomized study which evaluated the therapeutic efficacy of rituximab and dexamethasone vs. dexamethasone monotherapy indicated a significant advantage in term of sustained response for the combination arm (63% *vs.* 36%, p=0.004) with no increased incidence of serious adverse events.[18] Recently a new therapeutic schedule with lower dose rituximab (i.e. 100 mg iv weekly for 4 weeks) was also proposed with apparent similar response rate than standard dose.[19] All together, this data allows to consider rituximab a new active and safe therapeutic option for ITP patients which may be proposed before splenectomy in patients refractory to steroid therapy.

Thrombopoietin receptor (TPO-R) agonists act on TPO receptor promoting megakaryocyte proliferation and platelet release. The rationale for their use in ITP is the state of functional endogenous TPO deficiency, since most patients shown inadequate TPO serum level for their level of platelets. These agents, therefore, works by increasing platelet production in bone marrow through the same pathway as endogenous TPO. Up today the two most studied TPO-R agonists are Romiplostin or Eltrombopag. Romiplostin is a recombinant protein defined as a peptibody which has no homology with endogeneous TPO and is given as a weekly subcutaneous injection. Eltrombopag is an orally available agent which interacts with the transmembrane domain of TPO-R and initiates signalling cascades similar but not identical to that of endogenous TPO. TPO-R agonists have been shown to be highly effective in the treatment of ITP, reducing the incidence of bleeding, increasing platelet count increase in most treated patients who are not responsive to standard treatments, with very low incidence of adverse events.[20-23] Time to initial response may require some weeks and therapeutic activity is related with continual administration. These agents therefore may represent a valid alternative to steroid or IVIG for short to medium period of administration. Preliminary results suggest a possible long term use with good safety profile. Reversible reticulin increase was observed in some ITP patients treated with romiplostim without clinical sequelae suggestive of a myeloproliferative disorder. Longer follow up analysis is needed to considered these agent for long-term maintenance therapy.

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