Case Report:
Sustained Partial Response to Thrombopoietin-Receptor
Agonist-Romiplo stim-in Therapy of Refractory Chronic
Immune Thrombocytopenia

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Abstract
In spite of the multiple potential therapeutic modalities for the management of refractory chronic Immune Thrombocytopenia (ITP), still there are no solid protocols in this respect. The presented case fulfills the recent international consensus reports of refractory chronic ITP. It has lastly showed sustained partial response to therapy with the Thrombopoietin-Receptor Agonist (Tpo-RA), romiplostim or Nplate.

Key Words: Refractory chronic ITP – Romiplostim.

Introduction

THE recent international consensus report defined primary ITP as an acquired immune-mediated disorder characterized by isolated thrombocytopenia of a platelet count <100X10^3/µL and the absence of any obvious initiating and or underlying cause for thrombocytopenia. ITP can be classified into newly diagnosed, persistent (3-12 month duration) and chronic (≥1 year duration) [1]. The disease and its most widely accepted abbreviation, ITP, has variably been titled as immune thrombocytopenic purpura, idiopathic thrombocytopenic purpura and most recently immune thrombocytopenia. A platelet count <30X10^3/µL sustained for more than 3 months may be considered as a criterion for refractory ITP [2]. Refractory ITP is not common, but may be a prominent diagnosis in hematologists practice. One out of ten patients who are initially diagnosed with ITP may eventually be titled refractory by the definition of the need for further treatment after splenectomy [3]. There is currently no consensus on the best management of refractory ITP. In part, this reflects the need for individualized treatment due to the wide spectrum of patient’s requirements and responsiveness to therapies [4]. New therapeutic agents for patients with ITP that promote platelet synthesis, rather than minimize platelet breakdown, have been effectively maintained safe margin of platelet counts in patients titled as refractory chronic ITP [3]. Recently, a substantial proportion of adult ITP patients receiving Tpo-RAs can maintain a durable response after discontinuation of therapy [5].

Case Report

This case of young Saudi lady 24-year-old with chronic refractory ITP has recently showed sustained partial response to romiplostim-Nplate. Our patient has been titled as refractory ITP because of the need to therapy after failure of response to both glucocorticoids and splenectomy.

The patient was admitted to hospital for the first time around fifteen years ago when she was nine years old child. She presented to Aseer Central Hospital in Aseer area Southwest Kingdom of Saudi Arabia (KSA) with multiple contusions of the left arm. There was no history of significant weight loss, therapy or vaccination. She has eight brothers and four sisters—all of them are fairly healthy. She was afebrile with no pallor, jaundice, cyanosis, lymphadenopathy or stigmata of congenital condition. Abdomen was soft and non-tender with no organomegaly. Chest X-ray (CXR) showed clear lungs, normal bones and normal heart size. Laboratory investigations showed severe thrombocytopenia with platelets count of 25X10^3/µL [Sysmex Hematology Analyzer] and Bone Marrow Aspirate (BMA) proved increased megakaryocytes which were active and of low ploidy. Other parameters of Complete Blood Count (CBC) and Periph-
eral Blood Smear (PBS) examination were Within Normal Limits (WNL). Erythrocytes sedimentation rate (ESR) was 3mm/hr and direct antiglobulin test was negative. Routine plasma biochemical tests and routine coagulation screen were WNL. The case was consistent with a newly diagnosed ITP. Full dose of steroid with oral prednisolone 1mg/kg/day (1 5mg trice daily) together with oral vitamin-C 250mg twice daily was prescribed. Platelets continued to drop down to 3X10³/µL and then to fluctuate up and down throughout five months of therapy with prednisolone and vitamin-C. The poor response to prednisolone indicated Intravenous Immunoglobulin (IVIG) as a second line of therapy. IVIG was given over 7 days “1.0 gram/kilogram body weight (1.0g/kg bw) on day one and 0.4g/kg bw/day for the next 5 days”. It showed relative un-sustained partial response.

The patient was admitted after six months for re-assessment before deciding splenectomy. Anti-nuclear Antibody (ANA) test, anti-double-stranded deoxy-ribonucleic acid (anti-dsDNA) and anticardiolipin antibodies (IgG & IgM) were negative. Viral screen for Hepatitis-B surface antigen (HBsAg), Hepatitis-C virus (HCV) and Human Immunodeficiency Virus 1 and 2 (HIV) antibodies were negative. Chromosomal analysis (karyotyping) showed no apparent clonal anomalies and no microscopically-visible clonal aberrations. ABO/H and Rh blood grouping of the patient showed that she is AB Rh-D negative and DU negative. Total serum protein electrophoresis and immunoglobulins quantitation were WNL. Splenectomy was decided as a third line of therapy. Patient was immunized with polyvalent pneumococcal vaccine, hemophilus influenza type b vaccine and quadrivalent meningococcal polysaccharide vaccine ten days prior to surgery as a prophylaxis against over-whelming post-splenectomy infections (OPSI). The patholog-ical changes of the spleen were consistent with that of immune thrombocytopenia under steroid therapy. After splenectomy the patient was continued on prednisolone with escalation and tapering of the dose according to her response.

When the patient arrived 13-year-old she presented with menarche-induced vaginal bleeding with prolonged periods ~12 day with platelets count of 22X 10³/µL and bleeding time of 10 minutes. Contraceptive pills (progyluton) had been prescribed-to be used for 21 day and stopped for 5 days. Periods became more convenient.

During follow-up after splenectomy the possibility of over growth of accessory spleen as a cause for refractory ITP was considered by hematologist. Ultra-sound abdomen proved his suspicion to be correct. Laparoscopic splenectomy was performed, but still no response with platelets counts fluctuating between 5 and 38X10³/µL.

At the age of 15-year-old the patient presented with chronic dyspepsia and positive test for antibodies for Helicobacter pylori (H.pylori). The specific oral therapy was prescribed and the patient showed transient mild increase of platelets count to 55X10³/µL which continued for three months.

At the age of 17-year-old the patient started cyclosporine in a dose of 50mg on alternative days.

The first trial of the Thrombopoietin-Receptor Agonist (Tpo-RA) romiplostim or Nplate was two years ago when the patient was on tapering dose of prednisolone/cyclosporine to be discontinued after one week. Vitamin D3 was simultaneously prescribed in a dose of 6 drops per day for one month. Nplate was prescribed in a weekly dose of 10mcg/kg [470mcg] with escalation and tapering of the dose according to her response. The platelets count was fluctuating between 42 and 173X 10³/µL. without any complaint of bleeding manifestations.

Discussion

Chronic ITP is a long-term management disease in which many of the patients are unsatisfied with their health-related quality of life. This is largely due to the variable efficacy and risks of severe adverse effects associated with current therapeutic options. The selection of the treatment protocols to be applied should involve a discussion with the patient and consideration of the severity of bleeding, anticipated surgical procedures, medication side effects and health-related quality of life [8].

The pathogenic mechanism of thrombocytopenia in ITP was classically interpreted as increased platelet destruction mediated by autoantibodies. It is well known also that more complex mechanisms are involved in the pathogenesis of chronic ITP including both cytotoxic cell-mediated lysis and impaired platelet production [6,7].

The main target of management of patients with refractory ITP is to avoid the stage of having side effects of treatment worse than the symptoms of ITP. The goal of treatment of ITP is only to avoid the risk of bleeding, not to resume the normal platelet count. The response to therapy may be described as partial, complete or sustained. Partial response means a platelets count of 50-150X10³/µL while complete response means a platelets count of >150X10³/µL. Sustained response means that the target platelets count continued for >6 months.
For long time, most of the current treatments were designed to minimize the increased platelet destruction, either by immunosuppression or splenectomy [3]. Prednisolone (1mg/kg bw per day orally) is the standard initial regimen of treatment almost always prescribed for our patients. Because corticosteroid administration may change narrow morphological performance of a bone marrow aspiration and biopsy should be considered before the patient is treated with corticosteroids to confirm the diagnosis of ITP if the clinical presentation, patient age, or other findings are atypical for newly diagnosed ITP [9]. Prednisolone improves platelet counts not only by suppressing systemic monocyte-macrophage phagocytic function but also by reducing antibody production [10]. However, only 20% of patients receiving prednisone as first-line treatment have a sustained complete remission lasting more than six months after maintenance therapy of 5-10mg daily is discontinued [11]. Prednisolone should be tapered slowly, especially once doses of 1 mg/day are reached, to avoid adrenal insufficiency [12].

The intermittent intra-venous anti-D immunoglobulin infusion (IV anti-D IgG) is one of the initial therapeutic options of adult ITP before splenectomy in the dose of 50-75 g/kg/dose/month [12]. Being Rh-D negative and Du negative, IV anti-D IgG was unfortunately not one of the suggested therapeutic options for our patient.

Intravenous immunoglobulin (IVIG) was initially shown to be effective in ITP in 1981 by Imbach et al., [13]. It has been the drug of second choice (after corticosteroids) for many years [14]. For individuals who, electively, need a higher platelet count IVIG can be used at a dose of 0.4 gram/kilogram (g/kg) given over 4-6hr per day for up to 5 days. However, for Rh (D)-positive patients with ITP and intact spleens, IV anti-D IgG offers comparable efficacy, less toxicity, greater ease of administration, and a lower cost than IVIG [15,16]. In adult, either IVIG (1g/kg for one dose, repeated as necessary) or IV anti-D IgG (in appropriate patients) may be used as first-line treatment if corticosteroids are contraindicated [8].

Failure to respond to prednisolone, IV anti-D and/or IVIG should prompt the diagnosis to be reconsidered and a bone marrow reassessment, including cytogentic and flow cytometry, to be performed [12].

One of the therapeutic options which we have not tried in our patient, due to lack of availability most of the time is Intravenous (IV) anti-CD20 (rituximab). It is the most popular and relatively safe immunosuppressive agent currently used for treatment of patients with refractory ITP [3]. It is a humanized monoclonal anti-CD20 antibody with rare serious reactions which are mainly cardiopulmonary in the form of hypotension, bronchospasm, acute respiratory distress syndrome and cardiogenic shock [8,17].

The approach of combination immunosuppressant therapy appeared to be effective in severe and refractory ITP. Patients under combination therapy of azathioprine, mycophenolate mofetil and cyclosporine achieved a safe platelet count of above 30X10^9/L and doubling of baseline in ~3/4 of them which lasted for a median of 24 months. Treatment was well tolerated [18].

The spleen is considered the primary site of autoreactive T- and B-cell interaction and activation and of autoreactive antiplatelet antibody production [19]. The traditional therapeutic option following failure of initial glucocorticoid treatment is splenectomy [12]. Splenectomy remains the most effective treatment for ITP, with two-thirds of patients achieving durable complete remissions with normal platelet count and without a need for further treatment [20]. Although removal of an accessory spleen has been described for decades as an appropriate maneuver for patients with refractory ITP, there are few published data to support this practice. Most published case reports are in children, who seem to have a better steady rate of spontaneous remission in comparison to adults [21]. In spite of that, it is still advisable to consider accessory spleen in the differential diagnosis of refractory ITP or relapse after splenectomy.

Whether the eradication of H.pylori infection can increase the platelet count in patients with ITP is still a controversial issue. An evidence-based guidance of an overall response rate (platelet count ≥30X10^3/µL) as achieved in ~1/3 of cases. The response rate tended to be higher in countries with a high background prevalence of H.pylori infection and in patients with milder degrees of thrombocytopenia. It is suggested that the detection and eradication of H.pylori infection should be considered in the work-up of patients with seemingly typical ITP [22].

Syngeneic peripheral blood progenitor transplantation (Syngeneic PBPT) is a potentially curative option for resolution of refractory chronic ITP. It should be considered when other modalities have failed. Careful analysis of the risks and benefits of transplantation in comparison to the risks of continued ITP and other therapeutic modalities should be considered [23].
Thrombopoietin-Receptor Agonist [Tpo-RAs] romiplostim or Nplate is produced by recombinant DNA technology. It is recommended for adults at risk of bleeding who relapse after splenectomy or who have a contraindication to splenectomy and who have failed at least one other therapy. This agent may also be considered for adults at risk of bleeding who have failed one line of therapy such as corticosteroids or IVIG and who have not undergone splenectomy [8]. Romiplostim is well tolerated in the long-term administration and increased platelet counts are maintained in splenectomised and non-splenectomised refractory ITP patients. Many patients were able to reduce or discontinue other ITP medications [24].

Sequential switching from one Tpo-RA to the other could be beneficial for patients with severe chronic ITP with history of lack of efficacy, platelet-count fluctuations or serious side effects of the first one. The benefit was in the form of reasonable disappearance of platelet-count fluctuations and complete resolution of side effects [25].

Romiplostim is a second-generation thrombopoietic agent that stimulates the thrombopoietin receptor and platelet production with a minimal risk for development of thrombopoietin antibodies because of non-resemblance to endogenous thrombopoietin [27].

Recently, long-term romiplostim treatment with a median average weekly subcutaneous dose of 5.4g/kg increased and maintained platelet counts of 50-200X10^9/L for over 4 years in children with ITP with good tolerability and without significant toxicity [26]. To achieve the target platelet count of 50-200X10^9/L, doses of romiplostim could be increased ≤10µg/kg [28]. A substantial proportion of adult ITP patients receiving Tpo-RAs can maintain a durable response after discontinuation of therapy [8].

Conclusion:
In spite of the outstanding many research on pathogenesis of ITP we are still in great need for more declaration of pathogenesis which will facilitate better patient-specific approaches to diagnosis and management. Further recent studies on immunopathogenesis of refractory chronic ITP are still going on, the principal target is to provide more alternative therapeutic modalities.

It is still insisted that consideration of accessory spleen in the differential diagnosis of refractory ITP or relapse after splenectomy is advisable.

In the management of ITP, there is no agreement regarding the management choices. Even there is no confident guide to assess whether treatment is better than the protocol of watch and wait. Therefore reservation of treatment for patients with bleeding symptoms or risk of bleeding may be the current best management. Further published experiences about the use of Tpo-RAs in the management of refractory chronic ITP are recommended to prove the unique advantages of this therapeutic modality.

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