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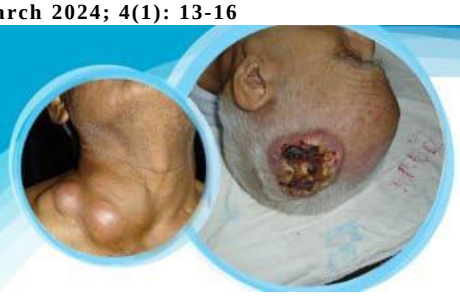

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Tessy Augustine
Specialist Paediatrician, Department of Paediatric Haematology and Oncology, Mediclinic City Hospital, Dubai, UAE

Corresponding Author:
Tessy Augustine
Specialist Paediatrician, Department of Paediatric Haematology and Oncology, Mediclinic City Hospital, Dubai, UAE

Romiplostim therapy in pediatric patients with persistent immune thrombocytopenia: A comprehensive review of efficacy, safety, and therapeutic implications

Tessy Augustine

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Abstract
Immune thrombocytopenia (ITP) in pediatric patients presents a multifaceted challenge, particularly when the condition persists beyond the acute phase, leading to increased risk of bleeding and potential progression to chronicity. Romiplostim, a thrombopoietin receptor agonist, has emerged as a promising therapeutic option to address the unmet needs of these patients. This review delves into the current body of evidence regarding romiplostim's efficacy and safety profile in pediatric patients with persistent ITP. It provides a nuanced understanding of romiplostim's role in preventing chronicity, enhancing platelet counts, minimizing bleeding events, and improving quality of life in this vulnerable population.

Keywords: Immune, thrombocytopenia, children, paediatric, romiplostim

Introduction
The journey from diagnosis to management of immune thrombocytopenia (ITP) in pediatric patients is fraught with uncertainties, especially when the condition persists, challenging clinicians to navigate between the risks of bleeding and the long-term implications of chronic disease. Romiplostim, a recombinant fusion protein, stands out as a beacon of hope, offering a targeted approach to platelet production regulation through thrombopoietin receptor activation. While initially approved for adults with chronic ITP, romiplostim's efficacy and safety in pediatric populations with persistent ITP have sparked considerable interest and warranted further exploration.

ITP is an autoimmune disorder characterized by suboptimal platelet production and increased platelet destruction [1, 2]. While a considerable number of patients manifest only minor symptoms like skin bleeds, a subset undergoes more serious forms of bleeding, such as intracranial hemorrhage [3, 4, 5]. ITP is estimated to occur between 2.8% and 8.8% per 100,000 person-years in the pediatric population (those younger than 18 years) in the United States and Europe [7, 8, 9], with the highest incidence reported in toddlers and young children (those younger than 2-5 years) [9].

In order to reduce hemorrhage in patients with ITP, achieving a sustained hemostatic platelet count is the primary treatment objective [3, 6, 10, 11]. Initial ITP treatment options that are deemed appropriate consist of anti-D immunoglobulin, intravenous immunoglobulin (IVIG), and corticosteroids [11, 12]. Medical interventions such as thrombopoietin receptor agonists (TPO-RAs) (romiplostim, eltrombopag, avatrombopag), rituximab, fostabatinib (a spleen tyrosine kinase inhibitor), additional immunosuppressants, splenectomy, [10, 11, 12, 13] are among the subsequent treatments.

Recent revisions have been made to the recommendations of the International Consensus Report (ICR) and the American Society of Hematology (ASH) [11, 12]. For patients with persistent (≥3-≤12 months) or chronic (>12 months) ITP, medical therapy is preferred over surgical therapy, if feasible, in order to prevent splenectomy, according to both guidelines [11, 12]. The ASH guidelines [12] recommend TPO-RAs over rituximab and rituximab over splenectomy in this context. During the initial year, medical therapies supported by "robust

evidence" (TPO-RAs, rituximab, and fostamatinib) are preferred over splenectomy, whenever feasible, according to the ICR guidelines [11].

This article aims to examine the clinical and practical factors to be taken into account when utilizing romiplostim for the purpose of achieving the most effective clinical management of immune thrombocytopenia (ITP). Additionally, it seeks to evaluate the role of romiplostim in ITP therapy within the framework of evolving guidelines for clinical practice and emerging data regarding the early use of romiplostim in ITP and remission.

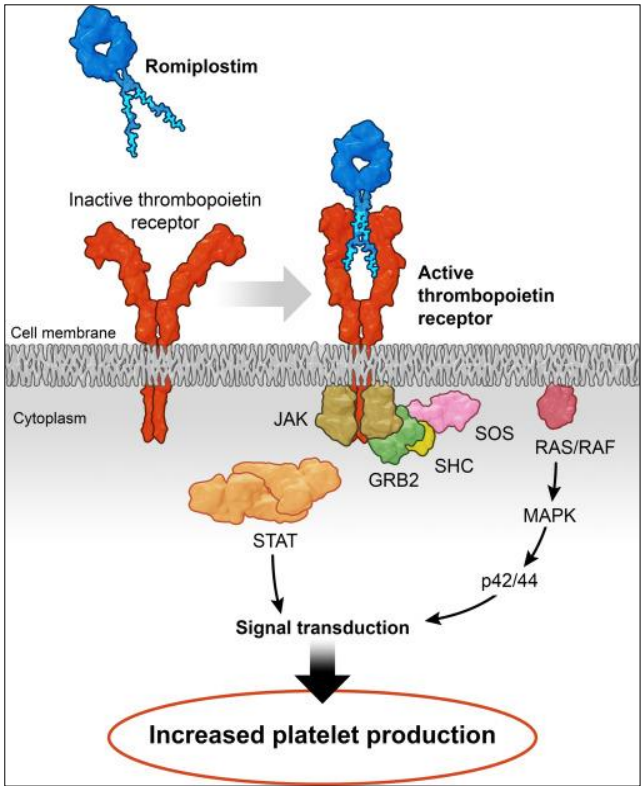

Fig1: Romiplostim mimics action of TPO

Methods

This review meticulously scours through the existing literature, employing a systematic approach to identify and analyze studies investigating romiplostim's utility in pediatric patients with persistent ITP. A thorough search strategy encompassing electronic databases and manual reference screening was employed to gather studies published. Keywords such as "immune thrombocytopenia," "romiplostim," "pediatrics," and "efficacy" were strategically chosen to capture the breadth of relevant literature.

Irrespective of age, corticosteroids, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin are the primary treatments for individuals with immune thrombocytopenia (ITP) [11, 12]. This is due to concerns about side events and the high cost associated with immunoglobulin-based therapies [14]. Common corticosteroid treatment plans consist of dexamethasone (40 mg/day for 4 days, continued for one or two further monthly cycles based on response) or prednisone (0.5-2.0 mg/kg/day for …6 weeks followed by steep reduction) [11, 12]. According to the latest ASH recommendations, it is recommended to use corticosteroids alone rather than in conjunction with rituximab [12]. The average response rate with corticosteroids is found to be between 53% and 65% after 6 months [15]. One clinical trial [16] demonstrated that high-dose dexamethasone pulses were linked to prolonged treatment-free remissions. However, a meta-analysis of five trials (N = 533) comparing high-dose dexamethasone (40 mg/d for one to three cycles) with prednisone (1 mg/kg for 2-4 weeks followed by rapid tapering) revealed no significant difference in platelet count response at 6 months with newly diagnosed ITP [17].

The majority of patients exhibit a positive response to corticosteroids, which often leads to their ongoing use despite the occurrence of heightened toxicity and the inability to attain sustained treatment-free remission [3]. The absence of a universally accepted diagnostic criteria for corticosteroid failure may result in the persistent and recurrent administration of corticosteroids. The current recommendations do not include a particular criteria for corticosteroid failure. However, a suggested definition is the need for continuous corticosteroid treatment for at least 2 months in order to maintain a platelet count of at least 30 x 10^9/L or to prevent bleeding [18]. The available data is restricted, however, a recent research revealed that a significant number of patients continue to be prescribed corticosteroids as their primary treatment, indicating their excessive use [19]. It is noteworthy that a minority of individuals diagnosed with immune thrombocytopenia (ITP) are able to sustain a satisfactory platelet response when given daily or alternate day dosages of 5 mg (regardless of body weight), while experiencing little toxicity [11].

Despite lacking approval for these specific purposes, romiplostim has shown efficacy in patients with recently identified severe and/or therapy-resistant immune thrombocytopenia (ITP) [64]. Additionally, when taken in conjunction with other therapeutic approaches, romiplostim has shown promise in managing ITP and life-threatening bleeding [20].

Subsequent Treatment

In cases where patients fail to sustain a satisfactory response after the reduction or cessation of initial medication, further therapies for immune thrombocytopenia (ITP) including rituximab, TPO-RAs, fostamatinib, immunosuppressants, and splenectomy [11]. According to current recommendations, the second-line therapy for patients with ITP for a period of at least 3 months should be based on the length of the illness and the patient's desire, taking into account the actual and possible negative effects [11]. Rituximab, TPO-RAs, and fostamatinib are viable alternatives to splenectomy due to their spleen-preserving properties. According to the latest ASH recommendations, there is no favoritism towards romiplostim over eltrombopag. However, TPO-RAs are recommended over rituximab [12]. The effects of TPO-RAs and splenectomy on patients with chronic ITP were shown to be balanced in terms of their benefits and drawbacks. Splenectomy was believed to be linked to greater rates of treatment-free remission compared to TPO-RAs. However, TPO-RAs may often avert the need of surgery [12]. The ASH and ICR recommendations prioritize patient engagement in the decision-making process for splenectomy. However, both guidelines suggest that splenectomy should be postponed during the first year of immune thrombocytopenia (ITP) if feasible, in order to allow for the possibility of spontaneous remission [12]. Significantly, in the event of an inadequate

response or unfavorable occurrences with romiplostim, there exists a possible advantage in transitioning to an alternative TPO-RA [21].

Results

A synthesis of clinical trials and observational studies reveals a compelling narrative of romiplostim's efficacy and safety in pediatric patients with persistent ITP. Across various cohorts, romiplostim consistently demonstrates its ability to elevate platelet counts to therapeutic levels, thereby mitigating the risk of bleeding and obviating the need for frequent rescue therapies. Moreover, the salutary effects of romiplostim extend beyond mere numerical improvements, as evidenced by enhanced health-related quality of life metrics and reduced disease burden reported by patients and caregivers alike. However, amidst the success stories lie nuances that demand attention. Adverse events associated with romiplostim, though generally mild and transient, warrant diligent monitoring, with particular emphasis on thromboembolic risks. Additionally, the optimal dosing strategies and long-term safety considerations in pediatric patients remain areas of ongoing investigation, underscoring the need for continued research and clinical vigilance.

Conclusion

Romiplostim emerges as a beacon of hope in the therapeutic landscape of persistent ITP in pediatric patients, offering a tailored approach to platelet regulation that transcends mere symptomatic relief. Its efficacy in enhancing platelet counts, reducing bleeding events, and improving quality of life underscores its pivotal role in preventing the progression to chronic disease and reshaping the treatment paradigm for pediatric patients with persistent ITP. However, as we tread this path of therapeutic innovation, a judicious balance between efficacy and safety must be maintained, with a keen eye on long-term outcomes and the evolving needs of our young patients. Enhanced comprehension of proper patient identification, dosage, adjustment, surveillance, and instruction might enhance compliance and results in patients with ITP undergoing treatment with TPO-RAs. Further research is required to have a comprehensive understanding of the tapering of TPO-RAs in order to prevent overtreatment or the occurrence of remission. While endogenous TPO levels might potentially indicate the probability of responding to a TPO-RA, it would be beneficial to have other predictors of response and identify markers of thrombosis risk. The investigation is now examining the potential impact of including TPO-RAs into the first treatment regimen on the initial response and long-term development of immune thrombocytopenia (ITP).

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