

Sustained Responses following Treatment with Romiplostim in Immune Thrombocytopenia: A Single-Centre Experience

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Received date: May 27, 2014, Accepted date: June 16, 2014, Published date: June 25, 2014

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Abstract

Background: Romiplostim is a thrombopoietin receptor agonist which is useful for the treatment of adults with chronic immune thrombocytopenia. This class of treatment is regarded as palliative, raising platelet counts whilst patients are receiving romiplostim, with the expectation that platelets will return to baseline after stopping therapy. Anecdotal reports have suggested that some patients show unexpected longer term responses when off treatment.

Design: We examined the outcomes for 21 consecutively-treated adult patients at our center to determine whether any patients had sustained responses after stopping romiplostim. A platelet count of $\geq 100 \times 10^9/L$ was considered a complete response, and from $50-100 \times 10^9/L$ this was considered a partial response. If the response after stopping romiplostim lasted 6 months or more this was considered a durable response.

Results: Of the 21 adults treated, 19 (90.4%) responded to romiplostim. After stopping romiplostim 5 patients (26.3%) had durable responses. Of these 5 patients, complete responses were seen in 4 (80%), and partial responses were seen one patient (20%).

Conclusions: Romiplostim has high efficacy in adults with chronic immune thrombocytopenia. Despite the expectation that romiplostim is a palliative treatment, 26.3% of patients maintained their platelet counts after the drug was stopped. The mechanism of action for such sustained responses remains to be explained.

Keywords: Immune thrombocytopenia; Romiplostim; Sustained responses

Introduction

Immune thrombocytopenia (ITP) is an organ-specific autoimmune disease leading to a low peripheral blood platelet count [1,2]. The underlying pathophysiology is complex and involves platelet destruction caused by antibodies directed at platelet glycoproteins and a relative platelet underproduction by the bone marrow. Until recently, most treatments have targeted only platelet destruction by inducing immune suppression. Recently a new class of therapy, the thrombopoietin receptor agonists (TRA), has been developed which enhances platelet production by the marrow. TRAs, which include the peptibody romiplostim [3,4], and the oral small molecule eltrombopag [5,6], are regarded as palliative therapies which elevate the platelet count in refractory patients, who continue to bleed, to cover invasive procedures or to delay or be a bridge to transplant. The expectation is that the platelet count will fall to baseline once the drug is stopped [7,8].

Romiplostim is a thrombopoietin peptide mimetic agent recently approved for the treatment of adults with chronic immune thrombocytopenia (ITP) [9,10]. In randomized controlled studies, this agent has demonstrated an increase in the platelet count in the majority of patients with ITP, both in splenectomised and non-splenectomised patients. Transient rebound thrombocytopenia after discontinuation of romiplostim is well recognised, possibly resulting

from enhanced clearance of endogenous thrombopoietin by the increased number of megakaryocytes. However, recent data show that sporadic, durable responses after treatment discontinuation are achievable with either agent in a proportion of patients [11-13].

The drug is licensed for use in adults only. The reported side effects from large clinical studies include: headache, Nasopharyngitis, fatigue, contusion, upper respiratory tract infection, diarrhoea and epistaxis. In clinical practice the drug is well-tolerated. Romiplostim should not be used during pregnancy and although there are no specific data on romiplostim in human breast milk, its use in breastfeeding mothers should be avoided.

We report the Royal London Hospital experience of treating adult patients with chronic ITP with romiplostim. Our patients had all failed numerous ITP therapies and romiplostim was used in an attempt to elevate the platelet count to a safe level for normal activities since all other treatments had been unsuccessful.

Materials and Methods

Data were collected retrospectively for adult patients started on treatment with romiplostim between June 2008 and December 2013. All patients were enrolled onto The UK Adult ITP Registry for which full ethical approval has been obtained.

Platelet count responses were defined as complete if the patient achieved a platelet count of $\geq 100 \times 10^9/L$, partial if $50-100 \times 10^9/L$, and durable if the response lasted 6 months or more.

Romiplostim was administered weekly by subcutaneous injection as per the manufacturer's instructions with dose adjustments depending on platelet responses.

Patients

All patients were adults with chronic ITP attending our clinic. The median age was 39 years (range 23-75 years). There were 10 male and 11 female patients. Seven patients (33.3%) had undergone prior splenectomy. All patients had received a number of prior treatments including immune suppression prior to starting romiplostim.

Results

The median platelet count at the time of starting romiplostim was $13 \times 10^9/L$ (range $2-48 \times 10^9/L$). The median dose of romiplostim was $5 \mu g/kg$ weekly (range $1-10 \mu g/kg$). The median duration of romiplostim treatment was 26 months (range 7-60 months).

Nineteen patients (90.4%) responded (platelet count $>50 \times 10^9/L$ without concomitant ITP therapy). In five patients (26.3%) remission was sustained for longer than 6 months after discontinuing romiplostim therapy. These patients had received romiplostim for a median duration of 32 months (range 17-60) before discontinuation of therapy. Characteristics of these patients are outlined in Table 1. Four out of five (80%) had not undergone splenectomy.

Age (years)	Previous treatments	Splenectomy	Max dose (mcg/kg)	Total duration of therapy (months)	Complete or partial response	Date treatment stopped
30	Prednisolone	No	2	22	CR	July 2012
44	Methylprednisolone, prednisolone, IVIg, anti-D, azathioprine, mycophenolate, cyclophosphamide, danazol	Yes	10	32	PR	April 2012
74	Prednisolone, IVIg, rituximab, mycophenolate, ciclosporine	No	2	17	CR	April 2013
26	Prednisolone, anti-D, rituximab, danazol,	No	2	60	CR	July 2013
55	Dexamethasone, IVIg, azathioprine, anti-D, mycophenolate	No	1	47	CR	July 2013

Table 1: Characteristics of patients who had a sustained response to romiplostim, IVIg: Intravenous Immunoglobulin; CR: Complete Response; PR: Partial Response

A complete response (platelets $\geq 100 \times 10^9/L$) was seen in 4 of 5 patients with durable response (80%) and a partial response (platelets $50-100 \times 10^9/L$) was seen in one of the 5 (20%).

Treatment was discontinued in one patient due to side effects (fatigue and sinus congestion). Two patients were switched to alternative treatment (eltrombopag) due to lack of response to romiplostim. One patient died due to causes unrelated to ITP and romiplostim.

12 patients are currently continuing with romiplostim therapy.

Discussion

To date most treatments for ITP are palliative with low efficacy. Most have not undergone rigorous randomised controlled trials to confirm efficacy or safety. Before the TPO receptor agonists were available, most treatments used were non-specific and were aimed at reducing platelet destruction. Toxicities are fairly common with most of the older therapies to date [14].

The thrombopoietin receptor agonists act through stimulation of the thrombopoietin receptor, inducing megakaryocyte proliferation and differentiation. As such, the thrombopoietin receptor agonists enhance platelet production but are not believed to play any role in reducing platelet destruction or modulation of the immune system.

Romiplostim has been shown to be highly effective for the treatment of adults with chronic ITP [15-17]. Similar to the findings of others, we have reported a high efficacy in our patient group which included several adults with long-standing ITP and in whom many previous therapies had failed, including splenectomy. Overall, romiplostim was well tolerated. Our median dose of $5 \mu g$ per kilogram was in line with previously reported data.

The main unexpected observation was of sustained responses in patients after stopping romiplostim. The thrombopoietin receptor agonists including romiplostim are not administered with curative intent. Since the mechanism of action is through the thrombopoietin receptor, the expectation is that the patient's platelet count will return to the pretreatment level once the romiplostim is stopped. Our observations confirm the earlier reported small anecdotal reports [11-13] and are supported by a French study which reported that of 28 patients responding to romiplostim 8 remained in unmaintained complete remission at a median follow-up of 13.5 months [18]. Further evidence comes from the interim analysis of the Phase 2 study of patients receiving romiplostim where 11 of 38 evaluable patients maintained their remission of all treatment [19].

There is more than one possible mechanism which might explain the lasting responses seen in our patients. For example, these patients may have undergone a "natural" remission of their ITP. However, because many of these patients had ITP for some years with little response to any therapy this is unlikely. Other investigators have proposed a change in immune regulation through an impact on T regulatory cells (Tregs) with restoration of immune tolerance [20]. A further mechanism may be through induction of tolerance to platelet glycoproteins perhaps by increasing the megakaryocyte and platelet mass to a critical level. There may be other potential interactions between romiplostim, platelet glycoproteins, the thrombopoietin receptor, and other molecules not identified and outside the remit of this study. Further investigation might include examining cytokine profiles and gene expression profiling in adults with chronic ITP before and after treatment to see if any immune modulation effects are observed.

In our retrospective study, and in the other reported studies, no specific clinical, treatment or laboratory features could be identified

that could predict for sustained response. Indeed one of the intriguing features in the reports are the long term responses in some patients who had failed all other treatment options and were considered truly refractory. While the thrombopoietin receptor agonists will mainly be used for short term treatment to cover invasive procedures and to treat patients who are at risk of bleeding and are refractory to other therapies prospective studies should be set up to confirm the observation of sustained response off therapy and to identify potential predictive factors of response.

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