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Usefulness of romiplostim for elderly patients with idiopathic thrombocytopenic purpura

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Abstract

Five elderly patients with idiopathic thrombocytopenic purpura (ITP) considered to require thrombopoietin receptor agonist (TRA) administration were treated with romiplostim at our department. The patients' conditions were as follows, respectively: 1) Splenectomy was difficult to perform and the response to steroid treatment was poor, 2) the disease was intractable, for which combination with steroid was effective and the steroid dose could be reduced later, 3) the performance status (PS) was markedly reduced due to concomitant diseases, 4) the disease was intractable, and another TRA caused an adverse reaction, and 5) PS was markedly reduced by active infection. These are characteristics frequently observed in elderly ITP patients, and only first- and/or second-line treatments were considered difficult to obtain the effect for these patients. Romiplostim was effective in all patients, and the safety was marked. It was suggested that TRA treatment is useful for elderly ITP patients difficult to treat following the current guidelines.

Key words: Thrombopoietin receptor agonist, Romiplostim, Elder, ITP, Idiopathic thrombocytopenic purpura

Introduction

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disease in which platelet destruction surpasses production, inducing thrombocytopenia.[1]

It was previously reported that age groups showing a high incidence of ITP are the 20s or 20-50 years old in females, and this has now been established. However, in a recent epidemiological survey, peaks of the incidence of the acute type were noted in infants younger than 5 years and the elderly older than 75 years, and a peak and major peak of the incidence of the chronic type were present in 26-30- and 76-80-year-old females, respectively. In males, a major peak was noted at 76-85 years old. Based on these, the incidences of acute and chronic types are now considered to be high in the elderly.[2,3]

According to the current Japanese guidelines for ITP treatment,[4,5] a Helicobacter pylori (H. pylori) test is performed, eradication therapy is conducted when it is indicated, and adrenocortical steroid administration and splenectomy are recommended as first- and second-line treatments, respectively. Several drugs are available as third-line treatment, but only thrombopoietin receptor agonists (TRAs) are covered by national health insurance in Japan. Romiplostim became covered in 2011, but there have been few reports of collected cases with elderly ITP.

Since many elderly persons have latent organ hypofunction, reducing drug therapy tolerability, long-term steroid treatment is difficult in many cases.[6,7] Surgery should be carefully selected because it increases postoperative morbidity and mortality in elderly patients.[8] Accordingly, the first- and second-line treatments are limited to be applied for elderly ITP patients in routine medical practice.

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We administered romiplostim to 5 elderly patients at our department considered to require TRA treatment. The conditions of these patients were as follows, respectively: 1) Splenectomy was difficult to perform, and the response to steroid treatment was poor, 2) the disease was intractable, for which combination with steroid was effective and the steroid dose could be reduced later, 3) the performance status (PS) was markedly reduced due to concomitant diseases, 4) the disease was intractable, and another TRA caused an adverse reaction, and 5) PS was markedly reduced by active infection. The drug was effective in all patients, and the safety was marked.

Here we discuss about new information which were obtained from these patients.

Case Report

Case 1: An 86-year-old male who poorly responded to steroids but was difficult to treat with splenectomy.

The patient was admitted for thrombocytopenia in May 2011. The platelet count was $1.0\times10^4/\mu l$; white blood cell count, $9\times10^3/\mu l$; hemoglobin, 10.3 g/dl. The platelet-associated IgG (PAIgG) was 52 ng/10^7 cells. On bone marrow testing, the nucleated cell count was $7.0\times10^4/\mu l$; megakaryocyte count, $60/\mu l$; with no dysplasia of any blood cell type. On abdominal CT, no splenomegaly was noted. The patient was diagnosed with ITP, and H. pylori was positive, for which eradication therapy was performed. Since the effect of eradication therapy was insufficient, steroid therapy was initiated about 1 week later. The platelet count did not increase despite steroid being administered for 1 month. Since the response to steroid was poor, second-line treatment, splenectomy, was necessary, but it was considered inappropriate because the patient was elderly. Thus, concomitant romiplostim administration was initiated.

Romiplostim administration was initiated in July 2011 at 120 μg/week, and the platelet count rose to $13.9\times10^4/\mu l$ after about 2 weeks. Since the count was stable thereafter, the steroid dose was gradually reduced to discontinuation, while maintaining the romiplostim dose at 80 μg/week. Currently, treatment is being continued with romiplostim alone (Case 1).

Case 2: A 71-year-old female with intractable ITP with a past medical history of diabetes for whom combination therapy with steroid was effective and the steroid dose could be reduced.

The patient was referred to our hospital for thrombocytopenia in March 2011. The platelet count was $1.5\times10^4/\mu l$; white blood cell count, $6.7\times10^3/\mu l$; hemoglobin, 12.3 g/dl. PAIgG was 192 ng/10^7 cells. On bone marrow testing, the nucleated cell count was $7.8\times10^4/\mu l$; megakaryocyte count, $30/\mu l$; with no dysplasia of any blood cell type. No splenomegaly was noted on abdominal CT. The patient was diagnosed with ITP. Since H. pylori was negative, steroid therapy was initiated. However the steroid therapy was insufficient, and so high-dose administration of γ-globulin followed by splenectomy was performed in May 2011. The platelet count transiently rose but started to decrease again, for which romiplostim administration was initiated

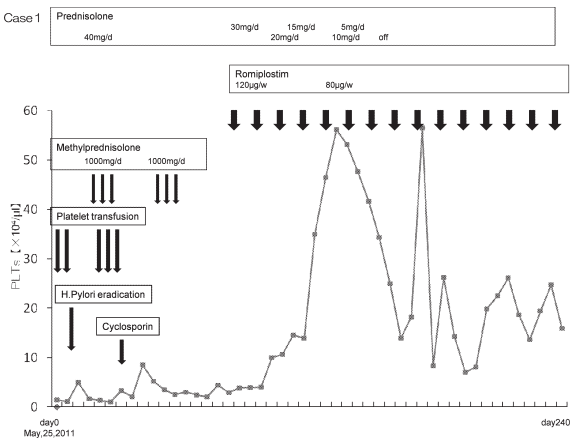

Fig. 1 Clinical course of an 86-year-old male who poorly responded to steroids but was difficult to treat with splenectomy (Case 1).

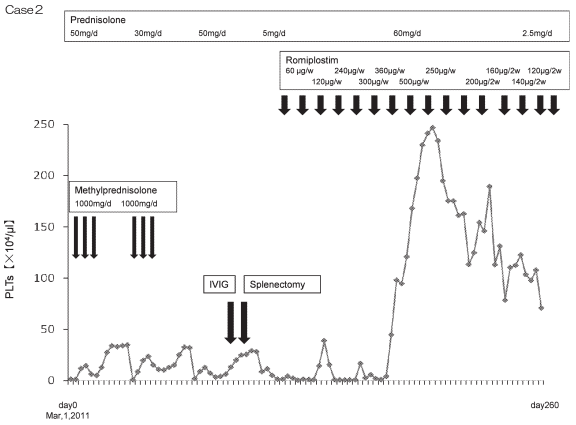

Fig. 2 Clinical course of a 71-year-old female with intractable ITP with a past medical history of diabetes for whom combination therapy with steroid was effective and the steroid dose could be reduced (Case 2).

at 60 μg/week in July 2011. At this point, the platelet count was $1.3\times10^4/\mu$l in the presence of the concomitant oral administration of predonine at 5 mg/body. When the dose of the 3rd administration was increased to 120 μg/week, the platelets transiently increased. The dose was elevated to 360 μg/week by the 7th administration, but the platelet count remained low ($0.9\times10^4/\mu$l). Thus, the romiplostim dose was increased to 500 μg/week and 60 mg/body of prednisolone was concomitantly administered on the 8th administration. The platelet count increased, and the doses of romiplostim and predonine could be gradually reduced. At present, the romiplostim and prednisolone doses have been reduced to 120 μg/body/2 weeks and 2.5 mg/body, respectively, but the platelet count is stable, with no decrease (Case 2).

Case 3: An 80-year-old female with markedly low PS due to complications.

The patient was being treated for chronic renal failure, chronic heart failure, and hepatitis C at the outpatient clinic of the internal medicine department. She fell and fractured her right femoral neck. During inpatient treatment in the orthopedic department, thrombocytopenia was noted. The white blood cell count was $4.4\times10^3/\mu$l; hemoglobin, 8.7 g/dl; platelet count, $1.4\times10^4/\mu$l. PAIgG was 300 ng/10^7 cells. On abdominal ultrasonography, hepatic cirrhosis, ascites and mild splenomegaly were noted. On bone marrow testing, the nucleated cell count was $7.8\times10^4/\mu$l, and the megakaryocyte count was 165/μl, based on which ITP was diagnosed in February 2012. Since H. pylori was positive, eradication therapy was performed. No steroid

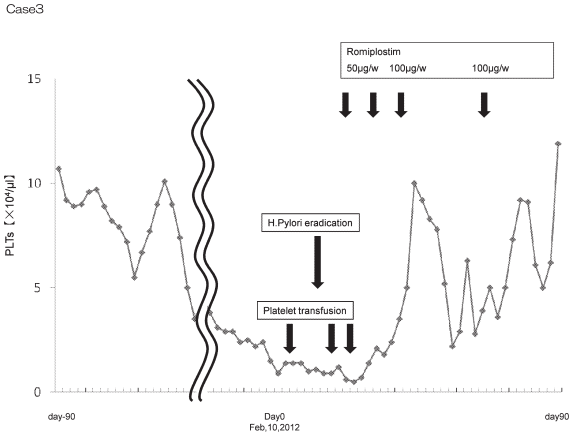

Fig. 3 Clinical course of an 80-year-old female with markedly low PS due to complications (Case 3).

treatment or splenectomy was performed in consideration of the poor general condition (PS: lower than 3), and treatment with romiplostim alone was initiated in March 2012. The platelet count was $0.5\times10^4/\mu$l at the initiation of romiplostim administration (50 μg/week). The count rose to $2.1\times10^4/\mu$l after one week and $5\times10^4/\mu$l after 2 weeks. Blood transfusion became unnecessary thereafter, and the patient was transferred to another hospital for dialysis in May 2012 (Case 3).

Case 4: A 78-year-old male with intractable ITP being treated for 4 years in whom an adverse effect was induced by another TRA, eltrombopag.

The patient was diagnosed with ITP by a physician in 2008, and H. pylori eradication was performed but ineffective. Predonine was administered but ineffective, and eltrombopag was additionally administered. Fever higher than 38° C developed after 20 days of eltrombopag administration. The fever was not reduced by antibiotic administration, but was reduced by the discontinuation of eltrombopag administration, suggesting eltrombopag-induced drug fever. Treatment was continued using predonine, but the disease repeatedly recurred. Thus, splenectomy was performed in 2011. Predonine (2.5 mg/body) was concomitantly administered, and the disease was temporarily remitted, but nasal bleeding occurred in December 2012, the platelet count decreased to $0.7\times10^4/\mu$l, and the patient was referred to our department. At the time of arrival, the platelet count was $0.6\times10^4/\mu$l; white blood cell count, $14.3\times10^3/\mu$l; hemoglobin, 10.5 g/dl. PAIgG was 191 ng/10^7 cells. On bone marrow testing, the nucleated cell count was $38.9\times10^4/\mu$l; megakaryocyte count, 75/μl; with no dysplasia of any blood cell type. The patient was diagnosed with ITP, and romiplostim administration was initiated at 125 μg/week as third-line treatment on December 22, 2012. The platelet count at the initiation of romiplostim administration was $0.8\times10^4/\mu$l. To avoid hemorrhagic risk, platelet transfusion was appropriately performed. Additional administration of another drug for third-line treatment, cyclosporine (150 mg/day), was initiated on January 8, the romiplostim dose was increased to 300 mg/body on January 12, and steroid pulse therapy was added on January 15. The platelet count recovered to $5.5\times10^4/\mu$l on January 18, 28 days after the romiplostim administration. The

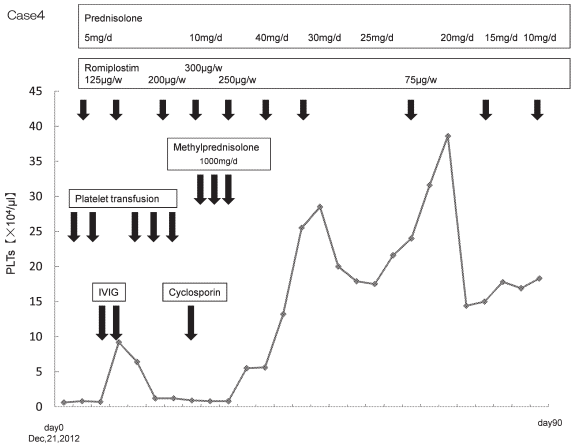

Fig. 4 Clinical course of a 78-year-old male with intractable ITP being treated for 4 years in whom an adverse effect was induced by another TRA, eltrombopag (Case 4).

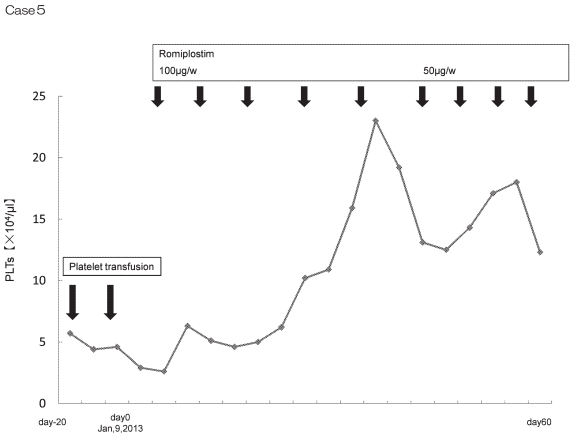

Fig. 5 Clinical course of a 91-year-old male with active infection and reduced PS (Case 5).

doses of romiplostim and predonine were gradually reduced thereafter. As of July 2013, the condition is being maintained with romiplostim alone (75 μg/body) without combination with other drugs (Case 4).

Case 5: A 91-year-old male with active infection and reduced PS.

The patient was admitted for exacerbation of non-tuberculous mycobacterial pneumonia and cor pulmonale. On January 9, 2012, the patient was referred to the hematology department by the respiratory medicine department for slowly progressing thrombocytopenia. The platelet count was $3.0\times10^4/\mu l$; white blood cell count, $3.4\times10^3/\mu l$; hemoglobin, 7.4 g/dl. PAIgG was 131 ng/10^7 cells. On bone marrow puncture, the cell count was $17.7\times10^4/\mu l$; megakaryocyte count, $156/\mu l$; with no bias of each blood cell system, or abnormal morphology of blood cells. The cause of thrombocytopenia was considered to be ITP. The cause of anemia was assumed to be gastrointestinal hemorrhage, although it was not conclusive because thorough examination, such as observation using a gastrointestinal camera, could not be performed due to the poor general condition, and the patient was being treated with a proton pump inhibitor (PPI). On abdominal ultrasonography, no splenomegaly was noted. H. pylori was negative. The general condition was markedly poor (PS: lower than 3), and the patient was being treated with oxygen inhalation for cor pulmonale. It was assumed that, if pulmonary hemorrhage occurs, it may be fatal, even though it is mild. Since it was difficult to perform excess steroid administration and splenectomy, treatment with romiplostim alone was initiated at 100 μg/week on January 23. At this point, the platelet count was $2.6\times10^4/\mu l$, but it rose to $6.3\times10^4/\mu l$ on 5 days, and $23.0\times10^4/\mu l$ on 21 days after the romiplostim administration, respectively. The romiplostim dose was then slowly reduced, and the platelet count could be maintained with 50 μg/week of romiplostim alone (Case 5).

Discussion

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disease in which platelet destruction surpasses production, inducing thrombocytopenia. Two immunological mechanisms of thrombocytopenia have been clarified: Platelet membrane-specific autoantibodies destroy platelets in one mechanism,[9] and reduce platelet production through acting on the megakaryocyte maturation system in the other.[10] Regarding the pathology of a humoral factor, thrombopoietin (TPO), it has been reported that, when platelets were destroyed in ITP, the blood TPO level did not rise, showing no difference from that in healthy subjects, unlike that in thrombocytopenia induced by a reduction of bone marrow megakaryocytes in aplastic anemia,[11] i.e., it is considered that the feedback system does not work because the bone marrow megakaryocyte count is almost normal in ITP, unlike that in aplastic anemia, or platelet turnover is enhanced and platelet-bound TPO is incorporated and degraded by the reticuloendothelial system, inhibiting the elevation of the TPO blood level. Therefore, it is considered that TPO administration increases the blood level in

ITP, which stimulates platelet production.[1]

Thrombopoietin receptor agonists for third-line treatment are second-generation TPA. The first-generation TPA (PEG-rHuMGDF) induced anti-PEG-rHuMGDF autoantibodies in clinical trials. These antibodies exhibited endogenous TPO-neutralizing activity, induced serious thrombocytopenia,[12] and manifested an aplastic anemia-like pathology in some patients.[13] Thus, the molecular structure of second-generation TPO receptor agonists was designed to share no homology with endogenous TPO. Romiplostim is a 59,000-Da-molecular-weight non-glycosylated recombinant protein in which 2 peptides comprised of 14 amino acid sequences without homology with TPO are connected to the human immunoglobulin FC region through polyglycine linkers and form a dimer through 2 disulfide bonds, and it competes with TPO to bind to the TPO receptor.[14] Eltrombopag is a 564.63-molecular-weight small non-peptide molecule different from romiplostim, and it binds to the transmembrane region of the TPO receptor,[15] which is different from the binding site of romiplostim. Both drugs activate the JAK-STAT and MARP systems, which increase platelets through the proliferation and differentiation of megakaryocyte-lineage cells.[14] Regarding the clinical effect, both drugs start to increase platelets after about 5 days of administration in a dose-dependent manner, reaching a peak after 10-14 days. In a Japanese phase-III clinical study of romiplostim, the rate of patients in whom the platelet count rose to 50,000/μl or higher was 16.7% in a placebo group and 95.5% in a romiplostim group, showing efficacy.[16] In a Japanese phase-II/III clinical study of eltrombopag, the effective rate after 6 weeks of administration (the rate of patients in whom the platelet count rose to 50,000/μl or higher) was 0% in a placebo group and 60% in an eltrombopag group.[17] Both romiplostim and eltrombopag exhibited favorable clinical effects, but the drugs are markedly different, and the action mechanisms are partially different.

In Case 4, an adverse effect (drug fever) was previously induced by eltrombopag, but it was predicted that romiplostim would induce no cross-reaction because of the differences between the drugs described above, and actually, no adverse effect occurred and the effect was favorable.

One of the most serious concern about the usage of romiplostim for elderly patients with ITP is thrombosis, because romiplostim has been shown to prime the platelets aggregation.[18] However, in two double-blind randomized control trials,[19,20] the incidence of thrombotic events was not increased in chronic ITP patients treated with romiplostim compared with placebo. This adverse event actually was not observed in our patients.

In drug therapy for elderly patients, the half-life (t1/2) of drugs may prolong and the maximum blood level (Cmax) may rise due to reduced renal and liver functions involved in the metabolism and excretion of drugs. It has been reported that 1.5-2 times more adverse drug reactions occurred in acute-phase inpatients aged 70 years or older than in those younger than 60 years,[6] and diverse complications such as diabetes, hypertension, chronic renal failure, congestive heart failure, fracture, cataract, skin symptoms, mental symptoms and so on occurred in patients undergoing long-term steroid treatment.[7] The incidence and severity may worsen in elderly patients because many of them show latent organ hypofunction. Moreover, anti-inflammatory and immunosuppressive actions are well-known pharmacological effects of steroids, and these may aggravate active infections and increase the risk of opportunistic infection in these patients. Case 3 had complications of chronic renal and heart failure and hepatitis C, and the induction of other complications by steroid treatment of ITP was a concern. Case 5 had active infection : non-tuberculous mycobacterial pneumonia, and required oxygen inhalation for cor pulmonale. Steroid treatment of ITP under these conditions may aggravate mycobacterial pneumonia and induce complications due to opportunistic infection.

In recent reports, romiplostim was administered to an 83-year-old male with ITP[21] who was hemorrhagic even with treatment with blood transfusion, steroid, and high-dose γ-globulin, and a 91-year-old male with ITP[22] being treated with a vitamin K antagonist for atrial fibrillation, and romiplostim was effective and safe for the initial development of ITP in both elderly patients, leading to a proposed concept of early management. Furthermore, TRA was useful for lymphoma-associated ITP in 4 patients with life-threatening B-cell lymphoma requiring anticancer drug treatment,[23] based on which TRA is also expected to be useful for salvage therapy.

As described above, early TRA treatment for

patients with severe complications or expected to develop such complications may be becoming a therapeutic trend.

Regarding combination with steroids, there has been a case reports in which simultaneous predonine and romiplostim administration increased platelets within a short time in ITP patients.[24] In our patients, steroid administration preceded, followed by combination with romiplostim in Case 1, whereas romiplostim administration preceded, followed by combination with the increased dose of predonine in Case 2, and the effects were marked in both. Although its mechanism is difficult to explain in detail, it was suggested that simultaneous immunosuppressive therapy and romiplostim administration improve the production and survival of platelet of patients with ITP within a short time, which is interesting.

The possibility of the dose reduction or withdrawal of steroids by combination with romiplostim has been shown,[25] as noted in our patients (Case 1, 2 and 4), and this is also advantageous for the treatment of elderly ITP patients.

Treatment options for elderly ITP patients are limited in the guidelines. TRA is expected to be useful for patients difficult to treat with existing therapies.

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