Case report

Recombinant ADAMTS-13 as a new alternative for the patients with congenital thrombocytopenic purpura

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ABSTRACT

Congenital thrombocytopenic purpura (cTTP), also known as Upshaw–Schulman syndrome is a rare disease, caused by ADAMTS13 deficiency. This condition may result in various complications, including haemolytic anaemia, renal dysfunction or thrombotic events. To this very day, the most common treatment of this condition is transfusion of fresh frozen plasma.

Recently, recombinant ADAMTS13 (rADAMTS13) has been introduced, representing a revolutionary advancement in the treatment of cTTP, and giving patients new, more comfortable alternative.

We present here a case report of a patient with congenital thrombocytopenic purpura, who after 30 years of being treated with FFP transfusions and developing complications from both the disease and its treatment, was successfully transitioned to rADAMTS13 therapy.

Key words: congenital thrombocytopenic purpura, Upshaw–Schulman syndrome, ADAMTS13, rADAMTS13

INTRODUCTION

Upshaw–Schulman syndrome (USS), also known as congenital thrombocytopenic purpura (cTTP), is associated with an inherited ADAMTS-13 deficiency. ADAMTS13 is a metalloproteinase that cleaves von Willebrand factor (vWF). Consequently, the plasma of the patients with USS contains large multimers of von Willebrand factor, which bind platelets and form thrombi in microvasculature. The main symptoms of USS include haemolytic anaemia, thrombocytopenia, renal dysfunction, neurological symptoms and fever [1]. Although rare, this disease can be fatal. According to some recent studies, its mortality rate ranged from 4.8% to 6.8%, with causes of death consisted of stroke, cancer unrelated, sudden death due to unknown cause, cerebral infarction, sepsis, uraemia and suicide [2].

The diagnosis should be confirmed by detecting severe ADAMTS13 deficiency, defined as an activity level of <10%, whereas the therapeutic goal is achievement of clinical response, defined as a normalization of the platelet count above the lower limit of the established reference range (150 G/L) and the decrease of LDH level to <1.5× the upper limit of normal (ULN) [3]. If the initial condition includes evidence of significant organ damage, stabilization of these parameters with improvement in function is also required to qualify as a clinical response. Clinical remission is a sustained clinical response which lasts for more than 30 days. Refractory TTP is defined as persistent thrombocytopenia (platelet count <50 G/L, without increase) and consistently elevated LDH levels (>1.5× ULN) after 5 plasma exchange treatments combined with adequate steroid treatment. If platelet count remains below 30 G/L, it classifies as severe refractory TTP [3].

The initial treatment for USS is transfusions of fresh frozen plasma (FFP), simply to replace the missing ADAMTS13 [4]. Treatment becomes more complex, when the patient develops an alloantibody, ADAMTS13 inhibitor, which drastically changes the course of treatment [5]. In such cases, other therapeutic options include plasmapheresis, also known as therapeutic plasma exchange (TPE), high doses of steroids and anti-CD20 monoclonal antibody therapy, specifically rituximab that suppresses ADAMTS13 inhibitor production by depleting B lymphocytes, administered both during exacerbation and prophylactically [6]. These therapies aim to induce immunosuppression and reduce antibody production, which allows for the recovery of ADAMTS13 levels [3]. Patients can now receive a novel treatment with recombinant ADAMTS-13 (rADAMTS13), which has a chance to become the most effective and also the most convenient treatment [7]. rADAMTS13 is a recombinant, glycosylated human ADAMTS13 protein, produced in a plasma protein-free environment using a Chinese hamster ovary mammalian expression system and it is specifically designed to replace human ADAMTS13 [8].

CASE PRESENTATION

A 55-year-old Caucasian female was diagnosed with USS in 1993 at the age of 24. The patient's main diagnosis was accompanied by hypertension, active hepatitis C virus infection, a history of hepatitis B viral infection and ischaemic stroke in 2010, which was a clear complication of congenital thrombocytopenic purpura. The main manifestations of USS in this patient were thrombocytopenia, anaemia and chronic kidney disease at stage G2 (defined as lasting minimum 3 months abnormalities of kidney structure or function, with glomerular filtration rate 60–89 ml/min per 1,73 m^3) [9]. The patient complained of chronic headaches and bruising. The patient was under the care of the haematology clinic and attended follow-up appointments every 2 weeks for platelet level monitoring and transfusions of 2 units of FFP. After each transfusion the patient was required to stay in the haematology unit for 2 days in order to monitor for serious complications and severe side effects.

Unfortunately, in March 2021 the patient developed an alloantibody against ADAMTS13 (ADAMTS13-inhibitor), with a level of 36 U/mL detected by the ELISA method. This complication was likely a result of frequent FFP transfusions. From that moment, the patient required 4 instead of 2 units of FFP.

At the end of June 2021, the patient was admitted to the hospital due to the appearance of neurological symptoms, primarily Broca's aphasia. Blood tests revealed an active disease flare up, with platelets at 64 G/L and LDH at 244 U/L. The patient underwent 6 plasmapheresis sessions, which resulted in the regression of aphasia and other neurological symptoms. Nevertheless, in July, the patient was scheduled for another 6 plasmapheresis sessions. A permanent therapeutic effect was still not achieved. Therefore, the patient had 9 additional plasmapheresis sessions in August, and was administered methylprednisolone alongside rituximab to attempt disease regression, which was eventually achieved. The patient's platelets increased to 155 G/L.

In September, the patient's platelets dropped again to 39 G/L. LDH level was at 470 U/L and the patient complained of a headache. She was admitted to the haematology unit, where she was qualified for another 6 courses of plasmapheresis along with prednisone. To intensify the therapy, the patient received 3 doses of rituximab at one-week intervals, starting at the beginning of October. In the same month, the patient required 3 more plasmapheresis sessions accompanied by prednisolone. The pattern repeated in November. In December, supposedly due to severe infection, 4 courses of plasmapheresis failed to improve the patient's condition. The patient was then administered 15 mL/kg of FFP. However, the patient's condition worsened, leading to respiratory insufficiency, which necessitated a transfer to the intensive care unit. At that time, her platelet level

was 67 G/L. After 2 eeks, the patient returned to the haematology clinic in order to continue USS treatment. The patient did not respond well to FFP and thus was again qualified for plasmapheresis, which was successful. Since then, the patient was admitted to the haematology unit every 2 weeks for 2 days and administered four units of FFP. The end of December 2023 was a breakthrough in the patient's treatment due to administration of single intravenous injection of recombinant ADAMTS13 (rADAMTS13) (2500 IU), which enabled the reduction of frequency hospitalizations. Prior to administration of rADAMTS13, activity of the patient's ADAMTS13 was at the level of 2.9% and inhibitor was below 0.5 UB/mL. Two weeks after the first administration of rADAMTS13, in the second week of January 2024, patient's platelet level reached 122 G/L. By the end of January it was already 160 G/L. The patient did not report any complaints or noticeable side effects from rADAMTS13. Since the first dose at the end of 2023, she has been receiving the drug through primary health care, and checks in at the haematology clinic every 2–3 months for examination and blood screenings. Figure 1 depicts patient's PLT levels on FFP and rADAMTS13 treatment.

DISCUSSION

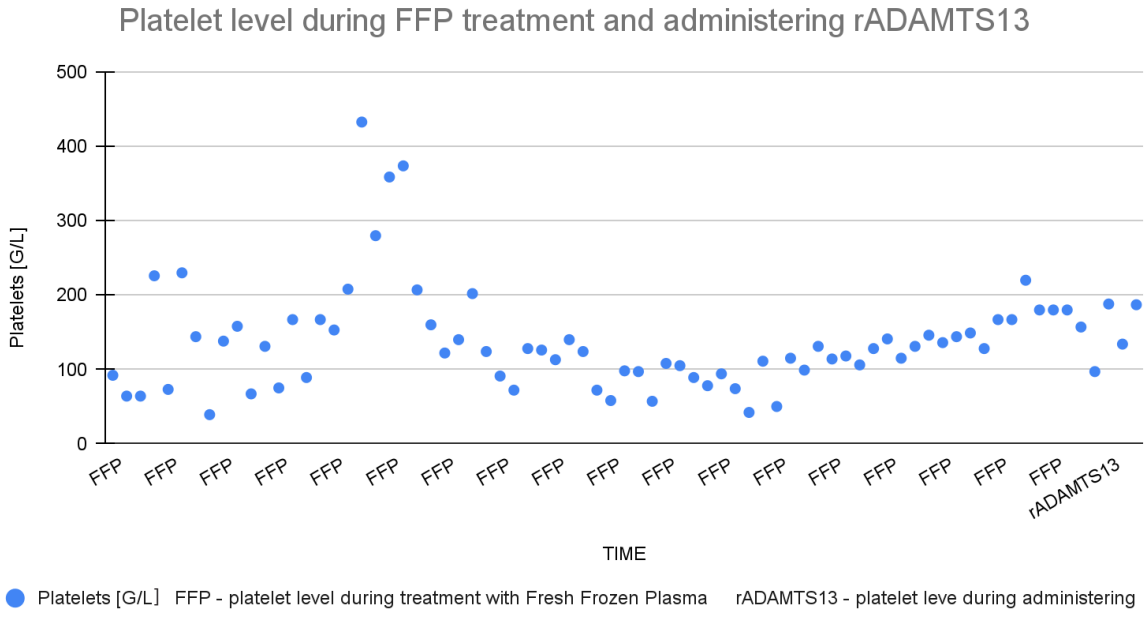
USS is undoubtedly a serious disease, with limited therapeutic options. Until recently, the treatment primarily involved transfusions of FFP every 2 weeks and eventually plasmapheresis (plasma exchange) during disease exacerbations, as well as, in some cases, steroids and plasma derived factor VIII concentrates [7]. Recently, a new drug, rADAMTS13, has been introduced and approved as a replacement therapy for patients with cTTP [10]. It seems that it has a chance to become the most effective and the most convenient treatment [7].

Nevertheless, we cannot underestimate the value of plasma exchange and transfusions of FFP – that treatment resulted in significant improvement of survival from approximately 10% to 80% in the 1970s [11]. FFP is a blood product, and its transfusion may be associated with various side effects, including acute haemolysis, allergic or anaphylactic reaction, transfusion-related immunomodulation, transfusion-related acute lung injury, nausea, itching, mistransfusion, and septic or bacterial contamination (most commonly hepatitis B virus and hepatitis C virus) [12].

FFP transfusion is a procedure, which can be burdensome for the patients, as the treatment creates time-gaps in their lives, counted in several hours of therapeutic infusion in a specialized centre every week, in some extreme cases even every week [7].

Plasmapheresis, used during exacerbation, when routine FFP does not improve the patient's condition, is even more inconvenient. This procedure lasts about 4–5 h, and must be conducted once a day for several days every 24–48 h, depending on the initial condition of the patient and response to treatment [13]. It requires close attention from medical personnel, as it is associated with numerous complications, such as haemolysis, apnoea, convulsions, nausea, vomiting, arrhythmia, hypotension, hypovolemia and coagulation abnormalities [13]. Furthermore, both FFP transfusion and TPE are procedures, which are based on blood products, and that is prohibited in some religious beliefs [3].

Figure 1. Platelet level (G/L) during FFP and rADAMTS13 (rADAMTS13) therapy. The graph shows that rADAMTS13 treatment enabled maintenance of PLT level comparable to the one during FFP treatment.



Recombinant ADAMTS13, on the other hand, is a drug that can be administered every 2 weeks as an intravenous infusion, taking approximately 2–5 min for a 70 kg patient and can easily be done during routine follow-up appointments [14]. This outpatient treatment may increase patient's compliance. It also benefits the medical personnel and other patients, as those receiving rADAMTS13 do not occupy hospital beds, which can be allocated to other patients awaiting their treatment. The most common side effects of rADAMTS13 include headaches, nausea, migraine, diarrhoea, abdominal pain, upper respiratory tract infections, vomiting, dizziness [14], but due to some recent studies, rADAMTS13 appears to have less frequent and less side effects; in one of the recent studies, only 10.3% patients receiving rADAMTS13 experienced treatment related side effects versus 50% patients who received standard care treatment; what is more, there were no therapy interruptions or discontinuation in the rADAMTS13 therapy, whereas, 18.2% of patients in the standard of care arm had interruptions/discontinuation related to therapy [7]. Additionally, rADAMTS13 presents a thrombolytic effect in microcirculation preventing complications from USS, without increasing the risk of haemorrhage, as demonstrated in the studies on the mice [15]. Conversely, undoubtful advantage of plasmapheresis is its binary function – supplying adequate levels of ADAMTS13 and capability to mechanically remove autoantibodies [3], although there is evidence that rADAMTS13 can, to some extent, neutralize the autoantibodies, what was shown in studies in vivo [10, 17] and in vitro [5]. New studies show, that rADAMTS13 allows to isovolemically provide equivalent enzyme content of around 7 L (28 units) of plasma, which is far more efficient than plasmapheresis [10]. One of the recent studies shows that rADAMTS13 in comparison to plasma infusions, provides stable levels of ADAMTS13 at the level over 10% [7]. In other studies it was shown that the maximum ADAMTS13 activity after rADAMTS13 treatment was 101%, as compared with 19% after standard therapy and moreover, no neutralizing antibodies developed [17].

CONCLUSION

Recombinant ADAMTS13 represents a new and innovative treatment for USS, and may soon replace FFP transfusion in standard therapy for cTTP. It is more comfortable to administer, and associated with fewer complications and side effects.

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MW proposed the idea of presenting the case report; MW was responsible for patient management; MW, WR and IF contributed to writing the article. All authors (MW, WR, IF, TR) contributed to revising and editing the manuscript.

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The authors had full access to the data and take full responsibility for its integrity. All authors have read and agreed with the content of the manuscript as written. The paper complies with the Helsinki Declaration, EU Directives and harmonized requirements for biomedical journals.