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Ofatumumab for acute treatment and prophylaxis of a patient with multiple relapses of acquired thrombotic thrombocytopenic purpura

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Abstract
Acquired thrombotic thrombocytopenic purpura (TTP) is an autoimmune disorder resulting in potentially life-threating systemic thrombotic microangiopathy due to production of antibodies directed against the von Willebrand factor-cleaving protease ADAMTS13. Typically managed with plasma exchange, glucocorticoids, and the first-generation anti-CD20 monoclonal antibody rituximab, patients with multiple relapses or refractory disease present unique management challenges. We describe a case of a young woman with multiple relapses of TTP despite standard therapy who was treated with ofatumumab, a second-generation anti-CD20 monoclonal antibody, after developing a severe hypersensitivity reaction to rituximab precluding its use. Ofatumumab was effective for the treatment of an acute relapse of TTP in combination with plasmapheresis and as a single-agent for prophylaxis. The patient has had no evidence of relapse 2 years after completion of acute treatment and 1 year after completing prophylactic therapy. Hypersensitivity to ofatumumab did not develop.

Keywords Thrombotic thrombocytopenic purpura · Ofatumumab · Drug hypersensitivity · Rituximab · Prophylaxis

Introduction

Acquired thrombotic thrombocytopenic purpura (TTP) is a rare autoimmune disorder resulting in thrombotic microangiopathy secondary to reduced activity of the von Willebrand factor-cleaving protease, ADAMTS13. TTP may present with thrombocytopenia, microangiopathic hemolytic anemia, neurologic dysfunction, renal dysfunction, and/or systemic inflammatory symptoms. Without treatment, mortality exceeds 90% [1]. Acute TTP is typically managed with plasma exchange (PLEX) to eliminate anti-ADAMTS13 antibodies and replete ADAMTS13. Glucocorticoids may be given, and the mouse-human chimeric anti-CD20 antibody rituximab, previously reserved for relapsed or refractory cases, is now used at initial presentation in many centers [2]. Ofatumumab, a fully human second-generation anti-CD20 antibody, is used to treat B-cell malignancies. Ofatumumab binds to a unique CD20 epitope and has demonstrated improved complement-dependent cytotoxicity-mediated B-cell kill compared with rituximab [3]. We present a case report of the use of ofatumumab to treat acquired TTP.

Case report

A 21 year-old woman with a history of acquired TTP presented to the emergency department with numerous ecchymoses and purpura and a laboratory evaluation significant for thrombocytopenia, elevated LDH, and schistocytes on the peripheral blood film, consistent with a third relapse of TTP. TTP was confirmed with ADAMTS13 activity measurement < 5% and ADAMTS13 inhibitor titer of 2.2 Bethesda units (BU). The patient was initially diagnosed with acquired TTP 3 years prior at age 17 after presenting with similar findings. At initial diagnosis, ADAMTS13 activity was < 5% and ADAMTS13 inhibitor titer was 1.6 BU. For the initial episode the patient was treated with plasma exchange (PLEX), 4 doses of rituximab 375 mg/m^2,

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and glucocorticoids. The first relapse occurred 30 months later and was managed successfully with PLEX and 4 weekly doses of rituximab. With the third rituximab dose, the patient developed headache, chest pain, nausea, and blurry vision; the infusion was not completed. Despite standard hypersensitivity pre-medications, the patient developed pruritis, hives, and angioedema within minutes of starting the fourth dose; no further treatment was given. A second relapse occurred 13 months later with similar management including a plan for four weekly doses of rituximab; however, the patient developed severe anaphylactic-type hypersensitivity with urticaria and angioedema during the third infusion of rituximab and the fourth dose was omitted. After resolution of this third episode, flow cytometry demonstrated rapid peripheral B-cell recovery. Prophylaxis with rituximab was attempted with pre-medications and maximal reduction of infusion rate, but the patient developed urticaria and angioedema within minutes of exposure.

The patient had a fourth episode (third relapse) of TTP just 3 months after the third episode. PLEX was initiated. Because of the history of severe anaphylactic-type reactions to rituximab and the short duration of remission, ofatumumab was used to treat TTP. Following three PLEX treatments, ofatumumab 300 mg was infused without complication, followed by three weekly infusions of ofatumumab 1000 mg each. Following completion of PLEX (six total treatments) and ofatumumab, ADAMTS13 activity was 97% and peripheral B-cell count by flow cytometry was 0%.

The patient was determined to have a high risk for recurrence, given four episodes of TTP with decreasing remission duration between relapses. Ofatumumab prophylaxis was initiated, with 1000 mg approximately every 8 weeks for five doses. ADAMTS13 activity checked at regular intervals was > 100%, with no detectable ADAMTS13 inhibitor. Following completion of five doses of ofatumumab prophylaxis without complication, the patient was observed closely, without TTP recurrence over 2 years since the last relapse and 1 year since completion of prophylaxis.

Discussion

The treatment of TTP is complex and based on limited data. The largest randomized controlled trial found that PLEX was superior to plasma infusion [1]. A randomized trial of PLEX with or without rituximab was launched at 19 sites but terminated early due to low accrual [4]. Case reports, case series, or small retrospective studies describing use of cyclophosphamide, mycophenolate mofetil, cyclosporine, or bortezomib provide limited data for use of other immunosuppressive agents [5–8]; all claimed success in these small numbers. A small prospective trial examining the use of cyclosporine versus prednisone during an acute episode had difficulty enrolling patients but findings suggested that prednisone was better than cyclosporine [9]. At the time of manuscript submission, a case report was published describing successful ofatumumab use in a patient with acquired TTP and rituximab hypersensitivity [10]. Our case supports the finding that ofatumumab is effective and safe in patients with acquired TTP who develop hypersensitivity to rituximab. We found that ofatumumab can also be used for prophylaxis without invoking hypersensitivity reactions over 15 months exposure.

Although data for ofatumumab treatment of TTP were unavailable when we treated our patient, the rationale for use was based on the efficacy of rituximab and the similar CD20 target. Rituximab is a mouse-human chimeric antibody inducing both antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Ofatumumab is a second-generation fully human antibody designed to have superior CDC to rituximab; in vitro studies have demonstrated increased lysis of B-cell lines exposed to ofatumumab compared with rituximab [3]. Ofatumumab is used routinely to treat chronic lymphocytic leukemia (CLL) and has shown equivalence with rituximab in treating other non-Hodgkin's lymphomas [11]. As maintenance therapy in a randomized trial of patients with relapsed CLL, ofatumumab administered every 8 weeks for 2 years demonstrated a statistically significant improvement in progression-free survival compared with observation [12].

Multiple published studies suggest that the use of rituximab with PLEX for a first episode of TTP and for prophylaxis provides benefit, with reduced time to platelet count recovery and lower likelihood of relapse [2, 13–15]. In a large cohort study of 91 acute acquired TTP patients, those receiving rituximab less than 3 days from admission were compared to patients receiving rituximab greater than 3 days from admission. Early use was associated with faster attainment of remission, fewer plasma exchanges and shorter hospital stay [2]. Fifteen patients in this cohort with TTP in first remission with high risk of relapse received rituximab prophylaxis; only 1 patient had relapsed TTP 70 months later. A recent retrospective study demonstrated a 30% reduction in the absolute risk of relapse among 16 patients receiving rituximab acutely at initial TTP episode in comparison with 21 who did not [14], corresponding to a number needed to treat of 3.3 to prevent 1 relapse [16]. In another study, a cross-sectional analysis of 12 year follow-up data compared relapse incidence with or without prophylactic rituximab in patients with acquired TTP and severe ADAMTS13 deficiency during remission, revealing a higher relapse-free survival in 30 patients treated with rituximab prophylaxis compared with 18 patients not receiving rituximab prophylaxis [15].

Conclusion

Our patient had previously received several courses of rituximab to treat acute relapsed TTP, with the development of severe hypersensitivity. The hypersensitivity to rituximab, the number of relapses, and the decreasing remission duration were compelling reasons to use ofatumumab to treat the third relapse and subsequently for prophylaxis. The every 8 week dosing for prophylaxis followed the dosing schedule of ofatumumab maintenance for patients with CLL [12]. We did not see the development of hypersensitivity to ofatumumab during prophylactic use over one year. Ofatumumab is a safe, effective, promising therapy for acute and prophylactic treatment of acquired TTP for patients who do not tolerate rituximab. Further study is needed to determine if it will have better efficacy than rituximab for first line therapy for TTP.

Author contributions HAS collected the data, analyzed and interpreted the data, and wrote/revised the manuscript; RF Grace revised the manuscript; JM Connors designed the report and critically revised the manuscript.

Compliance with ethical standards

Conflict of interest Al-Samkari, H: Consultancy (Agios Pharmaceuticals); Grace, R: Research Funding, Consultancy, Scientific Advisory Board (Agios Pharmaceuticals); Connors, JM: (Boehringer Ingelheim: Scientific Advisory Board; Bristol-Myers Squibb: Scientific Advisory Board, Consultant, Independent Review Committee; Unum Therapeutics: Data Safety Monitoring Board).

Research involving human and animal participants This article does not contain any studies with human participants or animals performed by any of the authors.

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