POST-ALEMTUZUMAB CHRONIC IMMUNE THROMBOCYTOPENIA REMISSION AFTER SWITCH TO OCRELIZUMAB

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ABSTRACT
CD52 depletion with the monoclonal antibody alemtuzumab is a very effective treatment for multiple sclerosis (MS) but unfortunately is also commonly associated with autoimmune manifestations. Usually these affect thyroid function and can be mild or even subclinical; the rarer, however, immune thrombocytopenia (ITP) can be severe, have a delayed onset and requires acute intervention; therefore, prolonged vigilance is needed. Herein, we report two patients with MS treated with alemtuzumab, who developed chronic ITP. Both cases suffered multiple relapses and proved refractory to conventional and non-immunological, second-line ITP management. Interestingly, B-cell depletion therapy administrated for the management of MS activity that had reappeared after alemtuzumab treatment resulted in sustained ITP remission. This observation suggests that B-cell depletion therapy can have a beneficial effect on immune deregulation, not only by eliminating MS activity but also secondary autoimmunity such as ITP; and consequently, that the mechanism of post-alemtuzumab ITP is B cell-mediated.

Keywords: Multiple sclerosis, alemtuzumab, immune thrombocytopenia, secondary autoimmunity, ocrelizumab

ΥΦΕΣΗ ΧΡΟΝΙΑΣ ΙΔΙΟΠΑΘΟΥΣ ΘΡΟΜΒΟΠΕΝΙΚΗΣ ΠΟΡΦΥΡΑΣ ΠΟΥ ΑΝΑΠΤΥΧΘΗΚΕ ΜΕΤΑ ΑΠΟ ΑΛΕΜΤΟΥΖΟΥΜΑΜΠΗ ΜΕΤΑ ΑΠΟ ΑΛΛΑΓΗ ΣΕ ΟΚΡΕΛΙΖΟΥΜΑΜΠΗ

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ΠΕΡΙΛΗΨΗ
Η εξάλειψη των CD52+ κυττάρων με το μονοκλωνικό αντίσωμα alemtuzumab αποτελεί πολύ αποτελεσματική θεραπεία της πολλαπλής σκλήρυνσης (ΠΣ), αλλά δυστυχώς συνοδεύεται συχνά από δευτεροπαθείς αυτοάνοσες εκδηλώσεις. Συνήθως αυτές αφορούν το θυρεοειδή και μπορούν να είναι ήπιες ή και υποκλινικές. Η πιο σπάνια ωστόσο εκδήλωση ιδιοπαθούς θρομβοπενικής πορφύρας (ΙΤΡ) μπορεί να είναι τόσο όψιμη όσο και σοβαρή, κατά συνέπεια να απαιτεί εγρήγορση αλλά και άμεση θεραπευτική παρέμβαση. Στην παρούσα αναφορά περιγράφουμε δυο περιπτώσεις ασθενών με ΠΣ που έλαβαν alemtuzumab και ανέπτυξαν χρόνια ΙΤΡ. Και στις 2 περιπτώσεις υπήρξαν πολλαπλές υποτροπές και ανθεκτικότητα της ΙΤΡ στις μη ανοσολογικές θεραπείες 1ης και 2ης γραμμής. Κατά ενδιαφέροντα τρόπο, η θεραπεία εξάλειψης των Β λεμφοκυττάρων, η οποία ετέθη λόγω ακτινολογικής ή και κλινικής ενεργότητας της ΠΣ, οδήγησε σε εμμένουσα ύφεση της ΙΤΡ. Η παρατήρηση αυτή μας οδηγεί στο να συμπεράνουμε πως η θεραπευτική εξάλειψη των Β λεμφοκυττάρων μπορεί να έχει ευεργετικές επιδράσεις στην ανοσολογική εκτροπή, όχι μόνο εξαλείφοντας τη δραστηριότητα της πολλαπλής σκλήρυνσης αλλά και φαινόμενα δευτεροπαθούς αυτοανοσίας όπως την ΙΤΡ, η οποία κατά συνέπεια φαίνεται να είναι διαμεσολαβούμενη από Β λεμφοκύτταρα.

Λέξεις κλειδιά: Πολλαπλή σκλήρυνση, alemtuzumab, ιδιοπαθής θρομβοπενική πορφύρα, δευτεροπαθής αυτοανοσία, ocrelizumab

INTRODUCTION

Alemtuzumab is a humanised anti-CD52 monoclonal antibody that targets circulating T and B lymphocytes, as well as NK cells; it is approved for the treatment of relapsing-remitting multiple sclerosis (RRMS).[1] Albeit its efficacy in limiting RRMS disease activity is high (in 60% of patients no evidence of disease activity was noted during a 6 year-follow-up period), secondary autoimmune manifestations have limited its application.[2] These secondary autoimmune adverse events commonly include thyroid disorders, which in some cohorts occurring in up to 55% of patients,[3] and more rarely immune thrombocytopenia (ITP) and autoimmune nephropathies, occurring in 2.8% and 0.2% of patients, respectively[2]; very rare hematologic anomalies such as post-alemtuzumab autoimmune haemolytic anaemia have also been reported.[4] Relative quantitative imbalance of B and T cells with an overshooting of B cells in the absence / reduced presence of T cells, and especially prevention of secondary autoimmune phenomena by low-dose rituximab have led to the hypothesis that these secondary autoimmunities are primarily B cell-mediated.[5,6]

ITP is characterised by low platelet count in the absence of systemic disease and be divided into three phases: newly diagnosed (0-3 months), persistent (3-12 months) and chronic (>12 months).[7] In addition, ITP can be considered primary or secondary, caused by e.g. drugs, infections, autoimmune diseases or lymphoproliferative neoplasms. The pathogenetic mechanism in many-but not all- cases involves autoantibodies against platelet transmembrane receptor GPIIb/IIIa.[8] Treatment includes high-dose corticosteroids, commonly followed by po tapering, and intravenous immunoglobulin (IVIG) as first-line/initial agents, whereas second-line therapies include the anti-CD20 monoclonal antibody (mAb) rituximab, thrombopoietin receptor agonists (TPO-RAs) and splenectomy.[9] Post-alemtuzumab ITP is marked by delayed onset, overall good responsiveness to first-line as well as second-line therapies, and sustained remission after treatment.[10] Here, we present two cases of relapsing, chronic post-alemtuzumab ITP, where the anti-CD20 mAb ocrelizumab was applied due to MS activity breakthrough, but also affected an increase in platelet count and stabilisation of ITP.

CASE REPORTS

Case one

A 39-year-old man was diagnosed with multiple sclerosis (MS) in February 2017 after developing right hand and leg numbness and weakness. After another relapse and an increase in lesion load over a 2-month period, alemtuzumab was administered in July 2017 and August 2018. His past medical and family history was unremarkable for autoimmune diseases, allergies, or haematological diseases. In December 2020, the patient presented with a haemorrhagic episode, low platelet count (PLT: 6.000/μL) and after a thorough investigation, ITP was diagnosed. Treatment with prednisone was initiated (80 mg/day po) and resulted in rapid platelet count improvement. Prednisone was gradually tapered off with simultaneous initiation of the po TPO-RA eltrombopag, under which the platelet count remained stable until October 2021, when it was discontinued. One year after the initial insult, a relapse with symptomatic thrombocytopenia occurred and was successfully treated with dexamethasone (40mg/day for 4 days iv). The third relapse of ITP occurred 2 months later, when the patient presented again symptomatic thrombocytopenia (PLT: 7.000/μL). Treatment comprised of dexamethasone (24mg/day for 4 days) and eltrombopag (75mg/day) and three days after dexamethasone initiation the platelet count was back to normal (Figure 1). However, due to the repeated relapses eltrombopag was continued as maintenance therapy.

After a new sensory MS relapse and a corresponding new C7 T2-weighted lesion in February 2023, infusions with ocrelizumab (600 mg IV every 6 months) were initiated in September 2023. Interestingly, the platelet count improved after each ocrelizumab administration (Figure 1) and eltrombopag was reduced and eventually stopped one year after ocrelizumab initiation. The platelet count remained within normal values until May 2024 (when these lines were written), while no haemorrhagic events or evidence of MS activity were noted.

Case two

A 48-year-old man with a past history of resolved ITP 30 years ago was diagnosed with RRMS in 2014, following an episode of left-side numbness and urinary retention. Treatment with glatiramer acetate (GA) was started without delay, however two relapses occurred, EDSS score increased to 4, and multiple new T2-weighted lesions were located with MRI. Relapses and associated disability worsening occurred more than six months after initiation of GA and new T2 lesions were detected in comparisons with a re-baseline MRI performed more than six months after the initiation of GA. Therefore, in April 2018 treatment was escalated to alemtuzumab, with the second cycle being administered in May 2019. In August 2019 the patient was admitted to the hospital following a haemorrhagic episode and a platelet count of 7.000/μL. After haematological and immunological workup, ITP was diagnosed and combined treatment with ivIg, corticosteroids and a platelet transfusion was administered, leading to

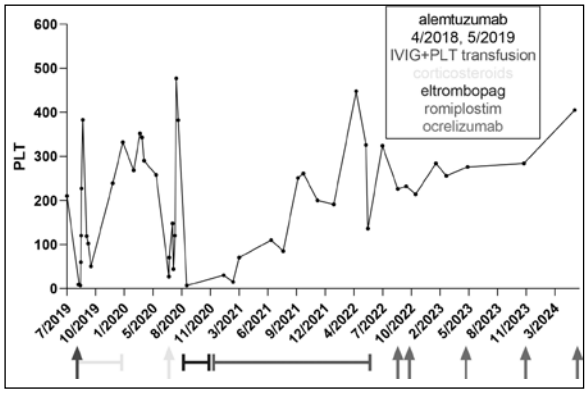

Figure 1: Platelet count is depicted as a function of time for patient 1, while coloured arrows and bar along the y axis represent different immune thrombocytopenia (ITP) therapies as indicated in the insert

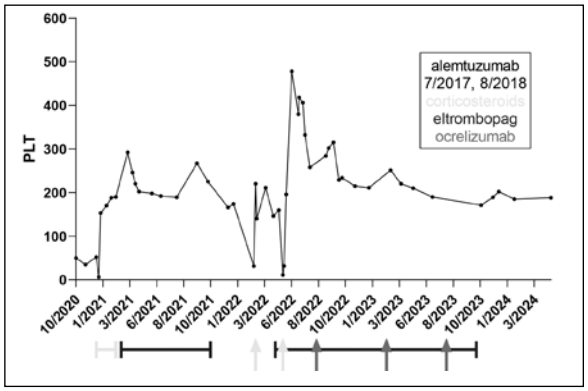

Figure 2: Platelet count is depicted as a function of time for patient 2, while coloured arrows and bar along the y axis represent different immune thrombocytopenia (ITP) therapies as indicated in the insert.

remission (Figure 2). In May 2020 however an ITP relapse occurred (PLTs: 27.000/μL), for which first corticosteroids, then eltrombopag were administered. Due to insufficient response, a switch to romiplostim (a thrombopoietin analog) was necessary and resulted in the patient achieving a platelet count of approximately 200.000/μL and being weaned off of romiplostim by June 2022 (Figure 2). In July 2022, new lesions were noted on routine follow-up MRI, and ocrelizumab was initiated in September 2022. Ocrelizumab administration every six months was associated with further improvement in platelet levels. Until May 2024 (when these lines were written) the patient fulfilled No Evidence of (MS) Disease Activity (NEDA-3) criteria, and the platelet count constantly improved with repeat ocrelizumab infusions in parallel absence of haemorrhagic symptoms.

DISCUSSION

We describe two patients with MS who received alemtuzumab, followingly developed chronic ITP with multiple relapses as a secondary autoimmune phenomenon, and achieved increased platelet counts and sustained ITP remission after repeated ocrelizumab infusions for the management of MS activity. In the first case, ocrelizumab likely enabled TPO-RA withdrawal and in the second case, ocrelizumab likely contributed to sustained remission and platelet count increase. The efficacy of the anti-CD20 monoclonal antibody rituximab as a second-line treatment in ITP and alemtuzumab-related ITP is well-established.[9,10] Here, we report similar or perhaps better efficacy of ocrelizumab, another anti-CD20 mAb that has been, in contrast to rituximab, approved for the treatment of MS.[11] Ocrelizumab has been shown to be 2 to 5 times more efficient than rituximab in mobilising antibody-dependent cell-mediated cytotoxicity (ADCC), whereas mobilisation of complement-dependent cytotoxicity (CDC) was 3 to 5 times less efficient.[12] Further, ocrelizumab was a bit more effective than rituximab in suppressing MS relapses, as shown in a recent multicentre cohort study.[13] These differences notwithstanding, our results are in line with those reported from the clinical development program of alemtuzumab[10] and build upon past experience to convey the message that CD20+ B cell depletion with ocrelizumab can effectively target post-alemtuzumab ITP. Although the natural course of ITP and post-alemtuzumab ITP is sustained remission after acute therapy, multiple ITP relapses and their cessation after CD20+ B cell depletion in the absence of other symptomatic therapy in both patients presented support its beneficial effect.

In addition to ITP, CD20+ B cell depletion has led to the remission of various secondary autoimmune phenomena following alemtuzumab treatment: Grave's disease with or without orbitopathy, acquired haemophilia A, autoimmune encephalitis, as well as haemolytic anaemia.[4,14–16] This implies that B cell activity could be the common denominator of secondary autoimmunity following alemtuzumab therapy. This aberrant B cell activity could be connected to earlier B cell repopulation compared to CD4+ T cells, slight overshooting of B cell levels in relation to their baseline, absence of T cell regulation, or qualitative B cells defects. Moreover, in both patients described here ocrelizumab was applied after the first signs of MS activity, either clinical or radiological. One could however consider that earlier application of CD20 depletion, prior to MS disease activity reappearance, might be of additional benefit. Specifically, low-dose rituximab has been applied post-alemtuzumab whenever B cells reach 50% of their baseline levels, resulting in a remarkable prevention of secondary autoimmune phenomena.[6]

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ETHICS APPROVAL

The study has been approved by the institutional IRB.

AUTHORSHIP CONTRIBUTION STATEMENT

PS conceived the idea of the manuscript. GK, DT, JT, CK, and PS treated the patients. GK drafted the manuscript and created the figures, and DT, JT, CK, and PS edited it.

DECLARATION OF COMPETING INTERESTS

The authors have no relevant competing interests to disclose. There are no prior publications or submissions of this article with any overlapping information, including original studies and patients.

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DATA AVAILABILITY

The data supporting the findings of this study are available upon reasonable request.

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