Acalabrutinib is an effective treatment for immune thrombocytopenia associated with chronic lymphocytic leukaemia, a case report.

*David Allsup[a,b] and Stefano Molica[a]

[a]*Queens Centre for Oncology and Haematology, Castle Hill Hospital, Hull University NHS Trust, Hull, United Kingdom HU16 5JQ.* [b]*Centre of Biomedicine, Hull York Medical School, University of Hull, Hull, United Kingdom, HU6 7RX.*

*Corresponding author David Allsup

Telephone number: - +44 1482 461294.

Email: - david.allsup@hyms.ac.uk.

Keywords:- chronic lymphocytic leukaemia, immune thrombocytopenia, bruton's tyrosine kinase.

Word count: - 1202.

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Letter to the Editor.

The association between immune thrombocytopenia (ITP) and chronic lymphocytic leukaemia (CLL) is well-described with a prevalence of 2.3% [1]. A diagnosis of CLL-associated ITP should be suspected when the platelet count is lower than 100 x 10^9/L without other clinical and laboratory features to suggest progressive CLL. In addition, secondary causes of thrombocytopenia such as infection, medications, or less frequently, thrombotic microangiopathies and heparin-induced thrombocytopenia should be excluded. CLL-associated ITP may be diagnosed before, at presentation, or at any point during the disease course and may be associated with more aggressive biological features of CLL, such as unmutated immunoglobulin heavy chain genes and poor-risk cytogenetics (17p and 11q deletions). Of note, CLL-cells are thought to be involved in various pathogenic pathways involved in ITP, including abnormal antigen presentation and cytokine production [2].

Current treatment guidelines recommend either corticosteroids, rituximab or thrombopoietin receptor agonists [3] for the treatment of CLL-associated ITP when therapy directed against the malignancy is not indicated. In contrast CLL-directed treatment should be offered to persons with ITP that is unresponsive to ITP-directed therapy, even in the absence of overt CLL progression [4]. The impact of targeted agents such as inhibitors of Bruton's tyrosine kinase (Btki) and B-cell lymphoma 2 (BCL-2i) on CLL-associated autoimmune cytopenias (AIC), including ITP, is controversial since such patients were excluded from the pivotal clinical trials of Btki and BCL-2i [5].

We present the clinical details of a patient with CLL-related ITP, unsuitable for therapy with corticosteroids who initially responded to the thrombopoietin receptor agonist

romiplostim. Upon relapse of ITP after the discontinuation of romiplostim the individual experienced a sustained platelet response to the Btki acalabrutinib.

An 85-year-old male presented with a several week history of increased bruising predominantly affecting the limbs. There was no other abnormal bleeding, and he was otherwise well. One week before presentation, he received the fourth dose of a COVID-19 mRNA vaccine. His past medical history was positive for glaucoma and hypercholesterolemia for which he was treated with atorvastatin. Physical examination found extensive bruising on the limbs but there was no palpable lymphadenopathy or hepatosplenomegaly. A full blood count demonstrated haemoglobin 120g/L, white count 10.4 x 10^9/L, lymphocyte count 6.4 x 10^9/L, and platelet count of 10 x 10^9/L. A coagulation screen and assessments of renal and liver function were normal. Levels of immunoglobulins were within normal ranges and there was no evidence of prior exposure to hepatitis B or C or human immunodeficiency virus. The patient declined an examination of the bone marrow and cross-sectional imaging was not performed. Examination of the blood film revealed profound thrombocytopenia with no platelet clumping and a modest lymphocytosis. Subsequent flow cytometric assessment of the peripheral blood revealed 7.3 x 10^9/L clonal B-cells CD5+, CD10-, CD19+, CD20+, CD23+, CD200+, CD79b-, ROR1+. Fluorescent in-situ hybridisation did not identify deletions of TP53 or ATM whilst the IGHV status was unmutated with utilisation of IGHV4-39 and 100% homology to germline DNA. A diagnosis of ITP associated with CLL was made. Corticosteroid therapy was not offered because of the concurrent glaucoma. Romiplostim was commenced at a dose of 3 microgram/kilogram which produced a dramatic increase in the platelet count from 5 x 10^9/L to 289 x 10^9/L over the course of one week. Unfortunately, only two, weekly, doses of romiplostim were administered due to difficulties in the administration of subcutaneous injections in the

remote rural location in the community where the patient resided. Subsequently the platelet count declined over a period of two months to a value of 10 x 10^9/L which was associated with a recurrence of symptomatic bruising, but no major bleeding episodes occurred. Six months after the initial presentation the blood count revealed Hb 112 g/L, white count 39 x 10^9/L, lymphocytes 30 x 10^9/L, and platelets 10 x 10^9/L. The patient had developed low-volume lymphadenopathy but did not meet strict criteria of progressive disease requiring CLL-directed therapy. The therapeutic approach to the symptomatic ITP was re-assessed to identify a treatment approach that would be clinically effective but deliverable for an elderly patient in the community at a rural location. There was a preference for oral rather than parenteral therapy with an anti-CD20 monoclonal antibody, accordingly, acalabrutinib at a dose of 100 milligrams twice daily was commenced with a consequential rapid resolution of patient's bleeding symptoms and lymphadenopathy with a progressive, sustained, increase in the platelet count. Five months after the initiation of acalabrutinib the platelet count continued to rise being 130 x 10^9/L when last assessed. A transient acalabrutinib-associated lymphocytosis was observed which is a recognised feature of Btki therapy (Figure 1).

Although BTKis are highly effective in the treatment of CLL, their impact on CLL-associated AIC is still a matter of debate. CLL patients with AIC have been generally excluded from clinical trials of BTKis. The few patients with partially controlled AIC enrolled in the phase 3 RESONATE trial experienced a 50% to 86% improvement in haemoglobin or platelet counts after the commencement of ibrutinib according to a post-hoc analysis [6]. In the largest retrospective study published to date the prevalence of AIC as ibrutinib treatment-emergent episodes was 1% [7]. Most persons with CLL-associated AIC experienced an improvement or resolution of AIC-associated abnormalities after the initiation of a targeted agent. Such findings are to be expected given that Btk is a central

mediator of B-cell receptor signalling and therefore of B-lymphocyte function [8]. Macrophage activation in response to ligation of the Fc receptor is also dependent upon Btk-mediated signalling [9]. Consequentially, Btki therapy may therefore modulate platelet counts in ITP by a reduction in pathogenic autoantibodies produced by non-clonal B-lymphocytes and by the inhibition macrophage Fc receptor-mediated platelet phagocytosis. Rilzabrutinib, an oral, reversible covalent Btki, led to a rapid and durable platelet response in 40% of persons with *de novo* immune thrombocytopenia who had received multiple prior therapies [10].

Acalabrutinib is a selective, next-generation covalent Btki with less off-target kinase inhibition compared to ibrutinib, the first in class Btki. Based upon the long-term results of two phase 3 studies, ELEVATE-TN and ASCEND, acalabrutinib was approved for the treatment of patients with treatment-naive and relapsed CLL [11,12]. Patients with active, uncontrolled AICs were not included in these trials, therefore information on the impact of this second-generation, covalent, BTKi on the clinical outcome of AICs associated with CLL is lacking.

The case presented herein suggests that acalabrutinib has no detrimental effect on CLL-associated ITP and suggests that this second-generation Btki is a possible option for patients with CLL complicated by ITP. A phase II clinical trial designed to evaluate the efficacy of acalabrutinib in treating relapsed or refractory autoimmune haemolytic anaemia in patients with CLL has completed recruitment (ClinicalTrials.gov Identifier: NCT04657094) with the preliminary results expected to be available at the end of 2023.

Our conclusions are limited by a failure to assess the bone marrow even though the clinical features and response to treatment with romiplostim indicate a predominant immune component to thrombocytopenia. The patient described in this report had a low tumour burden and a prompt and complete platelet response to romiplostim which

indicates an immune aetiology for the thrombocytopenia as opposed to bone marrow failure secondary to CLL. Furthermore, on discontinuation of romiplostim the symptomatic thrombocytopenia recurred but responded promptly to acalabrutinib.

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Figure Legend

Figure 1. Platelet and lymphocyte count responses to administered therapies.