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CLINICAL TRIALS AND OBSERVATIONS

Comment on Mingot-Castellano et al, page 1807

ADAMTS13 recovery in caplacizumab-treated TTP

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In this issue of *Blood*, Mingot-Castellano et al, on behalf of the Spanish Apheresis Group and the Spanish Thrombotic Thrombocytopenic Purpura Registry, present important data on caplacizumab treatment of patients with acute autoimmune thrombotic thrombocytopenic purpura (iTTP).[1] A total of 113 acute iTTP episodes in 108 patients are retrospectively analyzed.

Therapeutic plasma exchange (TPE) and corticosteroids were used in each instance, and rituximab was used in ≈75% of instances. In 75 episodes, the nanobody caplacizumab was given as adjunctive treatment; 38 episodes were not treated with caplacizumab. Baseline parameters in both groups were comparable. The main outcome studied was the time until partial recovery of ADAMTS13 activity (≥20% of normal) in episodes treated with vs without caplacizumab.

An earlier publication in *Blood* reported delayed recovery of ADAMTS13 activity (>30%) in 64 caplacizumab-treated compared with 50 non–caplacizumab-treated patients (median, 31 vs 11.5 days, respectively, after the end of TPE).[2] Moreover, failure to achieve partial ADAMTS13 recovery (>30%) within 58 days from end of TPE was 6 times more likely with than without caplacizumab treatment.[2]

Mingot-Castellano et al compared the time from iTTP diagnosis (equal to starting TPE) until ADAMTS13 recovery (≥20%) in acute iTTP episodes treated with caplacizumab within ≤3 days from starting TPE, caplacizumab started >3 days from starting TPE, and episodes without any caplacizumab treatment: the median (interquartile range) ADAMTS13 recovery times were 28.0 (17.2-47.5), 27.0 (19.0-37.5), and 29.5 (15.2-45.0) days in early, late, and not caplacizumab treated episodes, respectively (not significant). When calculating ADAMTS13 recovery time from TPE end, this amounted to 20 days in episodes with early start of caplacizumab (≤3 days from first TPE), 11.0 days with late start of caplacizumab (>3 days from first TPE), and 13.0 days with no caplacizumab. This significantly delayed ADAMTS13 recovery with early caplacizumab start was likely due to fewer daily TPE sessions needed and thus a shorter TPE phase.[1] The Spanish Registry data, therefore, do not suggest a delayed recovery of the autoantibody-induced severe ADAMTS13 deficiency in patients with iTTP treated with TPE and immunosuppression by concomitant use of caplacizumab,[1] and the question is raised whether the UK data reported by Prasannan et al [2] truly demonstrate a delayed ADAMTS13 recovery by caplacizumab or whether the different calculation of the recovery time in this study explains the discrepant findings. Of note, Mingot-Castellano et al otherwise confirmed the shortened time to platelet count normalization, reduced TPE requirement, reduced refractoriness, exacerbations, and relapses by caplacizumab, as observed in several other cohorts.[3-6]

Caplacizumab was approved as addition to TPE and immunosuppression for treating iTTP based on 2 randomized controlled trials (RCTs), Titan and Hercules; the integrated analysis of both trials suggested reduced mortality.[7] Aggregated data of the 2 RCTs and several cohort studies comparing caplacizumab-treated patients with (historic) controls showed an absolute risk reduction by caplacizumab for mortality of 2.87%, translating in a number needed to treat to avoid 1 death of 35.[5] An even 10% absolute risk reduction of mortality by caplacizumab was reported from the French Registry of Thrombotic Microangiopathies.[3] Bleeding complications are more common in caplacizumab-treated patients and are caused by the strong inhibition of the von Willebrand factor A1 domain interaction with the platelet glycoprotein Ib receptor.[6] Fortunately, all accumulated data so far show that severe bleeding is rare and the common mild bleeding events are manageable (eg, by alternate-day dosing of caplacizumab[5,8] or by using perioperative infusion of von Willebrand factor concentrate).[9] Despite some, mostly unfounded, objections against caplacizumab (erroneously assuming a higher relapse rate and a relevant bleeding problem), many expert centers favor its use based on the clear benefits.[5] Evidence supports that caplacizumab is not a rescue drug for refractory iTTP but should be given upfront to shorten the microvascular platelet clumping and avoid organ damage.[5,10]

Mingot-Castellano et al present additional good news suggesting that recovery of antibody-mediated severe ADAMTS13 deficiency is not delayed by including caplacizumab in the treatment regimen for acute iTTP episodes. Still, considering the seemingly discrepant data by Prasannan et al,[2] I believe that the ADAMTS13 recovery with or without caplacizumab should be further studied in a prospective manner, taking into account every detail of the management, such as exact mode of TPE, mode of immunosuppression with

corticosteroids and anti-CD20 therapy, as well as frequency and method of ADAMTS13 monitoring.

Conflict-of-interest disclosure: B.L. is chairman of data monitoring committees of studies investigating recombinant ADAMTS13 for the treatment of congenital and acquired TTP (Takeda), chairman of a steering committee investigating global impact of congenital TTP (Takeda), and chairman of the data monitoring committee of a study investigating caplacizumab for the treatment of autoimmune TTP without plasma exchange (Sanofi). ■

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Comment on Arora et al, page 1816

T cells reinforce NK cell–mediated ADCC

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In this issue of *Blood*, Arora et al report substantial progress in developing an approach to exploit and condition the tumor microenvironment (TME) to enhance rituximab (RTX)-mediated killing of cancer cells.[1] Extensive literature has been reported showing that RTX requires immune effector functions to kill targeted CD20-positive B cells,[2] and these killing mechanisms have been demonstrated to include complement-mediated cytotoxicity, antibody-dependent cellular phagocytosis mediated by macrophages, and natural killer (NK) cell–mediated antibody-dependent cellular cytotoxicity (ADCC). Because of high tumor burdens found in B-cell lymphomas, all of these tumor-killing mechanisms can be saturated or exhausted,[3-7] thus compromising RTX efficacy (see table). A key question, therefore, must focus on how to enhance or restore killing of RTX-targeted B cells by the different pathways. The present report of Arora et al extends the work of George Weiner's group[1] in this area by examining the action of CD4$^+$ T cells with respect to their potential to increase the ability of NK cells to execute ADCC of RTX-targeted cells.

Almost 20 years ago, Bowles and Weiner reported that NK cell–mediated ADCC of RTX-opsonized B cells induces substantial downregulation of NK-cell CD16, the Fcγ receptor that engages B-cell–bound RTX and is clearly required to initiate ADCC.[4] More recently, Weiner's group examined an in vitro model of RTX-mediated killing of Raji cells and found that contact between CD4$^+$ T cells and NK cells was needed to enhance and/or restore the ADCC activity of NK cells.[8] The key mediator in this reaction is interleukin 2 (IL-2), presumably secreted by T cells in contact with the NK cells. This observation has now been extended into both a novel humanized mouse model and a clinical correlative study.

In the humanized mouse model, the TME is constructed on the basis of injection of target Raji B cells accompanied by a mixture of human peripheral blood mononuclear cells. The TME is fashioned to contain human NK cells with or without an admixture of human CD4$^+$ T cells. Fine-needle aspirates (FNAs) of tumors growing in the mice

Exhaustion of RTX-mediated cytotoxic mechanisms

Mechanism	Observation	Possible remedy
ADCC	Reduced CD16 and CD25 on NK cells	Provide CD4$^+$ T cells in TME[1]
ADCP	Reduced FcγR on macrophages	Lower dose at more frequent intervals (48 h)[5,7]
CDC	Reduced CH50	Infuse fresh frozen plasma[3]

ADCP, antibody-dependent cellular phagocytosis mediated by macrophages; CDC, complement-mediated cytotoxicity; CH50, complement titer; FcγR, Fc gamma receptor.