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THROMBOSIS AND HEMOSTASIS

Comment on Kumar et al, page 1156

Desmopressin revisited in mild hemophilia A

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In this issue of *Blood*, Kumar et al[1] present the results of a randomized trial comparing the efficacy of induction of endogenous factor VIII (FVIII) by moderate-intensity aerobic exercise with intranasal (IN) DDAVP/desmopressin in adolescents with mild hemophilia A, to determine if the 2 approaches provide the same level of efficacy before more intense sports activity.

For patients with severe and nonsevere hemophilia, improved access to treatment and prophylaxis permits increased engagement in sports while maintaining adequate hemostatic levels of clotting factor activity. Studies have shown that factor levels of at least 20% may be required to prevent joint bleeding.[2] Thus, mild hemophilia may not be a benign disease after all and may present an increased bleeding risk with intense physical activities. IN desmopressin has been shown to increase levels of endogenous FVIII in nonsevere hemophilia.[3] Kumar et al, in 2016, reported the hemostatic benefits of exercise in 13 adolescent males with mild and moderate hemophilia A and demonstrated a 2.3-fold increase in FVIII:C immediately following exercise. The FVIII:C remained elevated at 1.9-fold, 1 hour after exercise.[4] In the current study, they expanded their observations and measured the changes induced by exercise and IN desmopressin, either independently or in combination. They demonstrated that IN desmopressin alone or in combination with exercise was associated with a sustained increase in FVIII:C compared with exercise alone. If confirmed to be clinically effective, this approach could be an option to prevent bleeding episodes before participation in sports/physical activity in patients with nonsevere hemophilia.

The National Hemophilia Foundation in the United States and the World Federation of Hemophilia have provided information on the risk of bleeding associated with different sports/physical activities. However, there is significant variability in individual physical abilities and joint health that influence the risk of bleeding. There are also differing opinions on what is an adequate protective level.[5,6] A single prospective study that assessed the factor levels and risk of bleeding by Broderick et al found that an FVIII:C of $>$ 50% was associated with less bleeding than that during inactivity with no factor replacement.[7] In the current study by Kumar et al, 67% (10/15) of participants randomized to receive IN desmopressin with exercise achieved $>$50% FVIII:C 75 minutes after the interventions that persisted in 60% (9/15) for an additional hour (135 minutes). Even monotherapy with IN desmopressin or exercise alone was associated with normal FVIII:C in 35% (6/17) and 24% (4/17) of participants at 75 and 135 minutes, respectively. Therefore, a trial of IN or intravenous desmopressin with assessment of FVIII:C at 90 or 135 minutes may identify the patients who may benefit from desmopressin stimulation alone, providing patients with a much less burdensome treatment option. Current desmopressin trials in patients with mild hemophilia only recommend assessment of FVIII:C 30 minutes after the administration. Obtaining additional levels at 3 to 4 hours would be more informative for sports participation lasting longer than 60 to 90 minutes.

The benefits of exercise and IN desmopressin may be extended to include women and girls (WG) with hemophilia, most of whom fall into the moderate and mild category. There is a growing understanding of the bleeding phenotype in this group of patients, although research in this population lags far behind that in males with mild hemophilia.[8] Candy et al reported a lower response to desmopressin in females with mild hemophilia.[9] It would therefore be important to determine the FVIII:C response to exercise in WG with mild hemophilia. The authors here indicate that they are currently studying the effect of exercise in WG and if successful in increasing the FVIII:C, this would again, provide a noninvasive management option that would be beneficial to promote general health while providing bleed protection.

Several challenges remain in the optimization of care of patients with mild hemophilia. Despite there being significant differences in the disease manifestations, most of the guidelines are derived from research on severe hemophilia. Diagnosis of mild disease is often delayed, as is early recognition of bleeding. Many studies have reported poor joint health in patients with mild hemophilia, usually from poor recognition of bleeds and delays in treatment.[10] With most efforts of the scientific community

focused on severe disease, it is encouraging to see research focused on mild hemophilia. It would be beneficial to develop guidelines for the management of patients with mild hemophilia, including WG, to expand research on the pathophysiology of inhibitor development, to develop immune tolerance induction regimens tailored for mild hemophilia patients, and to increase access to new diagnostic and therapeutic agents.

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TRANSPLANTATION

Comment on Ho et al, page 1167

MDM2 inhibition augments GVL effect

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In this issue of *Blood*, Ho et al[1] report that inhibition of mouse double minute 2 (MDM2) increases the potency of T-cell responses to acute myeloid leukemia (AML) and facilitates the graft-versus-leukemia (GVL) effect in murine models of allogeneic hematopoietic cell transplantation(allo-HCT).

HCT reduces the risk of leukemic relapse and is curative for many patients with AML, partly because of an immunologic GVL effect mediated by donor T cells that recognize minor and major histocompatibility complex (MHC) antigens in MHC-matched and MHC-mismatched HCT, respectively.[2] Unfortunately, about one-third of HCT recipients with AML relapse after HCT, and most patients with relapse after HCT die of their disease. There is a clear need to improve our understanding of the mechanisms of AML resistance to immune responses and to develop novel countermeasures in the context of HCT and targeted T-cell therapies. The article by Ho et al addresses this area of significant unmet medical need.

Several mechanisms of AML escape from allogeneic T-cell responses have been defined, including downregulation of HLA class II molecules in leukemia, secretion of lactic acid, and resistance to apoptosis.[3] Ho et al report a new strategy for countering AML immune evasion by inhibiting MDM2. The MDM2 protein functions as a ubiquitin ligase that recognizes the N-terminal transactivation domain of the proapoptotic tumor suppressor p53. MDM2 inhibits p53 transcriptional activation and facilitates proteasomal p53 degradation and export from the cell, which reduces intracellular p53. Because p53 upregulates the expression of some immune-related genes, including type I interferons,[4] and increases MHC expression[5] and peptide presentation on MHC class I molecules,[6] the authors hypothesized that MDM2 inhibitors could also reverse AML immune evasion after HCT.

In a comprehensive series of experiments that used human leukemia cell lines, primary AML cells in vitro and in xenografts, and murine cell lines in vitro and in vivo, the authors showed that inhibition of MDM2 affects both AML and T cells to favor effective anti-leukemic immune responses (see figure). Specifically, MDM2 inhibition induced MHC class I and II expression in murine and human AML cells and led to increased tumor necrosis factor–related apoptosis-inducing ligand receptor 1 and receptor 2 (TRAIL-R1/2) expression on leukemia cells, making the leukemia cells easier for T cells to recognize and also making them more susceptible to T-cell–mediated cytotoxicity. The effects of MDM2 inhibition on MHC molecules and TRAIL-R expression were confirmed to be p53 dependent and could also be induced by inhibition of MDMX.

Inhibition of MDM2 demonstrated beneficial effects on T cells and leukemia cells. Inhibition of MDM2 led to increased frequencies of $CD8^+CD27^{low}PD\text{-}1^{low}TIM\text{-}3^{low}$ T cells with features of cytotoxicity ($perforin^+CD107a^+TRAIL^+$) and longevity ($Bcl\text{-}2^+IL\text{-}7R^+$) and enhanced glycolytic activity. The mechanism of action of MDM2 on T cells was not evaluated in this study, but previously published data indicate that inhibition of MDM2 can increase intracellular levels of MDM2 by a feedback mechanism which, together with p53, can stabilize STAT5 in T cells.[7] The combined effects of MDM2 inhibition on AML and allogeneic T cells