– IV acute GvHD. For these reasons, the GRFS endpoint represents an unreliable surrogate for the ability of an intervention to prevent grade III – IV acute GvHD.

The current report by Koreth *et al.*[1] represents a well-controlled attempt to evaluate the merits of bortezomib for immunosuppression after HCT with reduced intensity conditioning regimens. The report is newsworthy, because the negative results do not support expectations that bortezomib-based regimens might have a major effect on the risk of grade III – IV acute GvHD, even with the substitution of sirolimus for methotrexate in Arm C. With the benefit of hindsight, one could question whether the expectations based on results of the phase I/II study were realistic.

The experience from testing bortezomib yields important lessons for planning future trials. First, grade III – IV acute GvHD should be defined as the primary endpoint in trials designed to test an intervention intended to prevent acute GvHD. Second, the benchmark incidence of grade III – IV acute GvHD should be set at 10 – 15%, depending on the relationship and HLA-matching between the donor and recipient. Third, early phase trials should be designed to test whether an intervention can reduce the incidence of grade III – IV acute GvHD to 2% or less, as it will not be feasible to determine whether any smaller effect size holds true in a phase III trial. Early phase and later phase trials should have rules that discontinue enrollment when initial results indicate that the intervention is not likely to reach this benchmark of success. Finally, although the GRFS endpoint should not be used as the primary endpoint in trials of interventions intended to prevent grade III – IV acute GvHD, it remains important to demonstrate that successful prevention of grade III – IV acute GvHD does not come at the expense of increasing the risk of non-relapse mortality or the risk of recurrent or progressive malignancy.

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Use of desmopressin in the treatment of hemophilia A: towards a golden jubilee

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Throughout the 1970s, the availability and safety of coagulation factors, employed for replacement therapy in patients with hemophilia (PWH), were very far from what they are nowadays. Plasma-derived concentrates of factor VIII (FVIII) and IX started to be industrially manufactured, but they were generally available in limited amounts in most countries, and thus used only for the acute treatment of bleeding episodes (so called 'on-demand regimen'), but not for the treatment of choice, i.e., the prevention of bleeds by means of regularly spaced infusions (prophylaxis regimen). Most importantly, these products, produced from plasma pooled from thousand of donors, transmitted the hepatitis viruses with extremely high frequency; the agent causing hepatitis B and, more often, the so called non-A, non-B virus, which was only identified in 1989 as the hepatitis C virus. These bloodborne viruses heralded the bleak era of infection with the human immunodeficiency virus (HIV), that started to contaminate plasma-derived coagulation factor concentrates at the end of the 1970s, eventually leading to the first appearance in PWH of the acquired immunodeficiency syndrome (AIDS) in 1982, which caused such a high toll of deaths during the 1980s and the 1990s.

With this background, it is not surprising that in the 1970s and earlier a multitude of research efforts were directed towards the development of pharmacological alternatives to blood products. These agents were felt particularly necessary in patients with mild hemophilia A who, having measurable plasma levels of FVIII of 6% of normal or more, bleed much less frequently than those with severe disease and unmeasurable FVIII levels. In general they have little risk of mortality and morbidity, and their main clinical problem is excessive bleeding after trauma or surgery whereas, at variance with severe hemophilia, spontaneous bleeding episodes and joint

bleeding are very rare. Early studies on pharmacological agents concentrated on epinephrine (adrenaline), which, administered to normal volunteers and patients with mild FVIII deficiency, was followed by a short-term plasma rise in the coagulant activity of FVIII.[1,2] These seminal pioneer observations stimulated the search for pharmacological compounds devoid of the cardiovascular side effects, which obviously made the therapeutic use of adrenaline in patients impossible.

An important step forward was made more than 40 years ago in the early 1970s, when Cash *et al.*[3] and Mannucci *et al.*[4] independently demonstrated that 1-deamino-8-D-arginine vasopressin (DDAVP, desmopressin), a synthetic peptide analogue of the antidiuretic hormone vasopressin,[5] raised plasma FVIII to 2-3 times above baseline levels following its infusion into normal volunteers and patients with mild hemophilia A, but not in those with severe disease and unmeasurable plasma FVIII. It remained to be demonstrated that the rise of the autologous FVIII released in plasma from storage sites upon the effect of desmopressin was as hemostatically effective as the allogeneic FVIII replaced by means of the infusion of plasmatic FVIII concentrates. To answer this clinically crucial question, desmopressin was used to prevent surgical bleeding, cautiously at first for minor procedures such as dental extractions, and subsequently for major procedures carried out in 23 patients with mild hemophilia A or von Willebrand disease.[6] The results obtained in this first clinical study were excellent, because the procedures were done without undue bleeding, and without the need for resorting to allogeneic replacement therapy with blood products containing FVIII.[6] These results were subsequently confirmed by several independent studies[7-9] and desmopressin, designated as an essential drug by the World Health Organization, consequently acquired an established role in the management of patients with mild hemophilia A.

Pertaining to the genuine role exerted by desmopressin in avoiding bloodborne infections associated with the use of plasma-derived FVIII products, the early adoption of this drug in Italy, where it was fist clinically employed in the late 1970s, led to a much lower prevalence of HIV infections in patients with mild hemophilia A,[10] compared to those with mild hemophilia B who could only use plasma-derived products because they were unresponsive to desmopressin (factor IX is not increased) and in American patients with mild hemophilia A who started using desmopressin much later, at a time when the transmission of HIV was halted following the advent of heat-treated plasma-derived coagulation factor concentrates and recombinant products.[10]

With this background, what is the significance of the enclosed report of Loomans *et al.*?[11] In the frame of a study carried out internationally in a retrospective large cohort of 169 patients with moderate forms of hemophilia A, they investigated whether or not this group of patients with low but measurable FVIII in plasma were responsive to the administration of desmopressin. Patients with moderate hemophilia are defined as having plasma FVIII levels between 1% and 5%, i.e., much lower than in mild hemophilia (6% or more); thus, they bleed more frequently, but less than those with severe hemophilia A. In the original clinical study of desmopressin, no patient with moderate hemophilia was included, as it was felt that the expected 2/3-fold rise of FVIII induced cautiously by this compound would not allow the attainment of plasma levels high enough to secure surgical hemostasis, and therefore prevent bleeding.[6] Subsequently, some patients with moderate hemophilia were indeed treated with desmopressin,[8,9,12,13] but the cases and results were too few to dissipate the fear that the drug could not be efficaciously employed in this category of moderately severe patients.

The value of the findings of Loomans *et al.* reported in this issue of *Haematologica*[11] is that they help to fill this gap of knowledge. In as many as 40% of their moderately affected patients, low baseline FVIII levels reached after desmopressin plasma values of at least 30%, and 15% of them attained levels as high as 50% or more. Importantly, Loomans *et al.* also showed that it is possible to predict the good responders to desmopressin prior to infusion, because the degree of their FVIII increase was relatively proportional to the baseline pre-desmopressin plasma levels of this moiety.

The main limitations of the findings reported in the study of Loomans *et al.*, based upon patients recruited in 25 hemophilia treatment centers from three continents (Europe, North America and Australia), are that the authors only evaluated the post-desmopressin changes of a surrogate biomarker of hemostasis, such as the plasma levels of FVIII coagulant activity, but did not investigate whether or not these changes corresponded to a beneficial clinical effect on hemostasis. Thus, these novel findings should prompt the pursuance of a prospective clinical study designed to demonstrate whether the plasma increase of this surrogate laboratory marker is paralleled by the efficacy of the drug in preventing or treating bleeding episodes in patients with moderate hemophilia, who nowadays are usually treated with recombinant FVIII products. Regarding the latter there is no longer any concern about the onset of bloodborne infections, but another adverse effect of replacement therapy is still looming large: the development of alloantibodies which inactivate FVIII coagulant activity and thus render this therapy ineffective.[14] As the autologous FVIII released by desmopressin is not seen as foreign by the recipient's immune system, the increase of plasma FVIII levels effected by this drug does not elicit the onset of inhibitors that, albeit less frequently than in severe hemophilia, are a complication of allogeneic factor replacement, particularly when some at-risk FVIII gene mutations are present in patients with moderate hemophilia.[15]

All things considered, I agree with the declaration of Loomans *et al.*, as stated in the title of the article herein. At variance with that which was hitherto believed, and after more than 40 years of clinical experience with desmopressin, this form of endogenous replacement therapy is also worth considering in patients with moderate hemophilia A.

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