cases of multiple myeloma. Interestingly, PSGL-1–P-selectin interaction leads to adhesion-related cell signaling and activaton of integrins, although Azab and colleagues did not address integrin-selectin interaction in their study. Prior studies have shown that myeloma cells through $\alpha_4\beta_1$ integrin and VLA-4 molecules bind to bone marrow stroma (VCAM-1 and fibronectin). To understand myeloma cell trafficking, adhesion, homing, and drug resistance better, future studies on the interaction of integrins and selectins seem necessary.

Although significant advances have been obtained, we are far from delineating the myeloma progenitor cell. We still do not know the exact nature of myelomagenesis and the primary genetic event. Finding new treatment options for genetically high-risk patients will obviously depend on progress in genomics.

Plasmacytic dendritic cells have been shown to be responsible for growth, survival, and drug resistance as well as immunodeficiency in myeloma.[9] Another targeting point seems to lie in interactions between myeloma cells and plasmacytic dendritic cells.

Myeloma bone disease is another very important problem. Bone disease is vey much related to MM cell–microenvironment interaction because RANKL/RANK cross-talk also enhances osteoclast formation and bone resorbing activity. Monoclonal antibody to RANKL and recombinant OPG with or without biphosphonate therapy has been used in the treatment of bone disease. Myeloma cells secrete soluble Dickkopf-1 protein that inhibits osteoblast precursors. Anti–Dickkopf-1 monoclonal antibody is very promising in phase1/2 trials.[10]

Combination therapy with newer drugs, immunotherapy, and bone healing agents together will take us closer toward the cure.

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CLINICAL TRIALS

Comment on Hay and DiMichele, page 1335

Getting rid of refractory hemophilia

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In a prospective randomized, multicenter study of immune tolerance induction (ITI) in patients with hemophilia A refractory to replacement therapy after the development of alloantibodies that inhibit factor VIII (FVIII) activity, Hay and DiMichele compared two regimens, a low dose of FVIII (50 IU/Kg thrice weekly) or a high-dose (200 IU/kg daily).[1]

These therapeutic regimens have reported to induce a similar overall success rate (roughly two-thirds of patients responding as defined by inhibitor disappearance and normal plasma FVIII half-life and recovery). This study, which enrolled patients from 17 countries on 4 continents, contributes data that should help define an evidence-based practice of ITI. It also stands as a milestone because it shows that investigator-driven, randomized clinical trials can be carried out and completed even in rare diseases such as hemophilia without the direct involvement of the pharmaceutical industry.

How to eradicate FVIII inhibitors and successfully treat the most challenging complication of hemophilia has been a long-standing issue. As early as 1977 Brackmann and Gormsen reported that, in a patient with severe hemophilia A, a long-standing, high-titer inhibitor disappeared completely by infusing high daily doses of FVIII for a prolonged period of time.[2] This striking and puzzling observation, which led to the development of the so-called Bonn ITI regimen (that broadly corresponds to the high-dose regimen evaluated by Hay and DiMichele[1]) was received with skepticism by the hemophilia community. The reasons for the skepticism were multiple: lack of an experimental basis for this novel approach; limited knowledge on FVIII immunology; the substantial cost of the huge FVIII dosages employed at a time when therapeutic coagulation factors still had limited availability; the challenges put on patients' resilience and venous access by daily or twice-daily factor infusions; and the fear of transmitting viral hepatitis and then later, HIV infection. Nevertheless, the persistent and unswerving efforts of the Bonn group to confirm and extend the original case report[3] led to several small, nonrandomized cohort studies[4,5] that confirmed that flooding the immune systems of these patients with the antigen (FVIII) did quench the production of the neutralizing antibody with a success rate ranging from 63% to 80%.[4,5]

How did studies subsequently advance on clinical implementation of ITI? Cognizant of the difficulties implicit in the interpretation of retrospective data from small cohorts of patients with a rare complication of a rare disease, some clinicians chose to gather and analyze data from registries. The International, German, and North American registries obtained broadly consistent results on the variables that influence ITI outcome.[6-8] The main predictors of success were low inhibitor peaks, low inhibitor titres before ITI start, and low anamnestic peaks after start. These factors provide clinicians with crucial information to select the most suitable patients for this expensive and demanding treatment.

Before the current study by Hay and DiMichele, the main unresolved question was the influence of FVIII dosage regimens on the ITI success rate, particularly after a Dutch study obtained a high success rate (83%) using as little as 50 U/kg of FVIII 3 times weekly, instead of the 200-300 U/kg daily doses used by the acolytes of the Bonn regimen.[9] This smaller dosage regimen, which achieved a high rate of ITI within a time frame similar to that of the high dosage (on average ~ 1 year from onset), was highly appealing due to decreased cost and patient acceptability.

Is there an answer to this question from Hay and DiMichele? Their study was designed to test the hypothesis of noninferiority, that is, that the ITI success rate is independent of the FVIII dosage. Even though equivalence between high and low dose was not formally established, my clinical interpretation of the results is that in good-risk patients (ie, those who were relatively likely to get rid of their anti-FVIII inhibitor), either regimen can be used successfully. Does this result imply that one should prefer the low FVIII dosage for reasons of cost and patient convenience? The low-dose regimen was associated with 2-fold more bleeding episodes than the high-dose regimen.[1] Moreover, the cost of the FVIII bypassing products (recombinant activated factor VII, and anti-inhibitor plasma-derived complex)[10] needed to treat the intercurrent bleeding episodes might nullify or substantially reduce any cost saving obtained in terms of less FVIII usage. Hence, one important piece of information still missing to make a meaningful therapeutic choice is a cost-effectiveness analysis. An answer to this question is particularly cogent at a time when the global economic crisis is mounting pressure on healthcare costs and austerity measures are imposed on drug spending, even for therapies as effective as those used in hemophilia that allow these patients to have a life expectancy similar to that of their peers without hemophilia (at least in high-income countries).[11] On the other hand, it is obvious that more bleeding episodes may definitely impair the safety and quality of life of patients treated with low-dose FVIII. Hence, the risk:benefit ratio of the two regimens and a quality-of-life analysis are needed to evaluate the two regimens.

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● ● ● PHAGOCYTES & GRANULOCYTES

Comment on de Bruin et al, page 1543

When IFN interferes with cell fate

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In this issue of *Blood*, de Bruin and colleagues demonstrate the ability of IFN-γ to influence the binary cell fate choices of granulocytic-monocytic progenitors (GMPs) during viral infection, favoring monocytic over the granulocytic differentiation.[1] This work provides mechanistic insights and a better understanding on how hematopoiesis can be remodeled during infections.

Infections are the most common stressors of the hematopoietic system. The ability of the BM to respond to infections by expanding the progenitor pool to produce more differentiated effector cells is a critical feature of the host's defense, which translates into the difference between resolving an infection or succumbing to it.

For many years, studies have been focused on understanding the functions of critical effector cells of the innate and adaptive immunity, such as neutrophils, monocytes, macrophages, and lymphocytes. Recently, new conceptual and technical advances, including the availability of a wide range of genetic models, have led investigators to look at the immune response from a new angle, opening a window on the interface between stem cell biology and immunity. Recent studies have shown that hematopoietic stem cells (HSCs) and multipotential progenitors play a critical role in host defense and their behavior can determine the abundance of specific lineages by shaping, at the very origin, the hematopoietic response to infection.[2-4]

This elegant work by de Bruin et al shows that IFN-γ can interfere with the binary cell fate decision of GMPs to differentiate into monocytes or granulocytes, compelling monocytic differentiation. Importantly, the authors show that loss of granulocytic differentiation does not occur by default, but by IFN-γ–mediated active suppression of G-CSF–triggered intracellular responses.

This finding stems from the initial observation that transgenic mice overexpressing CD70 (CD70TG) have an increased production of monocytes over granulocytes. In these mice, overexpression of CD70 in B cells causes a strong activation and expansion of Th1 effector T cells, via CD70-CD27 interaction, and results in the secretion of high levels of IFN-γ, pointing to a role for IFN-γ as inducer of monocytic differentiation in vivo. This hypothesis was confirmed using several complementary in vivo models. The authors show that normal monocyte levels can be restored in CD70TG in the absence of IFN-γ, and that monocytosis can be induced either by T-cell adoptive transfer in CD70TG/CD27$^{-/-}$ mice or by injection of a CD40 agonist in WT mice. As Th1 activation is an adaptive immune response occurring during viral infections, the authors tested the physiologic relevance of