to prevent this vicious sequence of events, Nilsson et al, in Malmö, Sweden, began attempts at prophylaxis in the 1960s,[2] and prophylaxis soon became the standard of care in Sweden. As more experience was gained, the Malmö group began regular prophylaxis at 1 to 1.5 years of age, before the onset of joint bleeds. FVIII (25-50 IU/kg/dose) was administered 3 times weekly or every other day.[3] Such frequent dosing was needed, as the half-life of FVIII is only 8 to 12 hours. Many other centers in Europe and in North America began using prophylaxis in the early 1990s. However, cost was often a major issue because of the increased use of FVIII concentrates for prophylaxis compared with episodic treatment. Despite this, many subsequent studies documented the benefits of prophylaxis beginning at an early age, including far fewer bleeding episodes; much less joint damage than seen in children on episodic treatment; decreased disability, hospitalization, and time lost from school; and improved quality of life.[4] However, such frequent intravenous dosing often necessitated the use of a central line (with its potential complications), and compliance with prophylaxis often decreased in teenagers and young adults.[5]

A longer-lasting FVIII was needed to reduce prophylactic injection frequency. Mahlangu et al demonstrate, in a phase 3 pivotal study, that a novel rFVIII Fc fusion product has a longer half-life than standard rFVIII, which resulted in a lower annualized bleeding rate when dosed prophylactically, 1 to 2 times weekly. Safety, efficacy, and pharmacokinetics were evaluated in 165 males with severe hemophilia A, aged ≥12 years. The rFVIII Fc fusion product was well tolerated and effective, and no subject developed an inhibitor to FVIII.[1]

Fc fusion technology uses a naturally occurring recycling pathway that delays the destruction of FVIII and cycles it back into the bloodstream, resulting in a longer circulating half-life. Fc fusion technology is also used in ≥7 US Food and Drug Administration–approved products for other chronic diseases, such as rheumatoid arthritis and platelet disorders. rFVIII Fc is a recombinant fusion protein composed of a single molecule of B-domain deleted rFVIII linked to the human IgG_1 Fc domain. This technology has the potential to have a major impact on the worldwide use of prophylaxis for severe hemophilia, which could ultimately prevent bleeding episodes and their sequelae.

Although it would be even more beneficial to have a product with a longer half-life than rFVIII Fc, Mahlangu and colleagues note the obstacles in developing such a product. These center on the protective effects of von Willebrand factor (VWF) on circulating FVIII, with VWF protecting FVIII from proteolytic degradation and binding to FVIII clearance receptors. However, this beneficial interaction between VWF and FVIII also limits further extension of FVIII half-life beyond that of VWF (16-17 hours).[1,6,7]

At present, no longer-lasting FVIII or FIX products are yet licensed. Only Biogen Idec's rFVIII Fc and rFIX Fc are under regulatory review. Other pharmaceutical manufacturers are pursuing other methodologies, including glycopegylation,[7] pegylation, and albumin fusion.

This is, indeed, an exciting time, with great promise for longer-acting FVIII and FIX products that could benefit persons with hemophilia around the globe.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

REFERENCES

1. Mahlangu J, Powell JS, Ragni MV, et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. *Blood.* 2014;123(3):317-325.
2. Nilsson IM, Blombäck M, Ahlberg Å. Our experience in Sweden with prophylaxis on haemophilia. *Bibl Haematol.* 1970;34:111-124.
3. Nilsson IM, Berntorp E, Löfqvist T, Pettersson H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. *J Intern Med.* 1992;232(1):25-32.
4. Manco-Johnson M. Comparing prophylaxis with episodic treatment in haemophilia A: implications for clinical practice. *Haemophilia.* 2007;13(Suppl 2):4-9.
5. Hacker MR, Geraghty S, Manco-Johnson M. Barriers to compliance with prophylaxis therapy in haemophilia. *Haemophilia.* 2001;7(4):392-396.
6. Powell JS, Josephson NC, Quon D, et al. Safety and prolonged activity of recombinant factor VIII Fc fusion protein in hemophilia A patients. *Blood.* 2012;119(13):3031-3037.
7. Tiede A, Brand B, Fischer R, et al. Enhancing the pharmacokinetic properties of recombinant factor VIII: first-in-human trial of glycoPEGylated recombinant factor VIII in patients with hemophilia A. *J Thromb Haemost.* 2013;11(4):670-678.

● ● ● LYMPHOID NEOPLASIA

Comment on Turesson et al, page 338

Determining the significance of MGUS

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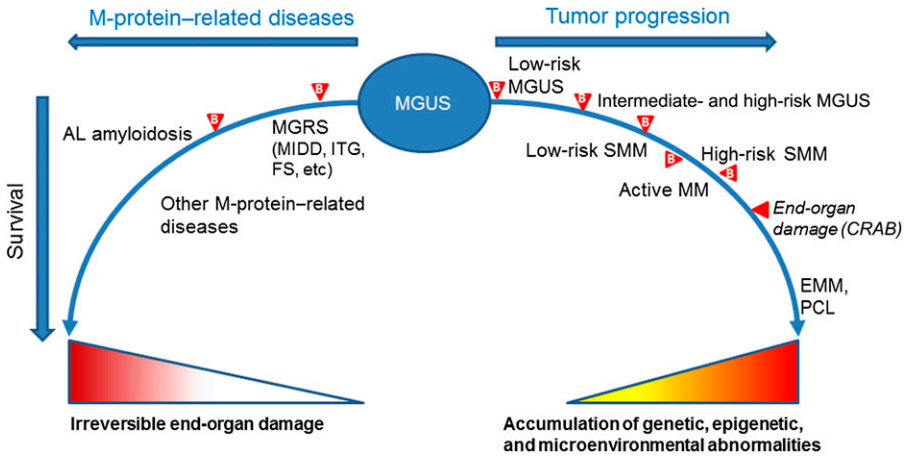
In this issue of *Blood*, Turesson et al study the risk of progression of monoclonal gammopathy of undetermined significance (MGUS) to lymphoplasmacellular and myeloid malignancies in a large population, validating current risk factors and adding immunoparesis as a predictor of progression.[1]

MGUS is one of the most common premalignant disorders in the general population, occurring in over 3% of individuals ≥50 years old. It is predominantly diagnosed incidentally and is characterized by the presence of a serum monoclonal (M) protein in the absence of symptoms, with an unrelenting annual risk of progression to multiple myeloma (MM) or related plasma cell (PC) disorders of approximately 1%.[2] Although virtually all patients with MM have a previously recognized MGUS, most cases of MGUS do not progress toward malignancy. Differentiating low-risk patients, who may not need further follow-up, from high-risk patients, who warrant close monitoring, is challenging.

Multistep genetic and microenvironmental changes lead to the transformation of MGUS into smoldering myeloma (SMM), MM, and, finally, to extramedullary myeloma or related malignancies. Intense research is ongoing to identify biologically relevant markers differentially expressed throughout this progression, which could be exploited to predict evolution or suggest therapeutic strategies that would prevent or delay progression. Despite important progress, we still lack reliable biological markers to predict which patients will progress and which will not, and MGUS is currently risk stratified based on clinical variables identified through epidemiologic studies. Both the Mayo Clinic



Spectrum of the possible progression of MGUS. Acquisition of somatic genetic and epigenetic abnormalities in the tumor cells and changes in the bone marrow microenvironment lead to the transformation of non-IgM MGUS into SMM, to MM, extramedullary myeloma (EMM), and plasma cell leukemia (PCL). IgM-MGUS can progress to smoldering Waldenström macroglobulinemia (WM), to WM, lymphoma, or other chronic lymphoproliferative disorders (not shown in the figure). The stages of progression are differentiated using biomarkers (B) and imaging. Recently, the diagnosis of "active myeloma" has been proposed, a condition anticipating the occurrence of end-organ damage (CRAB).[5] The clone may also produce end-organ damage through the M-protein. The protein may target the kidney in monoclonal gammopathy of renal significance (MGRS), including, among others, monoclonal immunoglobulin deposition disease (MIDD), immunotactoid glomerulopathy (ITG), and Fanconi syndrome (FS). The monoclonal light chains may deposit in tissues, causing progressive organ dysfunction; the most notable condition is AL amyloidosis. Biomarkers may help to anticipate the diagnosis of these conditions, before irreversible organ damage has occurred. Other M-protein–related conditions, such as autoimmune neuropathies and chronic cold agglutinin disease, are caused by the autoantibody activity of the M-protein.

and Spanish investigators have developed models predicting the risk of MGUS progression (reviewed in Merlini and Palladini[3]). The former is centered on serum biomarkers and identifies 3 risk factors (non-IgG isotype, serum M-protein concentration ≥15 g/L, and an abnormal free light chain [FLC] ratio), whereas the latter is based mainly on multiparametric flow cytometry identification of PC populations. Given its easier applicability, the Mayo Clinic model is more widely used and is incorporated in the International Myeloma Working Group's guidelines.[4] However, neither risk model has been independently validated in large patient populations with long-term follow-up. The study by Turesson et al fills this gap, analyzing a large Swedish cohort using retrospective data collected from medical records and case ascertainment from a national cancer registry. Although the study design has limitations, many findings are relevant. One notable observation is that the annual risk of progression toward lymphoplasmacellular malignancies is only 0.5% in the Swedish cohort, unlike the ~1% found in the population-based Mayo Clinic cohort.[2] This may be due to different study designs and populations. The negative impact of serum M-protein concentration ≥15 g/L and abnormal FLC ratio is confirmed in the Swedish cohort. The latter biomarker also plays an important role in identifying patients with highest-risk SMM (or "active MM," according to a recently proposed reclassification).[5] In the Swedish study, the suppression of noninvolved immunoglobulins (immunoparesis) increases the discriminatory power of the Mayo Clinic model to identify high-risk MGUS. Interestingly, isotype-specific paresis (suppression of IgGk in IgGλ MGUS) appears to be an early predictor of progression, although this needs confirmation.[6]

The study by Turesson et al falls within a comprehensive effort to redefine the risk categories of monoclonal gammopathies throughout the whole spectrum, ranging from the precursor state, to smoldering and active MM (see figure). The definition of active MM, in the absence of CRAB (calcium increase, renal insufficiency, anemia, bone lesions) is ongoing, exploiting validated and novel biomarkers and modern imaging.[5] The goal is to reliably intercept the disease at earlier stages of genetic and host immunologic abnormalities, when intraclonal heterogeneity is limited and the clone would be more amenable to therapeutic intervention, anticipating organ damage and prolonging survival. It is also important to identify patients with low-risk, benign MGUS who have an absolute risk of progression at 20 years, adjusting for competing causes of death, of only 2%.[2] These individuals may not require baseline bone marrow examination, skeletal radiography, or annual follow-up and, particularly the elderly, could be discharged to family physicians.[3] The Mayo Clinic risk model[2] efficiently identifies these subjects, who represent a substantial proportion (~40%) of MGUS cases.[4] Patients with intermediate- and high-risk MGUS, however, require close monitoring, including not only biomarkers of clonal progression but also biomarkers of organ damage caused by the M protein (see figure). The 2 most common and clinically relevant target organs are the kidney, in monoclonal gammopathy of renal significance,[7] and the heart, in light chain (AL) amyloidosis.[8] Organ failure can develop silently in subjects with MGUS. However, urinary albumin excretion and serum creatinine, with estimated glomerular filtration rate, can efficiently detect early kidney involvement, while NT-proBNP has 100% sensitivity, although it is not specific, in detecting early, reversible, cardiac dysfunction caused by amyloidogenic light chains.[8] Inclusion of these biomarkers in routine follow-up of individuals with MGUS and an abnormal FLC ratio (who are at higher risk of developing M-protein–related organ damage) may allow early detection of these insidious diseases. The underlying PC clones are usually small, indolent, and probably in an early stage of progression. Treatment of these "early clones" in patients with AL amyloidosis results in long-lasting complete responses translating into superior survival compared with that of MM patients.[9]

Although only a fraction of MGUS cases (21% of 70-year-olds)[10] are recognized during routine clinical practice, the current consensus is still that screening for MGUS should not be performed, considering the generally low risk of progression to malignancy, related emotional burden, and lack of effective interventions. However, because it is now possible to rapidly identify low-risk individuals (thus reducing the economic and emotional burden for approximately 40% of cases), we can focus on the remaining 60%, with careful monitoring, in order to detect progression promptly and anticipate end-organ damage.[4] If evidence of clinical benefit of early interventions[11] is

consolidated, we could likely reconsider our current practice, adopting a more proactive search for M protein in clinical practice.

Available biomarkers are enabling clinicians to risk stratify individuals with MGUS, optimizing their management. Novel, biologically relevant markers, in combination with imaging techniques, have the potential to change our clinical practice throughout the spectrum of monoclonal gammopathies.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

REFERENCES

1. Turesson I, Kovalchik SA, Pfeiffer RM, et al. Monoclonal gammopathy of undetermined significance and risk of lymphoid and myeloid malignancies: 728 cases followed up to 30 years in Sweden. *Blood.* 2014;123(3):338-345.

2. Rajkumar SV, Kyle RA, Therneau TM, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. *Blood.* 2005;106(3):812-817.

3. Merlini G, Palladini G. Differential diagnosis of monoclonal gammopathy of undetermined significance. *Hematology Am Soc Hematol Educ Program.* 2012;2012:595-603.

4. Kyle RA, Durie BG, Rajkumar SV, et al; International Myeloma Working Group. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. *Leukemia.* 2010;24(6):1121-1127.

5. Dispenzieri A, Stewart AK, Chanan-Khan A, et al. Smoldering multiple myeloma requiring treatment: time for a new definition? [Published online ahead of print October 21, 2013.] *Blood.* 2013.

6. Katzmann JA, Clark R, Kyle RA, et al. Suppression of uninvolved immunoglobulins defined by heavy/light chain pair suppression is a risk factor for progression of MGUS. *Leukemia.* 2013;27(1):208-212.

7. Leung N, Bridoux F, Hutchison CA, et al; International Kidney and Monoclonal Gammopathy Research Group. Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant. *Blood.* 2012;120(22):4292-4295.

8. Merlini G, Wechalekar AD, Palladini G. Systemic light chain amyloidosis: an update for treating physicians. *Blood.* 2013;121(26):5124-5130.

9. Dispenzieri A, Seenithamby K, Lacy MQ, et al. Patients with immunoglobulin light chain amyloidosis undergoing autologous stem cell transplantation have superior outcomes compared with patients with multiple myeloma: a retrospective review from a tertiary referral center. *Bone Marrow Transplant.* 2013;48(10):1302-1307.

10. Therneau TM, Kyle RA, Melton LJ III, et al. Incidence of monoclonal gammopathy of undetermined significance and estimation of duration before first clinical recognition. *Mayo Clin Proc.* 2012;87(11):1071-1079.

11. Mateos MV, Hernandez MT, Giraldo P, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. *N Engl J Med.* 2013;369(5):438-447.

Comment on Thompson et al, page 366

Neutrophil survival in the death zone

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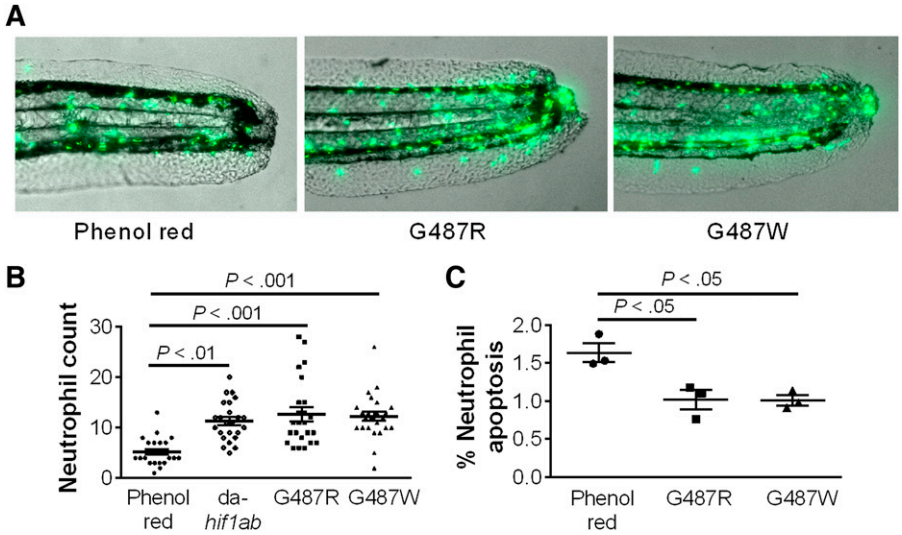
In this issue of *Blood*, Thompson et al reveal a key role for hypoxia-inducible factor (HIF)-2α in the adaptation of neutrophils to hypoxia. Tissue hypoxia is a common feature of trauma and inflammation. Infiltrating neutrophils must adapt to this low-oxygen environment to satisfy the metabolic and functional demands of an immune response.[1]

Much is known about the factors controlling neutrophil production and the recruitment of neutrophils to sites of inflammation. In contrast, the factors controlling the survival and clearance of neutrophils from tissues remain poorly defined. The net accumulation of neutrophils at sites of inflammation will be a function of recruitment and median neutrophil life span. Hypoxia increases neutrophil survival,[2] suggesting that hypoxia may impair the resolution of neutrophilic inflammatory disorders such as acute respiratory distress syndrome, bronchiolitis obliterans organizing pneumonia, and respiratory syncytial virus infection. The oxygen-sensitive HIF/von Hippel-Lindau pathway is fundamental to hypoxia adaptation. The HIF-1α and HIF-2α transcription factors are both induced by hypoxia in neutrophils.[3] However, HIF-1α and HIF-2α expression are not always coordinately regulated, and they can serve distinct functions in other cell types. Thompson and colleagues now demonstrate key roles for HIF-2α in extending neutrophil life span in zebra fish, mice, and humans.[1]

Humans with gain-of-function mutations in HIF-2α develop erythrocytosis because of exaggerated erythropoietin production[4] but are not known to be predisposed to neutrophilic inflammatory disease. Mice with targeted HIF-2α point mutations recapitulate the human syndrome of erythrocytosis.[5] Iron chelation with deferoxamine stabilizes HIF-1α and HIF-2α in neutrophils, but clinical use of this compound is also not associated with neutrophilic inflammatory disease



HIF-2α increases neutrophil life span. (A-B) Human-equivalent HIF-2α gain-of-function mutations in zebra fish impair the clearance of green fluorescent protein–labeled neutrophils after a tail fin transection. (C) The increased neutrophil number is associated with a decrease in TUNEL-positive apoptotic neutrophils. See the complete Figure 3 in the article by Thompson et al that begins on page 366.