to limitations of the registers (ie, lack of detailed clinical and laboratory information and only inclusion of first-degree relatives and patients born after 1936).

In summary, we found survival to be similar in familial and sporadic MPN patients. With increasing knowledge on the genetic basis of MPNs, screening of family members of MPN patients with the aim of identifying patients early in the disease course may soon be possible. Early detection and preventive measures may decrease the rate of thromboembolic complications. We recommend that family history of MPNs should be incorporated in the clinical workup of MPN patients. However, until we gain more insight regarding the potential genetic and clinical differences, clinical management should not differ between familial and sporadic MPN patients.

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To the editor:

How does dapsone work in immune thrombocytopenia? Implications for dosing

Dapsone is a standard second-line treatment of primary immune thrombocytopenia (ITP), with response rates of 27% to 63%. Most adult studies used 100 mg daily, but the rationale for dose selection is unclear, and no ITP study has sought an association between dose and response.

Dapsone's mechanism of action in ITP is not fully understood. Its metabolism into dapsone hydroxylamine (DDS-NOH) results in hemolysis, and the prevalent theory is that dapsone-induced hemolysis leads to erythrophagocytosis by the reticuloendothelial (RE)

system, preventing sequestration and destruction of platelets. The hemolysis is dose dependent, and in 15 healthy volunteers taking 25 to 300 mg, there was a reasonably linear relationship between hemolysis severity and the dapsone dose in milligrams per kilogram of body weight.[1] Intravenous anti-D is thought to act through a similar mechanism in ITP, and its dose influences the platelet count response. If dapsone's activity is principally though RE blockade, a dose-sensitive platelet count response would be anticipated.

An alternative hypothesis stems from dapsone's better-studied anti-inflammatory activity in skin disorders. Its mechanism of action is still debated but may involve inhibition of neutrophil adhesion and migration to the site of tissue damage, inhibition of their prostaglandin production, or myeloperoxidase-mediated cytotoxicity. In vitro dapsone results in a dose-dependent inhibition of neutrophil adhesion to basement membrane-bound antibody from patients with bullous skin disorders.[2] Adhesion is mediated by the mobilization and activation of the β_2-integrin molecule Mac-1 (CD11b/CD18). Several groups have shown that dapsone reduces adhesion of activated neutrophils through downregulation of Mac-1 expression. For example, dapsone at a concentration of 0.1 to 80 μg/mL reduced their adhesion to epidermal cells in a frozen section adhesion assay prepared from healthy skin preincubated with interferon.[3] Dapone also inhibits the CXC-chemokine interleukin (IL)-8 and has shown dose-dependent inhibition of bullous pemphigoid immunoglobulin G-induced IL-8 release from cultured keratocytes at a posttranscriptional level.[3] IL-8 is a potent chemotactic factor for leukocytes and is involved in their transmigration into the tissues. It regulates neutrophil expression of the β_2-integrins Mac-1 and CD11c/CD18 (p150,95), increases Mac-1 binding activity, and promotes neutrophil adhesion to endothelial cells through interaction with Mac-1.[4]

In ITP, antibody-coated platelets are cleared by circulating monocytes and macrophages of the RE system in an Fc-dependent manner. Complement fixation-enhanced RE clearance of opsonized platelets may also be an important mechanism.[5] Mac-1 is expressed on monocytes and macrophages. It appears to work cooperatively with complement receptor 1 (CD35) to achieve stable adhesion of complement-opsonized particles.[6] It is also involved in antibody-dependent cellular cytotoxicity and Fc receptor (FcR)-mediated cytotoxicity toward tumor cells, parasites, virus-infected cells, and erythrocytes.[7] Intravenous immunoglobulin is thought to act through modulation of FcγR expression. Dapsone may therefore interfere with FcR-mediated platelet clearance by reducing expression of Mac-1. Furthermore, platelets have recently been shown to be an important source of serum IL-8, with a significant association between platelet count and serum IL-8 in ITP patients.[8] Whether dapsone's inhibitory effect on IL-8 and Mac-1 is enhanced by low serum IL-8 in severely thrombocytopenic patients and whether dapsone influences macrophage FcR function is unknown, and the hypothesis awaits investigation. Interestingly, however, unpublished data suggest dapsone can inhibit expression of the β_2-integrin p150,95 in a macrophage cell line.[3]

Despite a linear relationship between dapsone dose (milligrams per kilogram) and serum concentration, evidence for a clear dose-response association is lacking in inflammatory skin disorders, and the dose range to achieve symptom control is wide; for example, 25 to 400 mg daily (mean, 141 mg) in 20 patients with dermatitis herpetiformis.[9] There is a 10-fold intersubject variability in DDS-NOH clearance, which is closely associated with variability in the oral clearance of dapsone ($r = 0.96$),[10] and topical studies suggest DDS-NOH may itself have anti-inflammatory properties.[3] Whether variation in DDS-NOH concentration accounts for dapsone's wide dose range is unknown.

Table 1. Dapsone: dosing, contraindications, cautions, adverse events, and monitoring

Dose and drug safety considerations	Details
Typical dosing regimens	
Leprosy	100 mg daily (in multiple drug regimens)
Malaria prophylaxis	100 mg weekly (with 12.5 mg pyrimethamine)
Dermatitis herpetiformis	50 mg daily titrated to 300 mg daily if required. In responding patients, reduced to the minimum effective dose (typically 25-100 mg).
Contraindications	Include hypersensitivity to sulphonamides or sulphones, severe anemia, porphyria, and severe glucose-6-phosphate-dehydrogenase (G6PD) deficiency
Cautions	Cardiac or pulmonary disease, anemia, and G6PD or methemoglobin reductase deficiency.
Adverse events	
Hemolysis	Occurs in most patients above 200 mg (or above 50 mg if G6PD deficiency). At 100-150 mg, hemoglobin falls by 2 0g/L in ~10%. Treatment does not need to be interrupted for mild hemolysis.
Methemoglobinemia	Cyanosis may be visible at levels >3%. Tachycardia, headache, nausea, weakness, and abdominal pain may occur at higher levels.
Hypersensitivity reaction	May present with rash (can be severe, eg, erythema multiforme, exfoliative dermatitis), fever, lymphadenopathy, hepatic dysfunction, or leukocytosis. Prevalence 1.4%. Most cases are within 6 weeks of onset. 10% fatality. Stop drug, consider systemic steroids.
Peripheral neuropathy	Rare. Primarily motor. Complete resolution typical with dose reduction or withdrawal
Other effects	Agranulocytosis, rash, photosensitivity, pruritis, tachycardia, headache, hepatitis, insomnia, psychosis, anorexia, nausea, and vomiting
Laboratory monitoring	
Baseline	Complete blood count (CBC) with differential and reticulocyte counts Liver and renal function G6PD level
Follow-up	CBC with differential and reticulocyte counts every 2 weeks for 3 months and then every 3-4 months (increase frequency if dose is increased) Liver and renal function every 3-4 months Methemoglobin as clinically indicated

In ITP studies, dapsone 100 mg daily is well tolerated, with 0% to 11% of patients discontinuing therapy because of side effects. However, hemolysis and methemoglobinemia are dose dependent and may limit further dose titration. Some important contraindications, adverse effects, and an approach to monitoring are presented in Table 1. *N*-hydroxylation occurs through the P-450 system, and coadministration of the P-450 inhibitor cimetidine 400 mg 3 times daily can reduce methemoglobin levels by 25% to 30%. Although potentially also reducing dapsone's anti-inflammatory effect, some authors have advocated its use at higher doses or for pronounced hematologic toxicity.[3]

The implication of both postulated mechanisms (hemolysis or immunomodulation) is that dapsone's efficacy in ITP is likely to be dose sensitive. The overall response rate to dapsone might be improved by careful dose titration in patients unresponsive to 100 mg daily, and a phase 2 dose-finding study is needed.

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To the editor:

Phase 1/2 trial of vorinostat in patients with sickle cell disease who have not benefitted from hydroxyurea

Worldwide, over 200 000 babies are born annually with sickle cell disease (SCD). In the United States, over 90 000 people have SCD.[1] Induction of fetal hemoglobin (HbF) is a well-established strategy to inhibit sickle hemoglobin polymerization.[2] To date, hydroxyurea, which induces HbF, is the only US Food and Drug Administration (FDA)-approved drug for SCD treatment. Hydroxyurea reduces morbidity,[3] but patients continue to suffer complications such as renal failure and strokes.[4] There is a significant need for novel therapies. Histone deacetylase (HDAC) inhibitors are powerful inducers of HbF in human erythroid progenitor cells in vitro.[5,6] Moreover, agents with HDAC inhibitory activity, including valproic acid and butyrate, have previously been shown to induce HbF in patients with SCD.[6-9] Vorinostat increased HbF in 3 patients undergoing therapy for Hodgkin lymphoma.[6]

We conducted a phase 1/2 study to evaluate the safety and efficacy of vorinostat (suberoylanilidine hydroxamic acid; Merck & Co) in adults with severe SCD who previously on hydroxyurea were intolerant or had no clinical improvement and no induction of HbF. A period of at least 90 days from hydroxyurea use was required for enrollment. Vorinostat is an oral hydroxamate-based pan-HDAC inhibitor, FDA approved in 2006 for the treatment of refractory cutaneous T-cell lymphoma. Given previous success with pulse-dose butyrate, patients received vorinostat in a pulsed fashion, once a day for 3 consecutive days every week to a maximum dose of 400 mg per dose (1200 mg/wk), for 12 to 16 weeks at the maximum dose.[8-10] The primary objectives of the study were to characterize the safety and tolerability of vorinostat in SCD patients and to determine the efficacy of vorinostat in inducing a 4% absolute increase or a 100% relative increase in HbF percentage levels (HbF%). Secondary objectives were to assess the effect of vorinostat on F-cell levels and to determine the changes in β-globin, γ-globin, and ε-globin RNA levels during treatment with vorinostat. Investigational New Drug approval was obtained from the FDA, and the study was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board. Informed consent was obtained in accordance with the Declaration of Helsinki. This trial was registered at www.clinicaltrials.gov as #NCT01000155.

Table 1. Patients with sickle cell disease on vorinostat

Patient	Age, y	Gender	Baseline Hb, g/dL	End-of-study Hb, g/dL	Baseline HbF%	Highest HbF%	Grade 3/4 toxicity*
1	44	M	5.9	7.5	1.5	4.6	Pain, headache
2	43	F	5.7	5.3	13.8	12.8	None
3	37	F	8	8.9	5.6	6	Pain
4	31	F	7	7.5	9.2	10	Pain
5	21	M	8	8	16.55	20.5	Pain

All patients had HbSS genotype and all toxicities resolved completely.
Hb, hemoglobin.
*Toxicity was graded based on Common Terminology Criteria for Adverse Events, version 4.0.

Five adult patients were enrolled in this study: 3 women and 2 men (Table 1). Three of the 5 patients completed dosing requirements of the study. All patients completed 12 weeks of observation. The first 3 patients were enrolled in an intrapatient dose escalation schedule of 100 mg/d, then 200 mg/d, each for 3 consecutive days a week for 4 weeks, and then 400 mg/d, 3 consecutive days per week for 16 weeks. The last 2 patients were enrolled to receive 400 mg/d, 3 consecutive days per week for 12 weeks, without an initial dose escalation. Safety assessments by history, examination, and/or laboratory tests were performed weekly. Median baseline hemoglobin was 7.0 g/dL (range, 5.7-8 g/dL), and median baseline HbF% was 9.2% (range, 1.5%-17.1%). After a median duration of 3 months on vorinostat, 400 mg dosing, only 1 of 5 patients met the criteria for success, with an HbF% increase from 1.5 at baseline to a maximum value of 4.6. The median F-cell percentage increased from 9.8% at baseline to 12.1%, and the median relative change in the ratio of