up-regulation of natural killer (NK) cells, activation of protein kinase C signaling pathways within histiocytes, or direct antiproliferative effects, could also explain the activity of interferon seen in these patients.[5] In any event, interferon—despite, or rather, because of its unnumbered effects—has once again emerged as an effective tool in a rare group of disorders for which there are limited options for many patients. ■

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HEMOSTASIS

Comment on Prandoni et al, page 3049

Unfractionated LMWH and the risk of HIT: are medical patients different?

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An advantage of low-molecular-weight heparin (LMWH) is its lower risk of heparin-induced thrombocytopenia (HIT) compared with unfractionated heparin (UFH).[1] In this issue of *Blood,* Prandoni and colleagues question whether heparin-induced thrombocytopenia (HIT) is reduced by low-molecular-weight heparin (LMWH) in *medical* patients.

Prandoni and colleagues prospectively evaluated 1754 medical patients who received LMWH for prophylaxis or treatment of thrombosis. HIT was observed in 14 patients (0.80%; 95% confidence interval [CI], 0.43%-1.34%), a frequency similar to the authors' previous prospective cohort study[2] of 598 medical patients receiving unfractionated heparin (UFH, 0.84%; 95% CI, 0.1%-1.6%). Thus, this new report *infers* that LMWH might not reduce HIT in medical patients. This contrasts with the approximate 10-fold reduction in HIT with LMWH compared with UFH for surgical thromboprophylaxis.[1]

	Type of study	Patient population	HIT			HIT antibodies		
			LMWH (%)	UFH (%)	*P*	LMWH (%)	UFH (%)	*P*
Prandoni et al; Girolami et al[2]	Prospective cohorts	General medical	14/1754 (0.80)	5/598 (0.84)	1.00	NR	NR	NA
Lindhoff-Last et al[3]	RCT	DVT treatment	1/720* (0.1)†	8/356 (2.2)†	.00087	45/720* (6.2)‡	75/356 (21.1)‡	<.0001
Pohl et al[4]	Prospective cohorts	Neurology	0/111 (0.0)	5/200 (2.5)	.17	2/111 (1.8)	41/200 (20.5)	<.0001
Greer and Nelson-Piercy[5]	Review	Pregnancy	0/2777 (0.0)	NA	NA	NA	NA	NA

Studies comparing UFH and LMWH in medical patients, plus a large review of LMWH treatment during pregnancy. Tests of significance are by Fisher exact test (2-tailed). RCT indicates randomized controlled trial; DVT, deep-vein thrombosis; NA, not applicable; and NR, not reported. *Combined short- and long-term–treated LMWH groups. †Endpoint shown is symptomatic thrombosis associated with antibody formation (as per Table 2 in Lindhoff-Last et al[3]); for true HIT endpoint (defined as thrombocytopenia plus positive antibody), values are LMWH = 0/762 vs UFH = 1/375 (0.3%); *P* = .33. ‡Per Table 2 in Lindhoff-Last et al.[3] Illustration by A. Y. Chen.

Previous studies of medical patients suggested that LMWH likely confers a lower risk of HIT (see table).[3-5] Lindhoff-Last et al[3] found a reduced frequency of anti–platelet factor 4 (PF4)/heparin antibodies (surrogate marker for risk of HIT) in a randomized comparison of LMWH and UFH for treatment of deep-vein thrombosis; their study also suggested that thrombotic events linked to antibody formation were reduced by LMWH. In neurology patients, Pohl et al[4] noted a marked reduction in antibody formation with LMWH compared with UFH, and a corresponding (nonsignificant) reduction in HIT frequency. Prandoni and colleagues tested for antibodies only when HIT was clinically suspected.

Why did this new study observe so much apparent HIT with LMWH? One possibility is that medical patients, who are usually admitted nonelectively with acute illness, are more likely to be falsely diagnosed with HIT. Indeed, in a placebo-controlled study[6] of enoxaparin for medical thromboprophylaxis, 4 of 5 subjects with thrombocytopenia and thrombosis (a scenario suggesting HIT) had actually received placebo. In contrast, surgical thromboprophylaxis studies of HIT have focused on elective orthopedic surgery,[1] a setting in which patients are generally well and nearing discharge at the time HIT typically manifests. The potential for false diagnosis increases if a relatively nonspecific laboratory assay is performed, such as an immunoassay that detects (non–platelet-activating) immunoglobulin M (IgM) and IgA anti-PF4/heparin antibodies. In this regard, a strength of the new report is that 11 of the 14 patients with putative HIT had a positive platelet activation assay, and the median absorbance value of the immunoassay for anti-PF4/heparin IgG was rather high (1.25 units). Thus, most of these patients likely had HIT.

As generation of the HIT antigens depends upon the appropriate stoichiometric concentrations of PF4 and heparin, factors such as transient perioperative platelet activation and

PF4 release, and postoperative thrombocytosis, may accentuate differences in immunogenicity of different heparin preparations or the pathogenic potential of the antibodies formed.

In contrast to a recent consensus conference recommendation,[7] Prandoni et al suggest that medical patients receiving LMWH should undergo routine platelet count monitoring for HIT. Given the important implications of these new data, their "outlier" status (see table) leads us to urge that HIT and HIT antibody end points be included in future studies of medical patients receiving LMWH. ■

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TRANSPLANTATION

Comment on Pavletic et al, page 3308

To T-cell deplete or not

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After more than two decades of clinical practice, we finally have results from the first randomized study of T-cell depletion of donor marrow before allogeneic transplantation.

It has been clear for more than 20 years that ex vivo depletion of alloreactive T cells from donor marrow reduces the incidence of acute graft-versus-host disease (GVHD) after hematopoietic stem cell transplantation.[1] However the effect on chronic GVHD has been less well delineated. Single-center studies using T-cell depletion regimens producing a 2- to 4-log depletion report a low incidence of chronic GVHD,[2,3] but other studies using antibodies with narrower specificity have reported a high incidence.[4] A retrospective registry study also showed that T-cell depletion did not reduce chronic GVHD when narrow specificity antibodies were used.[5]

In this issue of *Blood*, Pavletic and colleagues report the results of a study that for the first time examines the effect of T-cell depletion on the incidence of chronic GVHD in a prospective fashion. They report data from a National Heart, Lung, and Blood Institute (NHLBI)–sponsored phase 3 randomized study that compared outcomes with the use of unmanipulated marrow or T-cell–depleted marrow in unrelated transplant recipients. The authors also studied if there were factors that predict survival in patients with chronic GVHD. They confirm data from previous reports that the incidence of acute GVHD was much lower in the T-cell–depleted cohort but find no significant difference in the incidence of chronic GVHD or survival between recipients of T-cell–depleted or unmanipulated marrow. As the authors point out, this difference may reflect different pathogenesis of these 2 syndromes. Some factors associated with development of chronic GVHD (summarized in Pavletic et al's Table 1 and Figure 1), including older age and prior acute GVHD, have been described previously, but a new observation was the lower incidence seen in patients receiving higher CD34 doses. Prognostic factors for patients who developed chronic GVHD were also analyzed, and factors associated with a better outcome in each group were acute GVHD less than grade II, higher Karnofsky score, and a 6/6 matched donor.

Although this is the first randomized study to address this issue, there are some caveats that limit the conclusions. The first is that 2 T-cell depletion methodologies were used—elutriation and T10B9 antibody mediated with complement. Moreover each marrow manipulation regimen—the 2 T-depletion methods and the use of an unmanipulated product—was associated with a different conditioning regimen. As the authors point out, the comparison is therefore between the whole treatment "package" rather than marrow manipulation alone. An additional issue is that with both methodologies the degree of T-cell depletion was only one log so these conclusions cannot necessarily be extrapolated to other T-cell depletion regimens. A final confounding factor is that this study was initiated in 1995 when marrow was the only source of hematopoietic stem cells used for transplant from unrelated donors, and clinical practice has now changed so that peripheral blood is now a more common source of hematopoietic stem cells. Nevertheless, this report provides a basis for future studies comparing the effects of differing hematopoietic stem cell sources or manipulations on this devastating complication of transplantation. ■

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