Knee replacement and HIT without heparin

Theodore E. Warkentin  MCMaster University

In this issue of Blood, Bito et al report that dynamic mechanical thromboprophylaxis (DMT) is a risk factor for forming anti–platelet factor 4 (PF4)/heparin antibodies in patients undergoing knee or hip arthroplasty, which provides insight into a fascinating clinical problem: how can a patient develop heparin-induced thrombocytopenia (HIT) without heparin?1

HIT is an unusual drug reaction because its triggers extend beyond mere application of unfractioned heparin (UFH) or low-molecular-weight heparin (LMWH). For example, the risk of HIT is greater if heparin is given to surgical (vs medical) patients2 and among surgery or trauma patients if the trauma is major (vs minor).3 Although the basis for this higher risk of immunization in major surgery or trauma patients is unknown, a plausible explanation lies in the fact that HIT is not provoked by heparin alone but rather by formation of immunogenic PF4/heparin complexes, and it is likely that surgery and major trauma favor formation of such complexes (because PF4 is released from platelet α-granules during surgery– and/or trauma-associated platelet activation).

HIT occurs only in a small minority of those who form anti-PF4/heparin antibodies, particularly the subset who form high levels of immunoglobulin G class antibodies that evince strong platelet-activating properties.3 The high frequency of anti-PF4/heparin immunization means that serosurveillance studies can provide opportunities for exploring factors that are linked to risk of HIT beyond those that could be identified by studying only the (relatively) small number of patients who develop clinical HIT. By using serosurveillance, other nonpharmacologic risk factors for anti-PF4/heparin immunization have been identified, including type of surgery (knee > hip); body mass index (BMI; higher BMI > lower BMI for fixed-dose thromboprophylaxis), and timing of first heparin injection in relation to surgery (postoperative > preoperative in the setting of elective surgery, but preoperative > postoperative in the setting of trauma surgery).4 Most (if not all) of these observations can be explained by a stoichiometric model of immunization in which factors that (theoretically) increase concentrations of stoichiometrically optimal PF4/heparin complexes are associated with greater frequency of immunization.4

But there remain other HIT mysteries. Spontaneous HIT syndrome is a prothrombotic thrombocytopenic disorder with serologic features of HIT (detectability of anti-PF4/heparin antibodies with strong platelet-activating properties) but which occurs despite lack of preceding exposure to heparin.5 Interestingly, a large proportion of cases of spontaneous HIT syndrome have been reported in patients after orthopedic surgery, especially total knee arthroplasty (TKA).6 Another mystery relates to how HIT might occur in patients who receive anticoagulation with fondaparinux,7 the pentasaccharide anticoagulant modeled after the antithrombin-binding region of heparin, but which shows negligible cross-reactivity (enhancement of platelet-activating properties) with HIT antibodies.8 Interestingly, so-called fondaparinux-associated HIT has also been seen almost exclusively in TKA patients.9

It is therefore of considerable interest that Bito and coworkers (collaborating with the transfusionist and HIT researcher Dr Shigeki Miyata) have reported their prospective serosurveillance study of more than 2000 patients undergoing TKA or total hip arthroplasty (THA).1 Although many patients received UFH or LMWH thromboprophylaxis, more than half the study patients received either no anticoagulation or were given fondaparinux anticoagulation, with most also receiving DMT (via intermittent plantar or pneumatic compression device). The table shows the anti-PF4/heparin seroconversion rates among these various patient subgroups.

Table: Frequency of anti-PF4/heparin antibody formation in TKA and THA patients

<table>
<thead>
<tr>
<th></th>
<th>TKA patients</th>
<th></th>
<th>THA patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No anticoagulation</td>
<td>Fondaparinux</td>
<td>No anticoagulation</td>
<td>Fondaparinux</td>
</tr>
<tr>
<td>No DMT</td>
<td>57/370</td>
<td>15.4</td>
<td>63/296</td>
<td>21.3</td>
</tr>
<tr>
<td></td>
<td>P = .002</td>
<td></td>
<td>21/232</td>
<td>9.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>31/214</td>
<td>14.5</td>
</tr>
<tr>
<td>P = .002</td>
<td></td>
<td></td>
<td>6/130</td>
<td>4.6</td>
</tr>
<tr>
<td>P = .025</td>
<td></td>
<td></td>
<td>0/24</td>
<td>0</td>
</tr>
<tr>
<td>P = .147</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P = .051</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DOI 10.1182/blood-2016-01-690909
© 2016 by The American Society of Hematology

Comment on Bito et al, page 1036
Among TKA patients, the authors observed higher anti-PF4/heparin seroconversion rates in those who received DMT whether they received fondaparinux or no anticoagulation. Similar trends were seen among THA patients, although the result was statistically significant only for the fondaparinux-treated THA patients. When multivariate analysis was performed across the entire study population (whether anticoagulated with UFH, LMWH, fondaparinux, or no pharmacologic agent), use of DMT emerged as an independent risk factor for seroconversion (odds ratio, 2.01; 95% confidence interval, 1.34–3.02; \( P = 0.001 \)), which was also confirmed with an analysis that used propensity score matching of patients. A proportion of seroconverting patients formed strong antibodies (optical density, >1.4 units). The authors concluded that DMT increases the risk of an anti-PF4/heparin immune response even when heparin is not administered.

Bito et al clearly show that major orthopedic surgery itself can be associated with formation of anti-PF4/heparin antibodies and that this effect is enhanced by postoperative DMT. What could be the possible mechanisms of this effect? Does DMT enhance platelet activation, contributing to greater PF4 availability? Does DMT produce some element of tissue injury, thereby releasing polyanions (glycosaminoglycans? nucleic acids?) that interact with PF4, increasing the risk of triggering an anti-PF4/heparin immune response? Clearly, much more work needs to be done to explore the possible mechanisms involved.

The study by Bito and colleagues should help to persuade the skeptical clinician that a spontaneous HIT syndrome does exist and that a plausible trigger is indeed preceding orthopedic surgery, especially TKA. After all, if forming anti-PF4/heparin antibodies is common in postorthopedic surgery, even without heparin exposure, and if a proportion of these patients develop relatively strong antibodies, it is not hard to imagine that a rare patient exists who will form especially potent platelet-activating antibodies that can cause HIT even in the absence of ongoing treatment with heparin. Indeed, antibody pathogenicity in the absence of heparin is one of the key features of the pathological anti-PF4/heparin antibodies that have been identified in the sera of patients with so-called spontaneous HIT syndrome.5 Perhaps these studies also help absolve fondaparinux as being an independent trigger of HIT in the setting of TKA, because the surgery itself could be mainly responsible for triggering the HIT immune response.

Conflict-of-interest disclosure: T.E.W. has received lecture honoraria from Pfizer Canada and Instrumentation Laboratory, royalties from Taylor & Francis (Informa), and consulting fees and research funding from W.L. Gore. He has also provided expert testimony relating to heparin-induced thrombocytopenia.

REFERENCES

© 2016 by The American Society of Hematology

Comment on Brunstein et al, page 1044

**Treg adoptive therapy: is more better?**

Simrit Parmar and Elizabeth J. Shpall UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER

In this issue of Blood, Brunstein et al report on “Umbilical cord blood–derived T-regulatory cells to prevent GVHD: kinetics, toxicity profile, and clinical effect.” This is an important study demonstrating the potential for adoptive regulatory T-cell (Treg) therapy as effective graft-versus-host disease (GVHD) prophylaxis.1

Brunstein et al have pioneered the use of cord blood (CB)-derived Tregs for the prevention of GVHD, with continued improvements in this transformative adoptive cell therapy. In their first clinical trial,2 they were not able to generate the planned Treg doses ex vivo for almost 20% of the patients and the acute GVHD rates were marginally better than in their historical controls.

With improvements in the ex vivo expansion procedure, including the use of K562 antigen presenting expressing CD64 and CD86 in place of immunomagnetic beads expressing CD3 and CD28, and the refinements in the bead concentration described below, the investigators were able to generate CB Treg doses as high as 100 × 10⁶/kg.3 In a double CB transplant setting with 4 to 6 antigen matches, the Minnesota group now reports important reductions in the acute GVHD rates (9% vs 45%) in the controls (\( P = .05 \)).

This study underscores, however, that good manufacturing practice–compliant cell therapy procedures can be difficult and require meticulous diligence to generate the desired product. In the current study, the investigators performed their validation runs using an open selection system with a conjugated anti-CD25 magnetic microbead concentration of 1:350. During the actual clinical trial, they used
Knee replacement and HIT without heparin

Theodore E. Warkentin