Correspondence

To the editor:

Thrombopoietin in healthy donors

With concern we would like to react to the two Amgen-supported studies, presented in the September 1, 2001, issue of this journal, in which platelets harvested from thrombopoietin (TPO)-treated volunteer donors are used for prophylactic platelet support of chemotherapy-induced thrombocytopenia.1,2 We would have welcomed an accompanying editorial comment considering the ethics of TPO prescription in unrelated volunteer donors. Kuter et al1 mention the perception that single donor (SD) platelets are a better product compared to pooled random-donor concentrates as a rationale for the use of TPO for volunteer donors. However, no data supporting the presumptions mentioned: the reduced exposure to different donors is a theoretical risk and not based on an increased incidence of transmitted infections; the risk of bacterial contamination is indeed increased in pooled platelets but influenced by production center and prevented by bacterial monitoring; the lower occurrence of febrile reactions to SD platelets is based on studies performed prior to leukoreduction and not confirmed by studies using leukoreduced platelets3; and the reduction in HLA-alloimmunization is based on a small and outdated study using non-leukocyte-depleted transfusions in which HLA-immunization was postponed (instead of reduced).3 It is curious that the authors do not quote a more recent extensive United States trial not confirming the advantage of SD platelets to prevent HLA-immunization and platelet refractoriness.4

In the article by Goodnough et al2 it is concluded that the costs of apheresis may be reduced by splitting apheresis products with a high yield into 2 to 6 transfusion products. In the context of costs we would like to stress that in most parts of the world random pooled-platelet concentrates are still standard issue because of cost and existing infrastructures. Thrombapheresis is a bigger burden for the donor when compared to whole-blood donation because it is related to an increased risk for adverse events combined with longer duration of the procedure. Moreover, insufficient systematic follow-up studies have been performed to demonstrate that repeated exposure to extracorporeal circuit is inert.5,6 The fact that platelets are a perishable commodity will not be changed by administering TPO to healthy donors to increase the platelet yields of apheresis platelets, and thus we cannot follow this argument put forward by Kuter et al. The comparison with the use of other hematopoietic growth factors in healthy donors does not stand. Only recently granulocyte colony-stimulating factor (G-CSF) was accepted for use in healthy volunteer donors in Europe because of long-term experience in both patients and related healthy donors. We do not see any need for erythropoietin (Epo) administration to healthy volunteer donors outside the setting of autologous transplants. In the case of both G-CSF and Epo, autoantibody induction has proven to be extremely rare. The goal of blood transfusion service is to provide optimal safe blood products but not at the cost of increased risk to the donor. The proposition of administration of an unwarranted drug with unknown long-term side effects and potential “auto”-antibody inducing capacity upon multiple administrations to healthy unrelated volunteer donors should be withheld. Even if nonimmunogenic TPO will be developed, the blood transfusion services should refrain from administering this drug to volunteer donors until long-term experience in patients and possibly (as suggested by Kuter et al) in HLA-compatible related donors, in the case of HLA sensitization in patients with an extremely rare HLA phenotype, is accumulated as was the case with G-CSF.

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References


Response:

Thrombopoietin therapy increases platelet yields in healthy platelet donors

We agree with Verdijk that apheresis platelets have not been definitively shown to be superior to pooled random-donor platelets and are therefore not the standard of care in parts of the world. However, apheresis platelets do represent about two thirds of the product that is transfused in the United States,1 and this may increase if viral inactivation procedures become widely accepted. Whether or not this practice is appropriate was not the subject of our studies nor one we sought to defend. Extensive efforts have
been undertaken to increase the yield of apheresis platelet product, and our studies have demonstrated that a recombinant thrombopoietin might also be of benefit.1,4

Exposing healthy donors to hematopoietic growth factors has long been controversial, as has the concept of exposing donors to apheresis devices themselves. Donors have recently been asked to increase their donation of a variety of apheresis products (platelets, granulocytes, red cells, plasma) and peripheral blood stem cells. Shortages of apheresis platelets are not uncommon. To ask whether thrombopoietin (TPO) might join granulocyte colony-stimulating factor (G-CSF) and erythropoietin (EPO) as mobilizing agents was a valid clinical research issue that was approved by the appropriate institutional review boards and regulatory agencies, along with meticulous monitoring by the investigators to ensure the safety of the donors. There were no adverse consequences to any of the donors.

In questioning the “ethics of TPO prescription in unrelated volunteer donors,” Verdijk should distinguish between a preliminary phase 1/2 clinical trial that we performed and its widespread use in the blood supply industry. Upon completion of our trial and before embarking on further platelet donor studies, a very large safety study of paid healthy volunteers was conducted, and it was here that some were found to develop autoantibodies to TPO after multiple injections.5 This finding resulted in the discontinuation of our studies of platelet donors with this recombinant thrombopoietin.

We believe that we have established the simple principle that thrombopoietin therapy can increase platelet apheresis yields. If apheresis platelet collection continues to be an important source of platelets and if a “nonimmunogenic” thrombopoietin is developed, further studies would be warranted to determine whether this approach would be of widespread use to increase the supply of platelets. A program involving HLA-compatible related donors would be an ideal area for investigation.

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References


To the editor:

Adenosine diphosphate (ADP) does not induce thromboxane A2 generation in human platelets

Recently, Jin et al addressed the generally misunderstood problem of the factors responsible for adenosine diphosphate (ADP)-induced thromboxane A2 (TXA2) production by human platelets.1 They used stirred, washed human platelet suspensions to which fibrinogen but no CaCl2 had been added; as a consequence, the concentration of external Ca2+ ([Ca2+]o) was much lower than physiological. The main results of their study can be summarized as follows: (i) the ADP receptor antagonists A2P5P (anti-P2Y1) or AR-C67085 (P2Y12 antagonist) inhibits TXA2 production induced by ADP; (ii) the fibrinogen receptor antagonist SC49992 inhibited platelet aggregation and TXA2 production induced by ADP; (iii) the Fab fragment of ligand-induced binding site 6 (LIBS6) antibody, which induces a fibrinogen binding site on αIIbβ3, caused platelet aggregation and TXA2 production when added to platelet suspensions with fibrinogen; (iv) A2P5P (P2Y1 antagonist) or AR-C67085 (P2Y12 antagonist), when added together or alone, inhibited the secondary wave of aggregation and TXA2 production induced by LIBS6 plus fibrinogen; and (v) in the presence of physiological concentrations of Ca2+, there was no production of TXA2 by ADP-aggregated platelets. The authors concluded that ADP induces TXA2 generation in human platelets, which requires coordinated signaling through the integrin αIIbβ3 and ADP receptors.

We do not agree with the authors’ interpretation of their own results. Rather, we think that their results are in accord with well-established knowledge of the factors involved in ADP-induced TXA2 generation: (1) ADP does not stimulate TXA2 production directly; (2) it is the close platelet-to-platelet contact that is brought about by ADP-induced platelet aggregation that triggers the production of TXA2; and (3) this effect is greatly enhanced and can be seen in most healthy individuals when [Ca2+]o is decreased to micromolar levels.2-5 Based on this interpretation, it is not surprising that the experiments performed by Jin et al showed that antagonists of P2Y1, P2Y12, or the fibrinogen receptor, which inhibit ADP-induced platelet aggregation,abolished the TXA2 production. The dependency of TXA2 production and the ensuing platelet secretion on platelet aggregation is demonstrated by the observation that no TXA2 production or platelet secretion occurs from normal human platelets that are stimulated by ADP, even at high concentration, under conditions in which platelet aggregation does not occur: for instance, if the receptor function for adhesive proteins on αIIbβ3 is inhibited with inhibitory monomeric antibodies or Arg-Gly-Asp-containing peptides, or, more simply, if the platelet suspension is not stirred.

The mechanism by which platelet aggregation triggers TXA2 formation at low [Ca2+]o is presently unknown. But the mechanism is by no means selective for ADP-induced platelet aggregation, because similar effects occur when platelets are aggregated by other weak agonists,6 and it can be observed also when close platelet-to-platelet contact is brought about by LIBS6 and fibrinogen,1 or the agglutinating agents polylysine or ristocetin.7,8 The platelet-to-platelet contact caused by weak agonists, agglutinating agents or LIBS6 and fibrinogen causes the formation of trace amounts of TXA2 and the secretion of ADP, which supports the secondary full aggregation responsible for the production of large amounts of TXA2. None of these responses, including TXA2 production, is observed when the same agonists or agglutinating agents are added to the same platelet suspension under nonstirring conditions.6 This
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Robert M. Verdijk