CORRESPONDENCE

Safety of Filtered Leukocyte-Reduced Blood Products for Prevention of Transfusion-Associated Cytomegalovirus Infection

To the Editor:

In a recent Blood report, Bowden et al. concluded that filtration is an effective alternative to the use of seronegative blood products for prevention of transfusion-associated cytomegalovirus (CMV) infection in CMV seronegative marrow transplant patients. Furthermore, they suggest their results justify abandoning the maintenance of dual inventories of seronegative and seropositive/unscreened blood products and that serologic screening of blood products for CMV could be eliminated altogether. We believe their data do not support such strongly stated conclusions and, in fact, point to the possibility of important problems with filtered products.

We address the most striking finding first: an overall increased incidence of fatal CMV disease in the group receiving filtered products. In the group of 250 patients receiving filtered products, all 6 patients who showed evidence of CMV infection developed CMV disease, including 5 cases of fatal CMV pneumonia. In contrast, of 252 patients receiving seronegative blood products, only 4 showed evidence of CMV infection, and none had CMV disease. The investigators' actuarial analysis confirms an increased probability of developing CMV disease by day 100 in the filtered arm (2.4% vs 0%, P = 0.03). Also, it is unlikely that chance alone could account for six occurrences of disease among six infections in the filtered arm versus no disease among four infections in the seronegative arm (P = 0.005 by Fisher's exact test). We agree with the investigators that these findings are surprising and unexplained, but they cannot be ignored.

The investigators partly discount the difference in disease rates on the basis of their primary analysis, which included only those infections occurring between days 21 and 100 after transplant. However, even in this subgroup analysis there were 2 cases of fatal CMV pneumonia out of 3 infections in the filtered arm compared with no cases of CMV disease out of 2 CMV infections in the seronegative arm. Although the difference in actuarial estimates of CMV disease rates now do not achieve statistical significance (1.2% for the filtered arm vs 0% for the seronegative arm, P = 0.25), it is a fundamental error (a so-called type II error), to interpret this to mean the two arms are clinically equivalent.

The investigators designed their study to have sufficient power to detect, at best, a difference of 5% in the incidence of CMV infection/disease rates. However, the use of seronegative products results in a CMV transmission rate of just a few percent, and their study was not designed to rule out a doubling or even tripling of the risk for developing fatal CMV disease in the filtered arm. To put this in perspective, the investigators' data are consistent with the possibility of 2 to 5 extra CMV pneumonia deaths per 250 patients when filtered products are used in place of seronegative products. In our opinion this would be a clinically important difference, and their study cannot rule this out.

Thus, Bowden et al have demonstrated a real possibility that using filtered blood rather than CMV seronegative blood puts bone marrow transplant patients at an unacceptably higher risk of fatal CMV disease. To conclude equivalency of seronegative products and filtered products for the prevention of CMV disease is not warranted by their data.

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REFERENCES


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Response

We appreciate the opportunity to respond to the issues raised by Landaw et al. To some extent, their remarks reflect on the difficulties encountered in clinical studies comparing cytomegalovirus (CMV) seronegative blood and components with other strategies to reduce the risk of transfusion transmitted CMV infection. The very low incidence of CMV infection/disease with the use of CMV seronegative blood products requires large numbers of enrollees in studies designed to determine if other approaches (e.g. leukocyte reduction) are also able to prevent CMV infection by transmission. In addition, the limited sensitivity of CMV screening tests, particularly for early infections with low-titered antibodies, may allow already CMV infected individuals to be entered into clinical trials. To reduce the latter problems, we prospectively excluded from the primary analysis patients who showed evidence of CMV infection/disease within the first 21 days of study entry.

The results that we reported included the observation that we found more disease in the filtered blood arm by comparison with the seronegative blood arm when the data from day 0 to 100 post-transplant were analyzed. However, our Discussion emphasized that this observation carried no statistical significance once those enrollees developing CMV infection before day 21 were excluded from analysis as being probably already infected with CMV at the time of randomization but were falsely seronegative. Furthermore, as also mentioned in the Discussion, within 6 months of study termination,
two recipients of only CMV seronegative blood products became infected, and both developed disease, a reminder that screened blood recipients are not exempt from disease.

We agree that we could have been faulted for a type II error, failure to reject the null hypothesis when it is actually false, if our recommendations had been based on an inclusive analysis of all the outcomes in the two arms between day 0 and 100. Because we believe that infection during the first 21 days owes more to unrecognized virus than it does to transfusion transmission, we chose to draw our conclusions from outcomes occurring after day 21. We do not consider this more restrictive analysis subject to a type II error.

By reporting all of our data, even though our focus was on the day 21 to 100 information, other investigators who believe that early infections are a failure of the transfusion strategy used, rather than a result of the limitations of CMV serological testing, can consider alternative approaches to the management of their patients. However, the investigators still consider filtered blood products to be equivalent to CMV seronegative blood products in the prevention of CMV infection/disease.

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Safety of filtered leukocyte-reduced blood products for prevention of transfusion-associated cytomegalovirus infection [letter; comment]

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