blood advances

A leap in recognizing drug-induced immune hemolytic anemia

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Comment on Maquet et al, page 817

Drug-induced immune hemolysis remains a serious and unrecognized diagnosis. Combining data from pharmacovigilance and clinical care, the comprehensive study conducted by Maquet et al,[1] featured in this issue of *Blood Advances*, marks a leap forward in knowledge. Not only does it shed light on potential new causes of drug-induced immune hemolytic anemia and strengthen suspected associations, but it also underscores the remarkable potential of large-scale national and international databases in advancing our understanding of rare but clinically significant conditions.

Its counterpart, drug-induced immune thrombocytopenia, overshadows drug-induced hemolysis in documentation and knowledge.[2-4] The rarity of hemolysis likely plays a significant role in explaining the observed difference compared with thrombocytopenia and the lack of a simple approach to diagnose drug-induced hemolysis. Although there are many known drugs that can cause thrombocytopenia, in general, and immune thrombocytopenia, in particular, the list of drugs suspected or confirmed to be associated with acquired hemolysis has grown at a much slower pace. Large-sample studies or cohort studies, like the study presented by Maquet et al, are few, leaving us with a limited knowledge base.[4-7]

Several pathophysiological mechanisms involved in drug-induced immune hemolysis have been proposed. They reflect a continuum from a pure hapten–directed reaction, in which the drug adsorbs to the red blood cell and the antibodies target the drug with the red blood cells as collateral casualty, to formation of complex neoantigens, including both the drug and normal cell-surface structures. The culprit drug plays a role in the onset of immune recognition but may not always be necessary in the subsequent sustained immune reaction, causing drug-dependent and/or drug-independent antibodies.[8] The latter being impossible to distinguish serologically from primary warm autoimmune hemolytic anemia.[8,9] This complexity of mechanisms also clouds the diagnostic process, and the first step in reaching a diagnosis is to develop a suspicion. The final diagnosis is often based on circumstantial evidence, as confirmatory tests are usually not readily available.[4,8] The management of drug-induced immune hemolysis reflects this heterogeneity, including suspicion and withdrawal of the culprit drugs and standard treatment of autoimmune hemolytic anemia with immune suppression.[9]

A decline in drug-induced hemolysis has been proposed because of changes in prescription patterns and available drugs.[8] This would, however, not protect against the introduction of new drugs, but the list of new drugs causing drug-induced hemolysis has remained limitied.[7] The contemporary update provided by Maquet et al is based on findings using data from 2 very large databases and state-of-the art analytical approaches. The authors used the World Pharmacovigilance Database, with its >20 million drug reports, as the starting point to identify any novel associations between drugs and drug-induced hemolysis. Among 789 suspected red blood cellimmune-drug reactions, 59 new candidates emerged. All drugs with a known or new suspicion of inducing immune hemolytic anemia were subsequently tested using the French autoimmune hemolytic anemia cohort comprising >6500 patients diagnosed between 2012 and 2018. This dual-database approach not only enhanced the robustness and diminished the risk of spurious associations in the study, but the further use of both the case-control and case-crossover analytical approaches in the French cohort added to the confidence of the findings. Overall, 14 drugs, of which 3 had not previously been suspected in this context, were associated with onset of immune hemolysis. A further 15 drugs were identified with only 1 of the approaches, which

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still hints at some association and may be hampered by a lower power of detection in the case-crossover approach.

The 14 drugs that remain after this double test[1] may now be taken as highly suspicious drugs to be screened for in the assessment of new-onset acquired immune hemolysis, thereby lowering the threshold for considering the diagnosis. These drugs either carried a historical suspicion[7] of causing drug-induced hemolysis or had a new association in the Pharmacovigilance Database, and all were further identified using both analytical approaches in the French cohort. In addition, the study provides support for the notion of β-lactam antibiotics and ciprofloxacin and risk of immune hemolysis, previously suggested by Garbe et al.[5] An obvious caveat to the findings could arise from a confounding by, for example, low-grade lymphoma or autoimmune disease, in which both autoimmune hemolysis, treatment with an antibiotic, or other of the aforementioned drugs would be common. However, the exclusion of all potential secondary cases of autoimmune hemolytic anemia and the approach with a case-crossover design provides a high degree of protection from this pitfall.

The findings from the study by Maquet et al enable earlier and possibly more complete detection of drug-induced immune hemolysis and further new vistas in the field of pharmacovigilance, showcasing the potential of large national and international databases to unearth associations in rare clinical conditions. This approach is not confined to drug-induced hemolysis alone; it can serve as a guide for unraveling the complexities of many adverse drug reactions across a spectrum of conditions. With some modifications and enough data, it could test the association between fludarabin, low-grade lymphomas, and hemolysis, to assess whether fludarabine is a culprit or a bystander; or in a setting comparable with the present, assess the link between suspected drugs and bone marrow failure syndromes.

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