CLINICAL TRIALS AND OBSERVATIONS

Drug-induced thrombotic microangiopathy: a systematic review of published reports

Zayd L. Al-Nouri,[1] Jessica A. Reese,[1] Deirdra R. Terrell,[1] Sara K. Vesely,[1] and James N. George[1,2]

[1]Department of Biostatistics and Epidemiology, College of Public Health, and [2]Hematology-Oncology Section, Department of Medicine, College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK

Key Points

- Published data describe 78 drugs suspected of causing TMA.
- Only 22 (28%) of the 78 drugs have evidence supporting a definite causal association with TMA.

Many patients with syndromes of thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome, have been reported to have a drug-induced etiology, and many different drugs have been suspected as a cause of TMA. We established criteria to assess the strength of evidence for a causal association of a drug with TMA and systematically searched for all published reports of drug-induced TMA. We identified 1569 articles: 604 were retrieved for review, 344 reported evaluable data for 586 individual patients, 43 reported evaluable data on 46 patient groups. Seventy-eight drugs were described; 22 had evidence supporting a definite causal association with TMA. Three drugs accounted for 61 of the 104 patient reports with definite evidence (quinine, 34; cyclosporine, 15; tacrolimus, 12). Twenty additional drugs had evidence supporting a probable association with TMA. These criteria and data can provide support for clinicians evaluating patients with suspected TMA. (*Blood*. 2015;125(4):616-618)

Introduction

Syndromes of thrombotic microangiopathy (TMA), defined by microangiopathic hemolytic anemia, thrombocytopenia, and microvascular thrombosis with characteristic vessel wall abnormalities, have multiple etiologies.[1] Many patients with TMA have been reported to have a drug-induced etiology and many different drugs and other substances, including vaccines, complementary or alternative medicines, herbal remedies, beverages, toxins, and illegal substances, have been reported to cause TMA. We describe all of these substances as "drugs" and describe the syndrome as drug-induced TMA (DITMA).

The clinical features of patients reported to have DITMA suggest diverse mechanisms of adverse drug reactions.[2] Some reports suggest an idiosyncratic, acute immunologic reaction whereas others suggest a direct toxic effect, which may be either acute dose-related toxicity or chronic dose and duration-dependent toxicity. Some patients have had severe kidney injury and were described as having hemolytic-uremic syndrome (HUS); others have had minimal kidney injury and were described as thrombotic thrombocytopenic purpura (TTP). In this study, we include all potential mechanisms of adverse drug reactions and we use the term TMA to include patients described as TTP or HUS.[1]

We established criteria to assess the strength of evidence supporting a causal association of a drug with TMA and systematically identified and reviewed all published reports of DITMA. Our goal was to assist clinicians in their evaluation of patients with suspected TMA by developing standardized criteria for assessing clinical evidence.

Study design

Data sources, search strategies, article selection, and review

We searched 12 databases to identify English-language reports of patient data that described TTP, HUS, or TMA attributed to a drug or other substance (supplemental Table 1, see supplemental Data available at the *Blood* Web site). Articles were selected for review if their title or abstract suggested that they reported individual patient or group data on patients with a diagnosis of TTP, HUS, or TMA and a suspected drug etiology. All articles were reviewed independently by 2 or 3 of the authors (Z.L.A.-N., J.A.R., J.N.G.).

Mechanisms of DITMA

Two mechanisms were proposed for this study: immune-mediated reactions and dose- or duration-related toxic reactions.[1,2] Typical clinical features of an immune-mediated reaction were acute onset of symptoms following the recent initiation (defined in our criteria as within 21 days) of a drug administered daily or within hours of exposure to a drug taken intermittently (defined in our criteria as within 24 hours).[3] Clinical features of dose-related toxicity were either the acute onset of symptoms following exposure to a toxic substance or toxic dose of a drug, or the gradual development of toxicity, often manifested as kidney failure. When typical features of an immune-mediated reaction were not present, the drug was assigned to the toxicity category.

Evaluation criteria

Levels of evidence for an association of the drug with TMA (definite, probable, possible, unlikely) were determined using criteria that we adapted from our previous studies of drug-induced thrombocytopenia.[4] For individual patient reports, different criteria were established for immune-mediated and

Submitted November 10, 2014; accepted November 12, 2014. Prepublished online as *Blood* First Edition paper, November 20, 2014; DOI 10.1182/blood-2014-11-611335.

The online version of this article contains a data supplement.

The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

Table 1. Levels of evidence for drugs reported to cause TMA

Levels of evidence	Individual patient reports	Patient group reports	No. of drugs
Definite	104	0	22
Probable	55	5	20 additional drugs
Possible	363	40	27 additional drugs
Unlikely	64	1	9 additional drugs
Total	586	46	78

The 586 individual patients were reported in 344 articles. The 46 patient groups were reported in 43 articles. These 387 articles reported 78 drugs. In the column describing the number of drugs, each drug is listed only once according to its highest level of evidence. The analysis of all 387 articles is described, with their citation, in supplemental Table 3.

toxic mechanisms. For group data, assessment was based only on study design and patient outcomes (supplemental Table 2). For reports of immune-mediated reactions, a definite causal association with TMA could be established by either clinical criteria (repeated drug exposures associated with recurrent TMA or other systemic symptoms) or by laboratory criteria (documentation of drug-dependent antibodies to platelets or other cells). An important criterion was the exclusion of etiologies of TMA other than drug toxicity. ADAMTS13 deficiency was considered to be an alternative etiology of TMA and evidence against a drug association, unless drug-dependent antibody inhibition of ADAMTS13 activity was documented. When TMA was attributed to a calcineurin inhibitor following kidney transplantation, the role of the drug vs a recurrence of a TMA disorder, such as complement-mediated TMA, could only be distinguished by the clinical course following discontinuation or dose adjustment of the calcineurin inhibitor.

Results and discussion

The literature searches (conducted on March 27, 2014) identified 1569 articles: 604 articles were retrieved for review, 507 articles reported individual patient data, and 97 reported group data. Following review of the complete articles, 387 articles with evaluable data were included; they described 78 drugs as the cause of TMA. All 387 articles, with their citations, are described in supplemental Table 3.

The 344 articles reporting individual patient data described 586 patients with TMA attributed to 75 drugs. For 51 of these 75 drugs, we attributed the potential association with TMA to an immune-mediated mechanism; for 26 drugs, we attributed the association to a toxic mechanism. For 2 drugs, gemcitabine and oxaliplatin, most reports were consistent with a toxic mechanism but each of these drugs also had reports consistent with an immune-mediated mechanism. Nine (12%) of these 75 drugs (clopidogrel, cyclosporine, estrogen/progesterone, gemcitabine, interferons, mitomycin, quinine, tacrolimus, ticlopidine) accounted for 448 (76%) of these patient reports.

The 43 evaluable articles reporting group data described 46 patient groups with TMA attributed to 12 drugs, including 3 drugs which were not described in the reports of individual patients. One of the 12 drugs, cyclosporine, accounted for 20 of the 46 patient groups (43%).

Table 1 presents the levels of evidence supporting a causal association with TMA for the 78 reported drugs. Twenty-two (28%) of the 78 reported drugs had evidence supporting a definite association with TMA; for 11 of these 22 drugs there was only 1 patient report (Table 2). Among the 46 patient groups described, none had evidence for a definite causal association. Among all 586 individual patients assessed, 104 (18%) had evidence supporting a definite association with TMA. Quinine was the most common drug with evidence supporting a definite causal association with TMA, reported in 34 of the 104 patients. Quinine-dependent antibodies reactive with platelets or other cells were reported for 24 of these 34 patients; drug-dependent antibodies were not reported for any other drug. Drug-dependent inhibition of ADAMTS13 has not been reported.

Most reports of DITMA have been descriptions of previously reported drugs, and previous reports may cause diagnostic suspicion bias.[5] For example, following the initial report of TMA attributed to mitomycin in 1971,[6] there have been 61 subsequent individual patient reports of TMA attributed to mitomycin. The association with mitomycin was only possible in 54 patients, principally because it was often administered together with 5-fluorouracil. There were no reports attributing TMA to 5-fluorouracil. Similarly, of the 85 individual patients reported with TMA attributed to gemcitabine, the association was only possible in 73 patients. In one report of a patient with TMA attributed to gemcitabine, the description of his clinical course provided evidence supporting a definite, immune-mediated association of oxaliplatin with TMA.[7] In this report, gemcitabine may have been merely an innocent bystander.

For almost all drugs, the mechanism of DITMA is unknown. TMA resulting from inhibitors of vascular endothelial growth factors[8,9] has been established to involve injury to renal podocytes. TMA resulting from quinine may involve immune injury to endothelial cells.[10] Better understanding of the mechanisms of DITMA should provide a basis for better diagnosis and treatment. Currently, DITMA may often be unrecognized. Failure to recognize a drug as the cause of TMA, especially immune-mediated TMA, may have critical consequences if the patient is reexposed to the drug.

Table 2. Drugs reported to have a definite association with TMA

	Individual patient data			
	Immune		Toxic	
	Definite evidence	Probable evidence	Definite evidence	Probable evidence
Drug	No. of patients reported			
Bevacizumab	0	0	3	1
Cocaine	0	0	1	0
Cyclosporine	0	0	15	1
Docetaxel	0	0	1	0
Everolimus	0	0	1	0
Gemcitabine	1	0	4	5
Interferon α	0	0	6	0
Interferon β	0	0	3	2
Interferon polycarboxylate	0	0	1	0
Mitomycin	0	0	3	3
Muromonab-CD3	1	0	0	0
Oxaliplatin	1	1	0	0
Penicillin	1	0	0	0
Pentostatin	0	0	2	1
Quetiapine	1	0	0	0
Quinine	34	7	0	0
Sirolimus	0	0	8	1
Sulfisoxazole	1	0	0	0
Sunitinib	0	0	2	0
Tacrolimus	0	0	12	9
Trielina	1	0	0	0
Vincristine	0	0	1	0

Citations for these reports are in supplemental Table 3. There were no group data reports describing definite evidence for a causal association with TMA. In addition to the 22 drugs with reports of definite evidence, 20 additional drugs/substances were reported with probable evidence (adalimumab, bupropion, ciprofloxacin, clopidogrel, ecstasy, estrogen/progesterone drugs, famciclovir, ibuprofen, imatinib mesylate, ketorolac tromethamine, mefloquine, metronidazole, nitrofurantoin, oxymorphone, piperacillin, simvastatin, snake (*Hypnale* species) venom, tamoxifen, temafloxacin, trimethoprim/sulfamethoxazole).

Acknowledgment

This work was supported in part by the National Institute of General Medical Sciences of the National Institutes of Health, National Institute of General Medical Sciences under award number U54GM104938.

Authorship

Contribution: Z.L.A.-N. performed literature search and article review and reviewed the manuscript; J.A.R. performed literature search and article review, analyzed and organized data, and reviewed the manuscript; D.R.T. and S.K.V. created the concept for the project and the methodology of the systematic review and reviewed manuscript; and J.N.G. created the concept for the project, performed article review, analyzed and organized data, and wrote the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: James N. George, Hematology-Oncology Section, The University of Oklahoma Health Sciences Center, Room CHB 237, PO Box 26901, Oklahoma City, OK 73190; e-mail: james-george@ouhsc.edu; and Sara K. Vesely, Department of Biostatistics & Epidemiology, College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73190; e-mail: sara-vesely@ouhsc.edu.

References

1. George JN, Nester CM. Syndromes of thrombotic microangiopathy. *N Engl J Med.* 2014;371(7):654-666.
2. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet.* 2000;356(9237):1255-1259.
3. Aster RH, Bougie DW. Drug-induced immune thrombocytopenia. *N Engl J Med.* 2007;357(6):580-587.
4. George JN, Raskob GE, Shah SR, et al. Drug-induced thrombocytopenia: a systematic review of published case reports. *Ann Intern Med.* 1998;129(11):886-890.
5. Sackett DL. Bias in analytic research. *J Chronic Dis.* 1979;32(1-2):51-63.
6. Liu K, Mittelman A, Sproul EE, Elias EG. Renal toxicity in man treated with mitomycin C. *Cancer.* 1971;28(5):1314-1320.
7. Crouzet L, Edeline J, Le Du F, Boucher E, Audrain O, Raoul J-L. Haemolytic uremic syndrome and gemcitabine: jaundice is not always progression in cholangiocarcinoma. *Acta Oncol.* 2012;51(5):687-688.
8. Sartelet H, Toupance O, Lorenzato M, et al. Sirolimus-induced thrombotic microangiopathy is associated with decreased expression of vascular endothelial growth factor in kidneys. *Am J Transplant.* 2005;5(10):2441-2447.
9. Eremina V, Jefferson JA, Kowalewska J, et al. VEGF inhibition and renal thrombotic microangiopathy. *N Engl J Med.* 2008;358(11):1129-1136.
10. Glynne P, Salama A, Chaudhry A, Swirsky D, Lightstone L. Quinine-induced immune thrombocytopenic purpura followed by hemolytic uremic syndrome. *Am J Kidney Dis.* 1999;33(1):133-137.