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Drug-induced thrombotic microangiopathy: An updated systematic review, 2014-2018

To the Editor:

In 2015, we reported our systematic review of publications, 1946-March 2014, describing patients with drug-induced thrombotic microangiopathy (DITMA) and defining criteria for levels of evidence supporting a causal association of the drug with TMA. We identified 78 drugs that were reported to cause TMA; 22 of the 78 drugs had definite evidence for a causal association with TMA.¹ We also reported the DITMA experience of the Oklahoma Registry and the BloodCenter of Wisconsin.²

In March 2018, we updated our systematic review (Table S1, Supporting Information). Fifty-nine articles reported evaluable data for 111 individual patients with TMA attributed to 24 drugs; 2 articles reported group data on 3 drugs (Table S2). Twenty of the 59 articles presented data on 8 drugs (41 patients) that provided definite evidence supporting a causal association with TMA. Table 1 summarizes the data for these 8 drugs.

Opioids: oxymorphone-extended release (Opana-ER) and oxycodone-extended release (oxycontin). Nine reports described 28 patients with Opana-ER-induced TMA, all from the United States. Our previous review¹ identified only one report of Opana-ER-induced TMA. That report was the initial epidemiologic description by the Centers for Disease Control, however their data only supported a probable causal association with TMA. One of the 9 reports identified by our current

literature search described 18 episodes of TMA in 15 patients from one hospital for 14 months.³ Another report⁴ described 3 patients and definitively documented the etiology of Opana-ER-induced TMA. In 2012, extended-release oxymorphone tablets were reformulated to contain a crush resistant, insoluble inert ingredient containing high molecular weight (~7 000 000 Da) polyethylene oxide (PEO). The goal of this reformulation was to deter the intravenous abuse that involved crushing the tablets and solubilizing the oxymorphone. Hunt et al.⁴ determined that the cause of TMA was the PEO, not the oxymorphone. Their initial clue was the presence of gelatinous material that occluded the apheresis tubing during therapeutic plasma exchange. Using the same process that the patients used to solubilize Opana-ER tablets, they estimated that the patients' plasma concentration of PEO would be ~5 µg/mL. This concentration of PEO in guinea pigs recapitulated the pathologic features of TMA. PEO altered blood flow causing vessel wall shear stress and mechanical red cell damage; the intense hemolysis caused kidney injury.⁴

Oxycodone tablets were similarly reformulated with PEO to produce long-acting, tamper-resistant oxycontin, which was approved in Australia in 2014. Three reports, from Australia, 2015-2017, provided definite evidence for a causal association of oxycontin with TMA, presumably also caused by the PEO.

These data illustrate a new aspect of the global opioid epidemic. Clinicians evaluating patients with clinical features of TMA must be alert for IV opioids as a potential etiology.

Proteasome inhibitors. Recognition of proteasome inhibitors as a cause of TMA was also increased in our current review. Our previous review identified 3 reports of describing bortezomib-induced TMA, but the evidence only supported a possible or unlikely causal association.¹ In this review, there were 5 reports with definite evidence supporting a causal association for bortezomib (1 patient), carfilzomib (4 patients), and ixazomib (1 patient). The authors suggested that proteasome inhibitors as a class may have a risk for acute kidney injury with the hematologic abnormalities of TMA.⁵ Clinicians must be alert for the clinical features of TMA with the use of these 3 drugs and also the new proteasome inhibitors, marizomib, and oprozomib, currently in clinical trials.

Palbociclib, a selective inhibitor of cyclin-dependent kinases, CDK4 and CDK6, received FDA approval in 2015 for advanced ER+, HER-2-negative breast cancer. The principal previously reported adverse effects were neutropenic infections and thrombocytopenia. Our review identified the report of one patient who developed hemiparesis and fluctuating aphasia with microangiopathic hemolysis, thrombocytopenia, and acute kidney injury after 2 weeks of daily oral palbociclib. Two weeks after palbociclib was stopped, her hematocrit and platelet count recovered but her neurologic and kidney abnormalities persisted.

Intravenous immunoglobulin (IVIg). Although IVIg has been previously associated with venous thrombosis and kidney injury, these adverse effects are uncommon and may be related to specific IVIg products. The 2 patients, reported from Australia, had a failure of their kidney allografts and were treated with IVIg for BK virus infection. The patients became febrile and oliguric following the infusion; increased serum creatinine, thrombocytopenia, and anemia occurred during the next several days. Both patients had kidney biopsies

TABLE 1 Drug-induced thrombotic microangiopathy (TMA), 2014-2018: 8 drugs with definite evidence supporting a causal association with TMA that had not been previously reported with definite evidence

Drug	Patients (no.)	Comments
<i>Opioids</i>		
Oxymorphone (Opana ER)	28	9 reports, 28 patients. 1 report ³ described 18 episodes of Opana ER-induced TMA in 15 patients in one hospital for 14 months. 1 report ⁴ documented that polyethylene oxide (PEO), an inert ingredient added to Opana ER tablets to deter IV abuse, was the etiology, not the opioid.
Oxycontin	3	3 reports. Oxycodone reformulated with the addition of PEO was introduced in Australia in 2014. These 3 reports were published in 2015–2017, each describing 1 patient. The presumed etiology of TMA was PEO, the same as with Opana-ER.
<i>Proteasome inhibitors</i>		
Bortezomib	1	In this report, ⁵ only patient 3 had sufficient data for evaluation; he had recurrent TMA when bortezomib was resumed 18 months after his initial episode. 2 additional patients with TMA attributed to bortezomib were only presented in a table.
Carfilzomib	4	3 reports. In the Yui et al.'s report, ⁵ only patient 11 had sufficient data for evaluation; he had recurrent TMA twice with 2 recurrent doses of carfilzomib. Seven additional patients with TMA attributed to carfilzomib were only presented in a table.
Ixazomib	1	This patient only received one dose of ixazomib. The authors suggested that the adverse reaction manifested as TMA may be a class effect of proteasome inhibitors.
<i>Cyclin-dependent kinase (CDK4, CDK6) inhibitor</i>		
Palbociclib	1	TMA occurred after 2 weeks of daily palbociclib. The patient also received fulvestrant, which had been given continuously for the previous 3 years.
<i>Blood product</i>		
Intravenous immunoglobulin (IVIg)	2	1 report. Both patients had kidney allograft failure and BK viremia. IVIg was given to treat BK infection and facilitate immunosuppressive dose reduction. Symptoms promptly followed infusion. Authors speculated that TMA may be related to the brand of IVIg.
<i>Anticonvulsive agent</i>		
Valproic acid	1	Valproate commonly causes thrombocytopenia by dose-dependent marrow suppression. In this patient, TMA occurred during valproic acid intravenous infusion when serum levels (130-137 µg/mL) exceeded the therapeutic range (50-100 µg/mL).

Citations for all 20 reports are provided in Table S2.

documenting TMA; both recovered. The authors speculated that the TMA may be related to the specific brand of IVIg used in these 2 patients, which was different from the brand they usually used.

Valproic acid commonly causes thrombocytopenia by dose-dependent marrow suppression. This patient had received valproic acid for many years for epilepsy. Because of recurrent seizures and severe emesis, he was hospitalized and treated with IV valproic acid which reached a toxic level for 16 hours, when he suddenly developed thrombocytopenia, hemolytic anemia, and acute kidney injury. These abnormalities resolved during the following 5 days.

We previously described two mechanisms for DITMA, dose-dependent toxicity and immune (antibody-mediated) reactions.¹ The distinction between these 2 mechanisms is imprecise. For some drugs, such as Opana-ER, the mechanism for dose-dependent toxicity has been clearly defined.⁴ The distinct dose-dependent mechanisms of bevacizumab and interferons for causing TMA have also been clearly defined. The mechanisms for immune-mediated DITMA have been defined for quinine.⁶ Quinine-induced TMA is caused by enhancing antibody binding to target cells. Quinine binds to the complementarity-determining region of naturally occurring weak antibodies creating a hybrid paratope that increases their binding affinity 10 000-fold.⁶ Although drug-dependent

antibodies have been documented in many patients with quinine-induced TMA, they have documented in only two other patients: one with oxaliplatin-induced TMA and one with vancomycin-induced TMA.² The goal of our continuing systematic reviews is to increase awareness of DITMA and to identify additional drugs that can cause DITMA.

CONFLICT OF INTEREST

The authors have no conflict with this topic or these data.

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SUPPORTING INFORMATION

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Predictors of refractoriness to therapy and healthcare resource utilization in 378 patients with primary autoimmune hemolytic anemia from eight Italian reference centers

To the Editor:

Autoimmune hemolytic anemia (AIHA) is a rare and heterogeneous disease with a presentation/phenotype ranging from mild/compensated to life-threatening.^{1,2} Moreover, some cases show refractoriness to/relapse after first and further therapy lines, leading to significant and underestimated healthcare burden. Here, we retrospectively analyzed 378 primary AIHA cases (135 M and 243 F, median age 61 years, range 5-94) from eight Italian hematological centers and followed for a median of 4.3 years (range 1-27) focusing on predictors of

multiple refractoriness to second and further therapy lines and healthcare resource utilization.

Figure 1A shows clinical and laboratory characteristics of AIHA patients at onset, divided according to the serological type in warm (direct antiglobulin test-[DAT]-positive for IgG or IgG + C), cold (CAD, usually IgM driven, DAT-positive for C), mixed (both IgG and high titer cold agglutinins), and atypical forms (DAT negative, IgA only or warm IgM). Hemoglobin values were significantly lower and LDH higher in IgG + C wAIHA, mixed and atypical cases ($P < .001$ and $P = .0034$, respectively), and hemoglobin and LDH values were negatively correlated ($P < .001$). Absolute reticulocytes were reduced in CAD and mixed forms ($P = .0013$), and the reticulocyte index was lower in CAD ($P = .023$) and in cases with Hb ≤ 6 g/dL (53 vs 86 $P < .001$) (Figure 1B). Overall, inadequate reticulocytosis was observed in more than half of patients. Second therapy line was mostly administered in mixed, IgG + C wAIHA, and in CAD ($P = .011$), and the ultrarefractory cases requiring four or more lines of therapy were mainly CAD, mixed, and atypical AIHA. Infections were observed in 14% of cases, mostly wAIHA and mixed forms ($P = .02$). Thrombosis occurred in 15% mostly IgG + C wAIHA and atypical AIHA ($P = .04$). Evans' syndrome was more frequent in mixed AIHA and, to a lesser extent, in atypical ($P = .033$) and in severe forms (74% with Hb < 8 g/dL vs 26%, $P = .005$). Acute renal failure was reported in 3% of patients, with no relationship with AIHA type/Hb values.

Predictors of relapse/refractoriness were analyzed in a total of 304 relapses, of whom 211 (69%) after first-line, 69 (23%) after second-line, 19 (6%) after third-line, and 5 (2%) after further therapy lines. Multivariate Cox regression analysis demonstrated that anemia severity at onset was associated with an increased risk of relapse, with the following hazard ratios: 1.98 (95%CI 1.22-3.21) for patients with Hb ≤ 6 g/dL, 1.74 (95%CI 1.09-2.77) for cases with Hb 6.1-8 g/dL, and 1.61 (95%CI 0.99-2.62) for those with Hb 8.1-10 g/dL. Even considering hemoglobin as a continuous variable, each gram of reduction yielded a 7% greater risk of relapse (95%CI 2-13, $P < .013$). In addition, analysis showed increased hazard risks for forms other than wAIHA (1.21, 95%CI 0.95-1.54), and for Evans association (1.84, 95% CI 1.24-2.74). Notably, the presentation of an AIHA other than wAIHA together with Evans syndrome or with Hb < 8 g/dL resulted in a 2-fold higher risk of relapse; the presence of both Hb < 8 g/dL and Evans syndrome gave a 3-fold increased risk, and the association of the three conditions led to a ~4-fold increased risk of multiple relapses.

Seventy-five patients died during the follow-up, of whom 13 because of AIHA. Overall mortality was higher in more severe cases (24% for cases with Hb < 6 g/dL vs 18% for those with Hb > 6 g/dL, $P = .04$), with the following hazard risks: Evans syndrome (8, 95% CI 2.5-26, $P = .001$), acute renal failure (6.3, 95% CI 1.4-29, $P = .016$), and infections (4.8, 95% CI 1.5-15, $P = .007$). Thrombotic events did not result in increased risk of death.

Response to treatment is shown in supplementary material. In summary, ~80% of cases displayed an overall response (OR) after first line treatment with glucocorticoids, however only 25% had a sustained response. Rituximab and immunosuppressants were comparably used in second line (31% and 26%), with better responses for the former