Editorial

# Peering into the darkness of drug-induced thrombotic microangiopathy: complement, are you in there?

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Conventional management of drug-induced thrombotic microangiopathies (DI-TMAs) is centered around drug cessation and supportive care (1). This can be quite troublesome since many of these offending medications are important antineoplastic or immunosuppressive drugs that may not have equivalent alternatives (2). Furthermore, chronic kidney disease and other long-term morbidities are common after DI-TMAs, even with prompt discontinuation of the offending drug (3,4). End stage renal disease occurred in 24% of patients with gemcitabine-induced TMA in a prior study despite immediate drug stoppage (4). Outside of drug removal, there is no accepted therapy for DI-TMA and plasmapheresis does not appear to improve outcomes (5). Drug-specific antibodies have been identified for a handful of drugs, however the majority of DI-TMAs occur through unknown mechanisms (2). These challenges exemplify the significance of this treatment complication and the need for an effective therapeutic intervention. They also confirm that different types of DI-TMAs exist which means they should not all be managed in the same way.

DI-TMAs are a heterogeneous subtype of thrombotic microangiopathies (TMAs) that are categorized as immune-mediated or dose-related reactions (1,2). They historically have not been considered "complement-mediated TMAs", which traditionally include atypical hemolytic uremic syndrome (aHUS), paroxysmal nocturnal hemoglobinuria (PNH) and transplant-associated thrombotic microangiopathy (TA-TMA) (1). Pathologic complement activation in aHUS occurs sporadically or through familial complement gene mutations (6). Complement gene polymorphisms are also common in TA-TMA patients but do not universally lead to TA-TMA (7). These observations mean the "triggers" of TMA have an important role in the pathogenesis of this disease. Interestingly, calcineurin inhibitors are strongly associated with TA-TMA in multiple studies, but hematopoietic stem cell transplant (HSCT) recipients who receive calcineurin inhibitors and develop TMA are typically not categorized as DI-TMAs (rather, they are said to have TA-TMA and are therefore treated for TA-TMA) (8). This suggests that biological overlap may exist between DI-TMAs and TA-TMA, and that C5 inhibition may therefore be beneficial in DI-TMAs.

In this issue of the *Journal of Gastrointestinal Oncology*, Van den Eeckhaut *et al.* describe their successful experience with using the C5 inhibitor, eculizumab, to treat gemcitabine-induced TMA in a patient with pancreatic adenocarcinoma (9). Gemcitabine is a well-known instigator of TMA and the report by Van den Eeckhaut and colleagues adds to growing literature describing the successful use of eculizumab in gemcitabine-induced TMA (3,9-15). Grall *et al.* described 12 patients with gemcitabine-induced TMA who were treated with eculizumab and reported a complete hematological remission in 83% of patients and a higher glomerular filtration rate in eculizumab-treated patients at follow up compared to historical controls (3). In the current report, a 46-year-old male with pancreatic adenocarcinoma

presented with bleeding symptoms, laboratory evidence of hemolytic anemia and acute kidney injury, which promptly led to a diagnosis of TMA (9). DI-TMA was strongly suspected based on the patient's recent treatment history with gemcitabine as well as a normal ADAMTS13 level. Plasmapheresis, corticosteroids and N-acetylcysteine (NAC) were initially used but were not effective. The patient's kidney function continued to worsen, and dialysis was required. Eculizumab was started 18 days after the patient initially presented to the hospital and the authors report a rapid improvement in transfusion needs and eventual kidney recovery with discontinuation of dialysis.

Although most of the current literature on eculizumab therapy for gemcitabine-induced TMA is limited to observational studies or case reports, the data support a more formal investigation into the efficacy of complement blockade for gemcitabine-induced TMAs and other DI-TMAs. Rapid hematologic responses and kidney recovery after eculizumab therapy for DI-TMAs are consistently reported in the available literature, however many patients did not receive eculizumab until several weeks into their TMA course (3,10-15). In the cohort of 12 patients described by Grall and colleagues, the median time between TMA diagnosis and eculizumab therapy initiation was 15 days with a range of 4–44 days (3). Similarly, the current study reported that approval for eculizumab initiation was pursued 14 days after initial presentation and the drug was started 18 days after presentation (9). It is therefore possible that early or upfront eculizumab therapy may have further limited kidney injury and dialysis needs in these patients. This type of upfront approach should be the focus of future studies of eculizumab in this setting.

Despite growing literature on the use of C5 inhibition for DI-TMA, a few noteworthy barriers remain. First, many labs do not measure plasma sC5b-9 levels (also known as soluble membrane attack complex) which are used to quantify terminal complement activation in TA-TMA, PNH and aHUS (16,17). Elevated sC5b-9 levels in a suspected DI-TMA would support *in vivo* terminal complement activation and the use of a terminal complement inhibitor. Access to this testing must be improved to facilitate prompt therapy initiation as well as the diagnosis of a complement-mediated TMA. Second, eculizumab therapy is very expensive and this medication may not be available at smaller hospitals and/or may require a specific approval process. However, the high cost of eculizumab therapy must be compared to the potential costs of long-term dialysis, recurrent transfusions and intensive care unit needs or inpatient hospital admission duration. It is conceivable that these complications, which complement blocking therapy aims to prevent or improve, result in more healthcare-related costs than eculizumab therapy itself. Also, in current practice, DI-TMA patients commonly receive up front plasmapheresis which is both ineffective and expensive. Furthermore, unlike aHUS or PNH, patients with DI-TMA treated with eculizumab are unlikely to need life-long treatment and the median number of eculizumab doses was 4 (range, 2–22) in Grall *et al.*'s study of gemcitabine-induced TMA (3).

The third noteworthy barrier to the use of complement blockers for DI-TMA is the history and terminology of the disease itself. As described above, the majority of so-called DI-TMAs occur through an unknown mechanism and only a fraction are correlated with measurable drug antibodies (2). This is problematic because there are no widely accepted therapies for DI-TMAs outside of drug removal. Reports like the current one from Van den Eeckhaut *et al.*, suggest terminal complement activation contributes to DI-TMA (9). The role of complement in TA-TMA pathogenesis is well described and we continue to learn more about how specific extrinsic and intrinsic factors contribute to TA-TMA development (8). Medications such as calcineurin inhibitors or conditioning chemotherapy regimens with carboplatin, etoposide and melphalan are specifically associated with higher rates of TA-TMA in HSCT recipients (8,18-20). Despite this strong association with specific medications, these patients are still considered to have TA-TMA and are treated with complement-blocking therapies. It is possible that a similar biological process occurs in DI-TMAs as well, particularly those involving chemotherapy or immune modulating drugs. In fact, complement gene mutations were found in two patients who developed DI-TMA from chemotherapy (14). Complement mutations are also more common in patients who developed TA-TMA (7). TA-TMA researchers have hypothesized that TA-TMA occurs in patients who are predisposed to complement activation (e.g., have pre-existing complement gene mutations or pre-existing endothelial injury) and are subsequently exposed to specific therapies (e.g., chemotherapy) or complications (e.g., infections) that further promote complement activation and endothelial injury (21). A rational hypothesis is that a similar series of events can contribute to DI-TMA in non-HSCT patients as well.

It is therefore imperative that formal studies investigate the role of complement in DI-TMA and the efficacy of up-front complement blocking therapies. Not only is

 

this crucial from a DI-TMA therapy standpoint, but our experience with calcineurin inhibitors in TA-TMA patients is that they can be safely continued in many patients (along with appropriate complement-blocking therapy for TA-TMA) (8). Shah *et al.* recently reported that 5/7 patients with DI-TMAs from chemotherapy were able to continue chemotherapy safely with concurrent C5 inhibition (15). The combination of an effective therapy for DI-TMA and the ability to continue chemotherapy/immunomodulating therapies would have a profound impact on the clinical management of these patients and must be further studied.

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