Cellular, Tissue, and Gene Therapies Advisory Committee September 2-3, 2021 Meeting Presentation

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Clinical Findings of Thrombotic Microangiopathy (TMA)

Deepa H. Chand, MD, MHSA
Executive Medical Director, Medical Safety & Neuroscience
Novartis

Division of Pediatric Nephrology,
St. Louis Children's Hospital
Washington University School of Medicine

Disclosure

- Deepa Chand, MD, MHSA is an employee and shareholder of Novartis
- Dr. Chand is a practicing pediatric nephrologist at St. Louis Children's Hospital
- The views presented are reflective of Dr. Chand based on her clinical expertise and do not necessarily represent those of Novartis

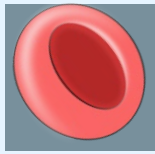
Agenda

- Introduction to TMA
- Overview of pathogenesis, and clinical course of TMA
- Clinical management of TMA
- TMA experienced after gene therapy
- Mitigation and monitoring strategies
- Research considerations
- Summary and conclusions

Definition and Incidence

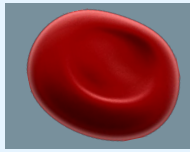
- TMA is a rare disorder
- Occurs as a result of microvascular damage

TMA Clinical Presentation



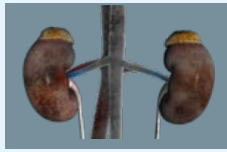
Thrombocytopenia

Platelet aggregation and consumption



Microangiopathic hemolytic anemia

Destruction of RBCs within the microvasculature



Acute kidney injury (AKI)

Possible organ dysfunction includes AKI, although any organ may be involved

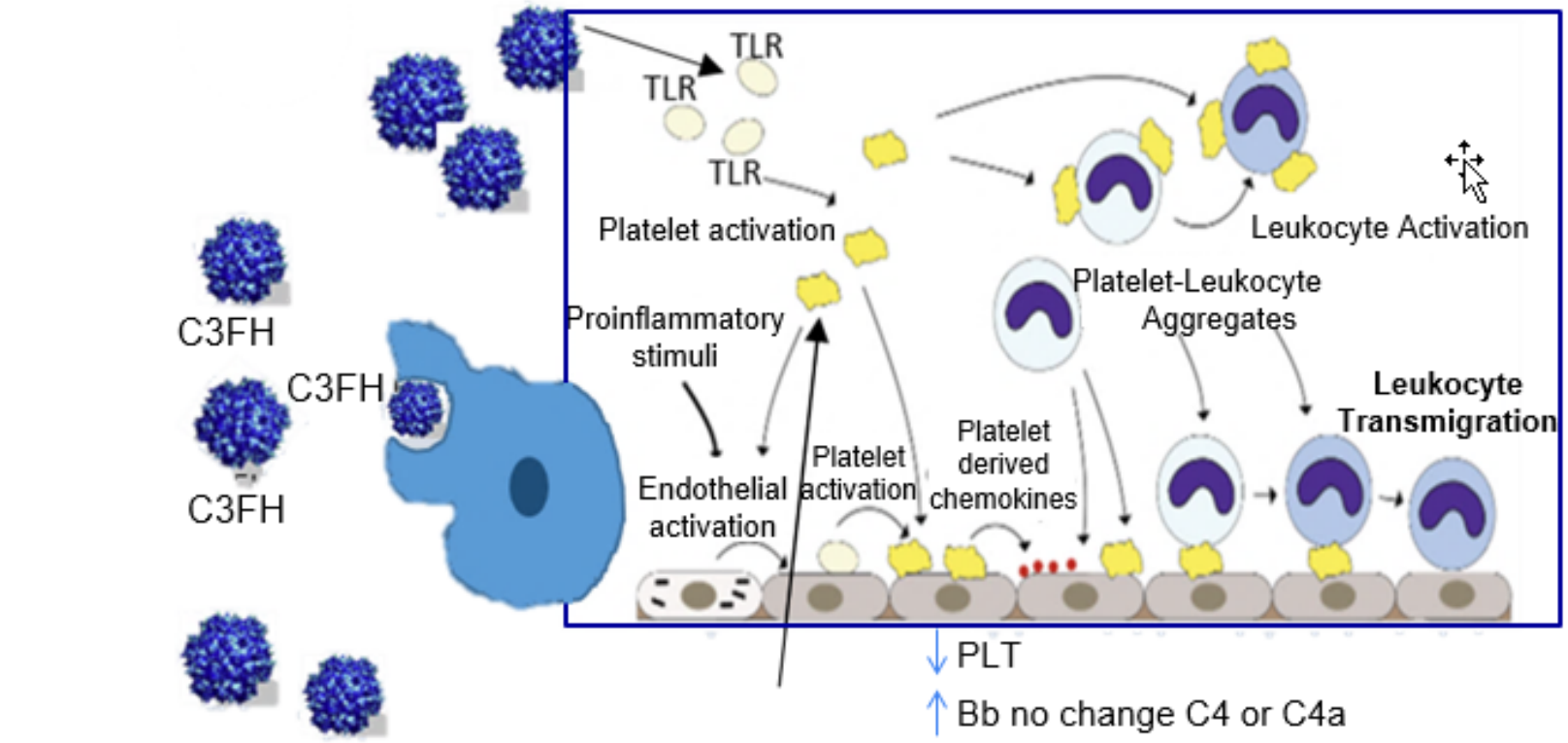
-TMA can occur in adults or children
-The occurrence in children is rare and approximates
1.0 – 3.3 cases/million/year

Pathogenesis

- Pathogenesis: endothelial injury either due to or as a result of acute and/or chronic uncontrolled dysregulation and/or excessive activation of the classical or alternative pathway of complement
- Cause(s) for dysregulation may not be evident in all situations
- Can be acquired and/or genetic
  - Acquired: Can occur in association with a wide range of viral, bacterial, fungal, and parasitic infections, although it is frequently unclear if this is a direct effect of the pathogen, or a trigger that unmasks a latent complement defect
    - Encapsulated organisms have been identified as a trigger because the capsular polysaccharide, which is a critical virulence factor, enables immune evasion
    - Can be associated with medicinal products
    - Underlying disease state may be a risk factor, predisposing to the development of TMA
      - Underlying coagulation abnormalities may be present in some disease states for which gene therapy is used
  - Genetic: Gene abnormalities resulting in uncontrolled complement activation

Complement Activation

Complement pathway activation can be a cause or result of endothelial injury



Drug-Associated TMA

- TMA has been associated with certain drugs and other substances

Potential substances reported to be associated with TMA

- Drugs and other substances, including vaccines and herbal remedies
- Better understanding of drug-associated TMA mechanisms may provide a basis for better diagnosis and treatment
- Diverse mechanisms of drug-associated TMA have been reported

Drugs associated with TMA

- In a review of 586 patients, 75 agents have been associated with TMA across a variety of drug classes

TMA, thrombotic microangiopathy; Al-Nouri ZL, et al. *Blood* 2015;125:616–618.

AAV9 Gene Therapies and TMA

- AAV based gene therapy is currently intended for monogenic disorders: e.g., Spinal Muscular Atrophy (SMA) and Duchenne Muscular Dystrophy (DMD)
- Uses a viral vector to deliver the replacement gene
- Administered as a single dose

- SMA: Onasemnogene abeparvovec (OA)
  - Only approved systemically administered AAV9-based gene therapy
  - Delivers the SMN gene to treat SMA
  - TMA is a risk that was identified based on post-marketing safety data

- DMD: SGT-001 and PF-06939926
  - Currently in clinical development
  - AAV9-based gene therapy delivering a microdystrophin for patients with DMD
  - Patients reported with AKI and thrombocytopenia, associated with TMA-like complement activation

Chand DH, Thrombotic Microangiopathy Following Onasemnogene Abeparvovec for Spinal Muscular Atrophy: A Case Series. J Pediatr. 2021;231:265-8.

Summary of TMA Cases with Gene Therapy for Spinal Muscular Atrophy

Of over 1400 patients dosed with OA, 9 cases have been reported[1]

- Time to onset: 6-12 days (commonly 7-9 days)
- Patient age at the time of dosing: 4 mo-4 years, all females
- Treatments used:
  - Fluid and electrolyte management, platelet or RBC transfusion, dialysis, plasmapheresis
  - Eculizumab (humanized monoclonal antibody that inhibits complement-mediated TMA) administered in 4/9 patients
- Outcome:
  - Recovered or improving (n=8)
  - Death due to sepsis after TMA recovery (n=1)
- Potential confounding variables:
  - Nusinersen (oligonucleotide used for the treatment of SMA, sometimes in conjunction with OA) was given in 7 of the 9 cases, which may put patient at increased risk for renal injury and thrombocytopenia as these are known adverse drug reactions
  - Concurrent infections with encapsulated organisms in 5/9 patients
  - Underlying coagulation abnormalities may be associated with SMA

1 Novartis Safety Data as of 31 Jul 2021.

Summary of TMA Cases with Gene Therapy for Duchenne Muscular Dystrophy

Of 15 patients dosed in DMD clinical trials, 4 cases of TMA have been reported
Compound: SGT-001(6 patients dosed); Compound: PF-06939926 (9 patients dosed)[1]

- Time to onset: within 2 weeks
- Patient age at the time of dosing: 7-12 years, all males
- Treatments used:
  - Fluid and electrolyte management, corticosteroids, platelet or RBC transfusion, dialysis
  - Eculizumab (humanized monoclonal antibody that inhibits complement-mediated TMA) administered in 3-4/4 patients[2]
- Outcome:
  - Recovered or improving (n=3)
- Potential confounding variables:
  - Unknown

1 Public Source Data as of November 2020; 2 treatment for 1 patient not disclosed.

Mitigation Strategies

- No known preventative measures
- Early detection of TMA is predominately based on recognition of key signs and symptoms
  - Initial presentation: fever, vomiting, hypertension, +/- decreased urine output
  - Renal involvement may range from hypertension to acute kidney injury (oliguria/anuria, edema)
  - If TMA is suspected based on clinical presentation, and in the presence of thrombocytopenia based on currently outlined laboratory monitoring, a focused diagnostic evaluation for anemia and possible renal dysfunction should be initiated
  - Consultation with a pediatric hematologist/pediatric nephrologist should be undertaken
- Product labeling should ensure appropriate monitoring and mitigation are addressed

Anticipation and early recognition are imperative to ensure the optimal clinical outcome

Limitations of Adjunct Laboratory Evaluations

- Hemoglobin: Anemia (low hemoglobin for age), can be seen in up to 20% of all children at any given point in time
  - The anemia seen in TMA is of a hemolytic nature, which would not necessarily be identified by isolated hemoglobin
- Serum creatinine: a product of creatine metabolism, released from muscle. It is not a reliable marker of renal function in SMA children due to progressive muscle weakness with resultant low muscle mass
  - Acute elevations in serum creatinine can occur from non-renal injury etiologies including intravascular volume depletion (e.g., due to vomiting, gastroenteritis, sepsis, etc.) and medications (such as cimetidine, trimethoprim, etc.)
- Lactate dehydrogenase (LDH): can be used to detect the presence of hemolysis, however, elevated LDH level is a non-specific marker of tissue damage and can be found in many different conditions other than hemolysis, including infections, iron deficiency, and inherited conditions (e.g., myopathies)

Management Considerations

Therapy must be individualized based on the clinical presentation and course

- Supportive management
    - Management of fluid/electrolytes
    - Platelet and RBC transfusion as clinically indicated (no absolute numerical threshold)
    - Management of hypertension
    - May warrant fresh frozen plasma and plasma exchange
- Genetic testing to evaluate for underlying causes
- Eculizumab
    - Used to inhibit complement-mediated TMA

Research Considerations

- Evaluate specific endothelial injury and complement pathway aberrancies
  - Exploratory biomarker evaluation in clinical trials to identify potential contributing factors

Summary and Conclusions

- Gene therapies have been developed for rare, life-threatening disorders with great potential benefit
- As with any therapy, individual patient benefit:risk should be considered
- TMA has been identified after AAV gene therapy, and pathogenesis remains unclear
- TMA is a clinical diagnosis which should be identified early through a focused diagnostic evaluation
- Consider contributing factors: disease state comorbidities (infection, coagulation abnormalities, etc.), concomitant medications, and genetic contributors
- Supportive treatment should be instituted immediately with subspecialty consultation obtained promptly
- Clinical characteristics of TMA as well as monitoring and mitigation strategies should be detailed in product labeling and patient educational materials