

Pediatric Atypical Hemolytic Uremic Syndrome Advances



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Introduction

- Atypical Hemolytic Uremic Syndrome (aHUS) is a rare form of Thrombotic Microangiopathy (TMA) caused by dysregulation of the alternate complement pathway (AP) [3].
- Characterized by a triad of thrombocytopenia, acute kidney injury (AKI), and microangiopathic hemolytic anemia [3].
- Genetic variants in complement regulatory proteins (CRPs) account for 50% to 60% of all aHUS cases with approximately 30-50% not having any known identifiable mutation [2].
- The number of therapeutic options today, all with differing mechanisms of action depending on the exact mutational-based pathophysiology.
- Assessing the pathogenesis, triggers, manifestations, and treatment options is vital as aHUS is associated with a mortality rate of 20% ad high morbidity as 48% of pediatric patients typically progress to End Stage Renal Disease (ESRD). [1,3]
- Our review sought to study the advances over the past twenty years due to multiple scientific breakthroughs.

Pathogenesis

- aHUS is characterized by overactivity in the AP and eventual activation of C5a and C5b.
- Genetic testing is recommended in patients who have at least two family members diagnosed with aHUS within the last six months as genetic abnormalities affecting complement system are present in around 60% of diagnosed aHUS patients.
- Diacylglycerol mutations associated to aHUS are particularly of interest as these are the first non-complement regulatory proteins associated with the disease.
- Triggers are required to clinical manifest the disease such as respiratory and bacterial infections, chemotherapy and systematic lupus erythematosus.[7]

Purpose

- We aimed to investigate the evolving clinical nature of aHUS in pediatrics, specifically focusing on triggers and novel therapeutic options.

Methodology

- Design** : This is a retrospective systematic review over the past twenty years on various advances in aHUS.

Results

- Various therapeutic interventions as compared to only plasma exchange/infusion and Eculizumab years back.

| | Current Therapeutics | Drug Class | Pathophysiology/ Mechanism of Action | Complement pathway proteins affected |
|----------------------|----------------------|--|--|--------------------------------------|
| Current Therapeutics | Eculizumab | Monoclonal Antibody, terminal complement inhibitor | Binds to C5 and prevents cleavage to C5a and C5b | C5a and C5b levels |
| | Ravulizumab | | Prevents the cleavage of C5 into C5a and C5b | |
| | Nomacopan | C5aR1 antagonist | Inhibits C3a, C4a, and C5a protein function | C3a, C4a, and C5a levels |
| | Avacopan | Recombinant protein derived from a tick C5 inhibitor | Inhibits C5 and leukotriene B4 | C5 and leukotriene B4 levels |
| | Cemdisiran | Short sequences of interfering RNA | Match mRNA for the C5 protein, with N-acetylgalactosamine | C5 levels |
| Biosimilars | ABP 959 | Biosimilar to FDA-licensed Eculizumab | Binds to C5 and prevents cleavage to C5a and C5b | C5a and C5b levels |
| | Elizaria | Russian biosimilar to Eculizumab | Binds to C5 and prevents cleavage to C5a and C5b | |
| Future Therapeutics | ALXN1720 | Anti-C5 mini body | Binds to C5 protein and blocks its activation | C5 levels |
| | Pozelimab | C5 antibody | Decrease hemolysis and C5 level | |
| | Tesidolumab | C5 monoclonal IgG1 antibody | Binds to C5 preventing its cleavage | C5a and C5b levels |
| | Crovalimab | Binds to a C5 epitope | Binds to C5b and prevents the formation of the MAC complex | C5a, C5b, and MAC complex proteins |
| | IFX-1 | Targets C5a protein directly | Binds to C5a | C5a levels |
| | Zilucoplan | Binds to the C5b protein & the C5b part of C5 | Inhibits C5b binding on C5 by binding to its C5 domain | C5b levels |
| | Avacincaptad Pegol | Binds to and inhibits the C5 protein | Prevents cleavage of C5 | C5 levels |
| | Avdoralimab | Anti-C5aR1 antibody | Blocks T-cell and natural killer cell activity through C5aR1 suppression | C5aR1 levels |
| | MAC Inhibitor HMR59 | Promotes CD59 production | Enhances synthesis of CD59, which blocks C5b-9 formation | C5b-9 formation |

Discussion

- aHUS induces multiple organ damage due to ischemia downstream occluded blood vessels resulting in extrarenal manifestations. [56,57]
- Recent reports emphasize the relationship of anti-complement factor H antibodies, anti-complement factor I autoantibodies and diacylglycerol kinase epsilon with aHUS.

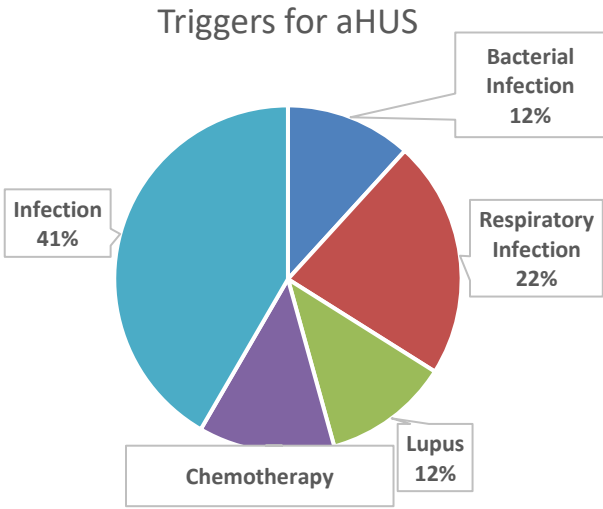


Figure 1: Potential triggering conditions in aHUS [Tomazos et al.]

- Emerging studies support a bidirectional relationship between aHUS and COVID-19 due to similar underlying complement pathophysiology.COVID-19 is postulated to be a trigger for the manifestation of aHUS in the presence of pathogenic CFH variants.
- Several cases showed possible correlation of hepatitis B vaccine to the development of aHUS symptoms. [5,6]

Conclusion

- Interventional therapeutics have seen the most advancements as pharmacokinetic and pharmacodynamic properties are modified as needed as well as their biosimilar counterparts or more cutting-edge successors.
- Advances in the diagnosis and management of aHUS will continue to drive down the mortality and morbidity rate, especially in pediatrics.

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