INTRODUCTION

- The complement system is an enzymatic cascade of more than 30 proteins that is activated via the classical pathway (CP), lectin pathway (LP), or alternative pathway (AP) upon recognition of bacterial surface antigens.
- Treatment of complement-associated disorders with complement inhibitors is a highly promising approach and efficacy has been proven clinically for PNH. However, breach of complement innate immunity can be accompanied by increased risk of bacterial infections.
- Recent studies have demonstrated that treatment with the terminal complement inhibitor eculizumab (a humanized monoclonal antibody) brings a thousand-fold elevated risk of Neisseria meningitidis (Nm) infection (1). Vaccination against Nm is required for eculizumab recipients, yet infection remains a risk in immunized individuals (2).
- Eculizumab was reported to inhibit killing of encapsulated Nm serogroups B and C in an in vitro study with whole blood from vaccinated donors, as well as in serum bactericidal activity against nongroupable Nm; whereas the selective AP inhibitor danicopan (ACH-4471) had much less inhibitory effect (2-3).
- Comstatin is a complement C3 inhibitor and can block activation of all three complement pathways. While comstatin-derived inhibitors are currently in clinical studies, the likelihood of increased infection risk associated with use of such inhibitors has not been assessed.
- In this study, we assessed the effects of complement inhibitors on serum bactericidal activity against encapsulated Nm isolates of serogroups B, C, W and Y.

OBJECTIVES

- Comparative evaluation of bactericidal activity of compounds danicopan (factor D inhibitor), comstatin (C3 inhibitor) and eculizumab (C5 inhibitor) against encapsulated Nm isolates of serogroups B, C, W and Y.
- The aim of this study is to provide the first assessment of the relative infection risks of danicopan, comstatin and eculizumab.

METHODS

- Reagents: Pre-vaccination and post-vaccination of both CMV-4 vaccine and Merck® vaccine serum from healthy donors were obtained following informed consent. Complement factor-depleted human serum, and GVB™ buffer were purchased from Complement Technology, Inc. (Tyler, Texas USA). Neisseria meningitidis (Nm) serogroup B (strains H44/76 and NZ88/254), serogroup C (strain 2443), serogroup W (strain M9262), and serogroup Y (Z6434 or 860800) were gifts from Dr. Dan M. Granoff. Danicopan was synthesized at Achillion Pharmaceuticals. Eculizumab solution was a gift from Dr. Dan M. Granoff. Comstatin was purchased from TOCRIS. Nm was grown in Frantz Medium as described earlier (3).
- Serum Bactericidal activity (SBA): Briefly, human serum (20%, final conc.) from pre-vaccination and post-vaccination donors were pre-incubated with either danicopan (1 μM), comstatin (10 mM) or eculizumab (50 μg/ml) for 10 minutes. Nm was added and reactions were incubated at 37°C for 60 minutes. Colony forming units were quantitated following overnight growth on chocolate agar plates. Heat-inactivated (56°C, 30 min) pooled human serum were used as control serum. SBA was defined as positive when bacterial viability is less than 50% of the control.
- Serum Bactericidal activity against Nm is primarily mediated by CP. AP appears to be involved in clearing Nm when there is insufficient antibody-titer.
- AP inhibition by danicopan partially compromised SBA in pre-vaccination serum, but did not alter SBA potency in post-vaccination serum.
- Danicopan showed a comparative advantage over comstatin and eculizumab in SBA of donor 3 serum against the 5 Nm isolates.
- Oral FD inhibitor such as danicopan and potentially the second generation inhibitor ACH-5228 may present a lower risk of infection to encapsulated Nm than C3 or C5 inhibitors when sufficient anti-Nm antibody titer is present.

CONCLUSIONS

REFERENCES


17th European Meeting on Complement in Human Diseases, Sep 14-17, 2019, Madrid, Spain