Aquaporumab: An Anti-Aquaporin-4 Monoclonal Antibody Blocker Therapy for Neuromyelitis Optica

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Introduction:
Neuromyelitis optica (NMO) is an inflammatory demyelinating disease that predominantly affects the optic nerves and spinal cord. Circulating autoantibodies (NMO-IgG) against the astrocyte water channel aquaporin-4 (AQP4) cause complement- and cell-mediated astrocyte damage with consequent neuroinflammation and demyelination. Within five years of diagnosis, more than 50% of individuals are visually impaired or require ambulatory assistance. Current NMO therapies include non-specific prophylactic immunosuppression and plasma exchange for acute exacerbations.

Methods:
We engineered non-pathogenic recombinant monoclonal anti-AQP4 antibodies ('aquaporumab') to selectively block NMO-IgG binding to AQP4 in the absence of effector function. Aquaporumab comprises a tight-binding anti-AQP4 Fab and a mutated Fc that lacks functionality for complement- and cell-mediated cytotoxicity. Aquaporumab was tested for its ability to block NMO-IgG-mediated cytotoxicity in vitro, ex vivo, and in vivo using cell culture, spinal cord explant, and animal models.

Results:
Aquaporumab significantly blocked NMO-IgG induced cytotoxicity in vitro. In AQP4-expressing cell cultures, aquaporumab inhibited complement-mediated cytotoxicity by 90% (P < 0.001) and cell-mediated cytotoxicity by 84% (P < 0.001). In an ex vivo spinal cord explant model, aquaporumab markedly reduced NMO-IgG-mediated astrocyte loss and demyelination. Last, in an in vivo mouse model, blocking antibody significantly reduced NMO-IgG mediated AQP4 and myelin loss (P < 0.01).

Conclusion:
The efficacy of aquaporumab blocking antibody supports a primary role of NMO-IgG in disease pathogenesis and introduces the possibility of targeted therapy for acute and prophylactic treatment. Blocker therapy to prevent binding of pathogenic autoantibodies to their targets may be useful for the treatment of other autoimmune diseases.

References:

Key Words: Neuromyelitis optica, aquaporin-4, therapy, monoclonal antibody

Financial Disclosure: Jeffrey Bennett has filed for intellectual property on aquaporumab therapy. Alan Verkman has filed for intellectual property on aquaporumab therapy. The remaining authors had no disclosures.