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MENINGOCOCCAL VACCINATION IN IMMUNODEFICIENCY – IS A TARGETED APPROACH SUFFICIENT?

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INTRODUCTION

- Immunodeficiency is associated with increased risk for meningococcal disease (MD).
- A hallmark of inherited deficiencies in complement pathway proteins is an increased risk for MD including repeated episodes.[1]
- The UK Joint Committee on Vaccination and Immunisation (JCVI) interim position statement recommends meningococcal ACWY conjugate and meningococcal B vaccines for children and adults with immunodeficiency[2,3] such as asplenia, splenic dysfunction or complement deficiency – conditions that may be inherited as well as acquired.

METHODS

- We reviewed literature on MD and immunodeficiency.

CONCLUSIONS

- **Patients with inherited and acquired immunodeficiencies, including patients treated with eculizumab, are susceptible to (recurrent) meningococcal infections.**
- **This increased risk for meningococcal infection poses a significant health risk to these patients and their contacts.**
- **Although the JCVI's interim position recommends to receive meningococcal vaccine,**
  - **Because the first manifestation of an immunodeficiency may be an episode of MD, such patients may only receive meningococcal vaccination after the first episode of MD.**
  - **The effectiveness of vaccination has not been demonstrated clinically and protection against disease may be limited by the individuals' specific complement deficiency.**
- **Protecting individuals with immunodeficiency indirectly, by herd effects achieved through universal and catch up vaccination programmes, may be the most effective means to protect these cohorts, as well as infants who cannot be vaccinated early enough in life to achieve direct protection.**
- **Analysis of a few of the rare, non-B strains isolated from immunocompromised patients indicates a degree of homology with certain meningococcal serogroup B vaccine (Bexsero®, Novartis Vaccines and Diagnostics) antigens, and additional investigation to uncover potential coverage is warranted.**

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RESULTS

- Complement deficiency is difficult to detect and the first indication may be an episode of MD caused by any serogroup, including those rarely seen in healthy individuals.[4]
  - Deficiencies of complement system components C1q/r/s, C3–9 and Factors B, D and I have been associated with meningococcal disease. [5,6]
  - In a recent study conducted in South Africa, DNA samples of 109 patients with culture-confirmed MD were tested for C5 and C6 deficiency and 12.8% tested positive (C5, 2.7%; C6, 15.2%) whereas, based on a preliminary survey of C5 genetic defects in South African infants, the expected frequency is from 1/1,111 to 1/22,500.[7]
  - In a study conducted in the Netherlands, 46 patients > 10 years of age who developed MD due to uncommon serogroups (X, Y, Z, W-135, 29E) were retrospectively investigated for complement deficiency. Complement deficiency was found in 50% of patients: C3 deficiency syndromes (n = 5), homozygous deficiency of a terminal component (C5, C6, C7, or C8; n = 9), and properdin deficiency (n = 9). MD recurred in >50% (5 of 9) of patients with terminal complement component deficiency.[8]
  - The risk of MD in patients with terminal complement deficiency is 7,000–10,000-fold higher than in the general population.[9]
  - Recurrent MD has been observed in 50–60% of patients with terminal complement deficiency – this risk is 100–150-fold higher than in the general population.[9]
  - MD due to meningococcal serogroups W-135 and Y is particularly common in terminal complement component deficiency and properdin deficiency.[4,8]
  - A recent case study described a deficiency in complement factor B in a 32 year old woman who had experienced 4 clinically significant pneumococcal and meningococcal infections in her lifetime. The condition was identified after the most recent infection required prolonged admission to the intensive care unit for type 1 respiratory failure. Upon recovery she received a quadrivalent meningococcal vaccine, a 23-valent pneumococcal polysaccharide vaccine and continuous prophylactic amoxicillin and had not had further severe infections.[10]
- Treatment with the monoclonal antibody eculizumab[11], a targeted complement inhibitor (to the C5 complement protein), and illnesses such as membranous glomerulonephritis, increase the risk of MD.[12,13]
  - **Figure 1** shows the black box warning that appears on the package insert for eculizumab (Soliris®; Alexion Pharmaceuticals), warning patients of risk for serious meningococcal infections.

Figure 1. Black box warning for eculizumab (Soliris®; Alexion Pharmaceuticals).

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS
See full prescribing information for complete boxed warning
Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early.

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies
- Immunize patients with a meningococcal vaccine at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risks of developing a meningococcal infection. (See *Serious Meningococcal Infections* for additional guidance on the management of the risk of meningococcal infection.)
- Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS prescribers must enroll in the program. Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747).

  - In a study performed in the UK, among 153 patients treated with Eculizumab (for paroxysmal nocturnal haemoglobinuria) over a 10 year period, 3 patients developed invasive MD, a rate of 0.6 per 100 patient years on therapy.[12]
  - Membranous glomerulonephritis has been associated with low levels of C3 and development of MD.[6,14]
- In a large scale retrospective study the incidence and mortality due to infections (and other conditions) was assessed in 8,149 cancer-free hospitalized U.S. veterans who had undergone splenectomy with a follow-up of ≤ 27 years. An increased risk of hospitalization was observed for pneumonia, meningitis, and septicaemia infections (rate ratios=1.9–3.4) and the risk of death due to pneumonia and septicaemia was increased (rate ratio =1.6–3.0).[15]
- Estimates for the number of patients over the age of 6 months in the UK with splenic hypofunction conditions are: sickle cell disease 12,500, splenectomy 55,000, coeliac disease 70,000, ulcerative colitis 120,000, eculizumab treatment unknown.

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