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Letter to the Editor

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Response to: Eculizumab package insert recommendations for meningococcal vaccinations: call for clarity and a targeted approach for use of the drug in neuromyelitis optica spectrum disorder

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Dear Editor,

We thank Avasarala et al. for their editorial on meningococcal infection prevention in patients with neuromyelitis optica spectrum disorder (NMOSD) receiving eculizumab.[1] While we appreciate the authors' concerns and agree that its manufacturers (Alexion) have a responsibility to promote optimal patient safety, it is critical that clinicians treating patients with eculizumab adhere to the latest vaccination recommendations, consider individual risk profiles, and monitor patients for early signs of meningococcal disease.

The authors suggest that Alexion should determine which meningococcal vaccine should be used for patients receiving eculizumab; however, it would be inappropriate for Alexion to promote another manufacturer's product. The Advisory Committee on Immunization Practices (ACIP; part of the Centers for Disease Control and Prevention [CDC]) does not make recommendations on which vaccine is preferred in this setting, and therefore it is the prescribing clinician's decision as to which vaccine they decide is best and available for the individual needs of their patient.

The authors mention that clinicians are referred to external vaccination recommendations in the prescribing information rather than to the Risk Evaluation and Mitigation Strategy Prescriber Safety Brochure or a schedule provided in the package insert. While this may be burdensome for clinicians, no manufacturer can produce unilateral recommendations in the package insert; thus, it is appropriate to consult the ACIP's recommendations.

Also, if clinicians were directed to the particular vaccination recommendations used during the phase 3 Prevention of Recurrent Episodes of Depression with Venlafaxine for Two Years (PREVENT) study, which the Food and Drug Administration used to approve eculizumab, they would be directed to a potentially outdated source, because ACIP recommendations have since been updated.

Multiple vaccination recommendations can be confusing, and references may become redundant with new findings. Use of the ACIP's recommendations ensures that best practice is up to date. Clinicians should be referred to the most recent vaccination schedules, given the potential for new vaccine development. The ACIP has recently updated their recommendations on meningococcal serogroup B booster schedules.[2]

The authors state that there was no clear meningococcal vaccination protocol used for PREVENT.[1] This is incorrect. Patients in the United States included in PREVENT were vaccinated according to the ACIP recommendations available at the time, receiving meningococcal vaccination ≥2 weeks before their first dose of eculizumab or treatment with appropriate antibiotics until 2 weeks after vaccination. Moreover, rituximab was discontinued 3 months before PREVENT, owing to its impact on vaccine efficacy and incompatibility with eculizumab.[1] Patients enrolled in PREVENT could use other concomitant immunotherapies throughout the study, which may have impacted meningococcal vaccine efficacy.

For clarity, Alexion provides clinicians with these vaccination recommendations for patients aged ≥19 years with NMOSD receiving eculizumab.

The authors provided a figure summarizing the serogroups most commonly responsible for meningococcal infection in the United States. While interesting, serogroup distribution trends for the general United States population may not apply to patients in other countries, or to patients with complement disorders who are receiving immunomodulatory drugs.

The authors cite published data for 16 eculizumab-treated patients with invasive meningococcal disease, of whom 11 were infected with nonencapsulated strains. As current meningococcal vaccines are directed against serogroups ACWY and B, which are encapsulated strains, it is

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Vaccine type	Primary vaccination[2]	Booster/revaccination[2,3]
MenACWY *Menactra*® ***OR*** *Menveo*®	• Administer two doses ≥2 mo apart	• Revaccinate every 5 y as long as an increased risk of meningococcal infection persists
MenB *Bexsero*® ***OR*** *Trumenba*®	• Options based upon vaccine brand MenB o MenB-4C (Bexsero®): two doses ≥1 mo apart ***OR*** o MenB-FHbp (Trumenba®): three doses (at 0, 1–2, and 6 mo); if dose 2 was administered ≥6 mo after dose 1, dose 3 is not needed Note: MenB-4C and MenB-FHbp are not interchangeable (use same product for all doses in the vaccination series)	• One dose of MenB booster 1 y after primary series, revaccinate every 2–3 y if an increased risk of infection remains

Additional recommendations	
Scenario	Recommendations
Urgent treatment in unvaccinated patients	• Administer vaccine(s) as soon as possible • Provide 2 wk of antibiotic prophylaxis
Antibiotic use	• Make antibiotic choices in conjunction with infectious disease consultations
Meningococcal infection risk	• Vaccination reduces, but does not eliminate, the risk of meningococcal infections

Abbreviations: MenACWY, meningococcus serogroups ACWY; MenB, meningococcus serogroup B; FHbp, Factor H binding protein.

unlikely that these infections would have been prevented by vaccination.[4] In the context of 53,798 estimated patient-years (PY) of eculizumab exposure spanning 13 years of treatment since eculizumab was approved in 2007 for paroxysmal nocturnal hemoglobinuria (PNH), a total of 16 cases of meningococcal infection, identified by the CDC between 2008 and 2016, is low (data are derived from a Periodic Benefit–Risk Evaluation Report from October 2019).

A recent pharmacovigilance study compiled over 10 years of eculizumab use (equivalent to 28 517.7 PY) between March 2007 and October 2016 found a consistent safety profile for eculizumab in the treatment of PNH and atypical hemolytic uremic syndrome.[5] These data showed that meningococcal infection rates (0.25 per 100 PY) for patients treated with eculizumab were higher than those observed in the general population. Importantly, the meningococcal-related fatality rate in patients receiving eculizumab (10.5%) was slightly higher than that in the general population (8.6%), and rates of meningococcal infection decreased from 0.57 to 0.16 per 100 PY between 2007 and 2016.[5] While these data are for eculizumab use in indications other than NMOSD, they provide insight into meningococcal infections in patients receiving eculizumab for serious diseases with complement involvement. These findings suggest that the vigilance strategy of timely and intense intervention at the first indication of meningococcal infection, currently employed by clinicians, is successful.[5]

Last, the authors suggest that patients with NMOSD should be stratified based on C5 activation and membrane attack complex disposition. Unfortunately, there are presently insufficient data to support this recommendation. Instead, we support the notion that identification and management of infection, as well as vaccination, protect patients with NMOSD receiving eculizumab.

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