Guidelines for the prevention of meningococcal disease in adult patients receiving eculizumab for the treatment of atypical haemolytic uraemic syndrome

Summary of recommendations

1. All patients receiving eculizumab should be vaccinated with both a tetravalent A, C, W and Y conjugated vaccine and the multi component serogroup B vaccine Bexsero. In addition we recommend that all patients should receive prophylactic antibiotics as soon as they start eculizumab which they should remain on as long as they are on eculizumab. We would recommend two weeks of Ciprofloxacin 500mg bd (or adjusted dose in children) followed by long-term prophylactic penicillin (Pencillin V) or erythromycin (if penicillin allergic).

2. Antibody titres should be tested at 4-6 weeks post-vaccination. A serum sample should be sent to the Manchester Medical Microbiology Partnership for meningococcal A, B, C, W and Y serum bactericidal antibody. Local microbiology laboratories will be able to organise this. Patients with a sub-optimal response should be re-vaccinated.

3. No further vaccination should be given if a sub-optimal response is seen after 2 doses of vaccine.

4. In responders antibody titres should be measured at yearly intervals following initial vaccination and revaccinated if titres fall.

5. Patients should continue with prophylactic antibiotics whilst on eculizumab.

6. Throat swabs should be taken to check meningococcal carriage and exclude antibiotic resistance.

7. Patients with aHUS should be vaccinated when they are listed for transplantation and antibody titres checked at 4-6 weeks post-vaccination.
**Background**

*Neisseria meningitides* causes a serious, life threatening infection. It is most prevalent in neonates, young children and young adults, but can occur at any age. Recurrent, life threatening infection is seen in patients with inherited deficiency in the terminal pathway. It is also more prevalent in patients with acquired deficiency in the terminal pathway induced by treatment with the anti-C5 monoclonal antibody eculizumab. Therefore these guidelines have been developed to prevent meningococcal disease in patients receiving eculizumab for the prevention or treatment of atypical haemolytic uraemic syndrome (aHUS).

Five serogroups of meningococcus cause disease in man, A, B, C, W and Y. There is a geographical variation in the prevalence of these serotypes and this has been further influenced by the introduction of routine vaccination. Prior to the introduction of routine vaccination meningococcal serogroup B was the commonest infection, followed by serogroup C. The currently available tetravalent vaccines do not protect against serogroup B, but have led to a significant reduction in infections form the other serogroups. Therefore serogroup B now causes over 80% of meningococcal infection in the UK. This pattern of infection is not seen in other countries.

**Vaccination against Neisseria meningitides**

The conjugated tetravalent meningococcal vaccines, Menveo (Novartis) and Nimenrix (GSK) provide protection against the serogroups A, C, W and Y. These vaccines differ in their formulation but are otherwise equivalent. They reduce the risk of meningococcal infection (A, C, W and Y) but do not provide complete protection.

A multi component serogroup B vaccine, Bexsero (Novartis), is now also available. This is a two dose vaccine with a one to two month interval between doses depending on age. Like the tetravalent meningococcal vaccines it may not provide complete protection against infection with group B strains. A summary of the product characteristics for Bexsero is available [here](#).

**Recommendations**

1. All patients receiving eculizumab should be vaccinated with both a tetravalent A, C, W and Y conjugated vaccine and the multi component serogroup B vaccine Bexsero. In addition we recommend that all patients should receive prophylactic antibiotics as soon as they start eculizumab which they should remain on as long as they are on eculizumab. We would recommend two weeks of Ciprofloxacin 500mg bd (or adjusted dose in children) followed by long-term prophylactic penicillin (Pencillin V) or erythromycin (if penicillin allergic).

Meningococcal disease is more common in patients who are treated with eculizumab. The available tetravalent vaccines provide protection against serogroups A, C, W and Y. The multi component serogroup B vaccine Bexsero provides protection against serogroup B. All patients receiving eculizumab must be vaccinated and evidence of vaccination provided. In some instances treatment with eculizumab cannot be delayed to allow immunity to develop but these patients will be covered by the prophylactic antibiotics.

2 Antibody titres should be tested at 4-6 weeks post-vaccination. A serum sample should be sent to the Manchester Medical Microbiology Partnership
for meningococcal A, B, C, W and Y serum bactericidal antibody. Local microbiology laboratories will be able to organise this. Patients with a sub-optimal response should be re-vaccinated.

The response rate varies with age with reduced responsiveness reported in young children (<5 years). In adults response rates of >85% are reported. There is no data on the response rate to meningococcal vaccination in patients with CKD or after transplantation. However, the response rate to other vaccines is lower in patients with advanced CKD and after transplantation (Duchini et al., 2003). Therefore confirmation of a protective response is recommended.

3 No further vaccination should be given if a sub-optimal response is seen after 2 doses of vaccine.

These patients are unlikely to respond to further vaccination. There is some data that repeated administration of vaccine may induce a state of hyporesponsiveness.

4 In responders antibody titres should be measured at yearly intervals following initial vaccination and revaccinated if necessary

Although early response rates are high in the general population there is a gradual waning of bactericidal titres. Therefore titres should be monitored and patients vaccinated again if titres fall.

5 Patients should continue with prophylactic antibiotics whilst on eculizumab.

It is not clear whether the response to vaccination in aHUS patients will be as strong or offer the same level of protection as it does in the general population. Moreover, the efficacy of vaccines depends in part on the activity of complement. In a patient receiving eculizumab, with blockade of terminal complement pathway activity, the efficacy of vaccination may only be due to opsonophagocytosis. Thus, even in the presence of an adequate response to vaccination it is recommended that all aHUS patients being treated with eculizumab receive long-term prophylactic antibiotics. This will usually be with Penicillin V or erythromycin, if intolerant of or allergic to penicillin. If neither antibiotic is suitable the choice of antibiotic should be based on microbiological advice.

6 Throat swabs should be taken to check meningococcal carriage and exclude antibiotic resistance

The highest rate of meningococcal carriage is seen in young adults, with over 20% asymptomatic carriage (Christensen et al., 2010). Penicillin resistance is rare but should be excluded before long-term prophylaxis is given.

7 Patients with aHUS should be vaccinated when they are listed for transplantation and antibody titres checked at 4-6 weeks.
There is limited data on the effect of immunosuppressive drugs on the response to meningococcal vaccination but responses may be reduced. It is therefore recommended that vaccination takes place as soon as the patient is listed for transplantation.
