Review

What Nephrologists Should Know About Infection Prevention Measures Before and During Eculizumab Administration in Children?

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Eculizumab is a recombinant humanized monoclonal antibody that acts as a terminal complement inhibitor. It works by binding to complement protein 5 and inhibiting its cleavage, thereby preventing the production of the complement terminal complex known as C5b-9. Eculizumab has been prescribed by physicians in Iran in both the adult and pediatric fields for the treatment of various diseases. Patients who receive this product are at an increased risk of life-threatening infections, with meningococcal disease being one of the most prevalent threats. Therefore, children receiving eculizumab, should receive meningococcal vaccine. Furthermore, the most effective method to prevent infection in these patients is a combination of vaccination and prophylactic antibiotic usage. Antibiotic prophylaxis should be initiated immediately after the initiation of eculizumab and continued for four weeks after discontinuation of the drug.

This review aims to address physicians' questions particularly pediatric nephrologists regarding any necessary changes in routine vaccinations for children receiving eculizumab. Additionally, the article discusses infections that may occur more frequently in this population and emphasizes the importance of vaccination and preventive measures. The review also aims to introduce the most up- to- date recommendations for infection prevention before and during eculizumab treatment.

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INTRODUCTION

Eculizumab, is a monoclonal antibody that inhibits the terminal complement pathway, and is used to treat various diseases in both pediatric and adult patients. Some of these diseases include paroxysmal nocturnal hemoglobinuria (PNH), refractory generalized myasthenia gravis, neuromyelitis optica spectrum disorder and atypical hemolytic uremic syndrome.[1,2] Additionally, it is used to prevent delayed graft function in solid organ transplantation.[3]

Its target is the complement protein C5, and by binding to this protein, it prevents the activation of a complement terminal complex named C5b-9 which is the cause of several autoimmune conditions.[4]

Eculizumab received food and drug administration (FDA) approval for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) on March 16, 2007[4,5] and in 2011 the FDA approved its use in the treatment of atypical hemolytic uremic syndrome -associated thrombotic microangiopathy.[5]

Patients receiving this medication require frequent dosing, usually every 2 weeks,[6] and are at an increased risk of life-threatening infections

from various microorganisms especially Neisseria species, such as invasive meningococcal infection.[1] The risk may increase by 600 to 2000 times more than normal.[7] Eculizumab may also increase the risk of infection with uncommon serogroups (e.g., Y and W) as well as more common serogroups (including B or C) of *Neisseria meningitidis*. It should be noted that the risk of other bacterial infections such as *Neisseria gonorrhea*, although more prevalent in adults, may also be increased in sexually active, high-risk teenagers.[1,3]

Eculizumab has been used in Iran for some time by specialist physicians; however, due to its limited use, it is important for clinicians to enhance their knowledge about it. This article reviews the latest recommendations for infection prevention prior to and during the administration of Eculizumab. The main goals of this article are to provide information about important changes in the vaccination schedule for patients receiving eculizumab, particularly children, and to emphasize the importance of including the meningococcal vaccine in the vaccination program for these individuals. Currently, meningococcal vaccine is not included in Iran's National Immunization Program (NIP) for the general population.[8] This review aims to provide a local guideline for pediatric nephrologists and other relevant pediatric subspecialists on the use of this vaccine in Iran. It may serve as a preliminary instruction for developing a comprehensive vaccination guideline for individuals who receive eculizumab in Iran.

SEARCH METHODS

This review study conducted a search on documents published between March 2007 and March 2023 to retrieve relevant studies for preparing a narrative review article. The following databases and resources were searched: Google Scholar, Cochrane Library, and PubMed. The terms "Eculizumab and infection", "Eculizumab and infection prevention", "Eculizumab and vaccine", "Eculizumab and pregnancy" and "Eculizumab and lactation" were searched. Additionally, UpToDate, the last edition of the Red Book, and the Schedule and Guideline of Immunization published by the National Immunization Technical Advisory Group of the Ministry of Health and Medical Education of Iran (last revised in 2015) were reviewed. The Blue Book of Vaccination, a supplement to Iran's immunization guideline, was also reviewed. The study included research focusing on infections caused by eculizumab therapy, as well as studies providing data on infection prevention measures related to eculizumab therapy in the English language. The author excluded animal studies and articles studying complement inhibitors other than eculizumab. Additionally, articles published in languages other than English or outside the selected date range were excluded. Letter to the editor and editorials were also excluded. The author evaluated the relevance of the studies to the scope of the study. Papers meeting the following criteria were selected: academic papers that had undergone rigorous peer review by experts in the field, ensuring their quality and credibility, and followed established standards of medical care related to the administration and use of eculizumab therapy. The reference lists of related articles were also examined to identify relevant studies.

It should be noted that reference number 6 has not yet been approved by the NHS Trust. Currently, there are no official guidelines available for vaccinating patients under 18 years old who are undergoing eculizumab treatment.

GENERAL POINTS

Eculizumab should not be used during an active infection if possible and its administration should be delayed until the infection is resolved.[3] Children receiving eculizumab should be vaccinated according to Iran's Expanded Program on Immunization (EPI) if they are eligible and have no other contraindications. In addition to the vaccines included in the EPI, patients on eculizumab should also receive meningococcal[9] and pneumococcal vaccines if they have not already received them.

Despite being vaccinated, children on eculizumab are at high risk for certain significant infections particularly meningococcal infection. Therefore, antibiotic prophylaxis is recommended alongside vaccination to reduce the risk of infection.

If the patient has not already received meningococcal vaccines, the best time for vaccination is two weeks before the administration of the first dose of eculizumab.[1] However, if urgent treatment is needed and there is not enough time between vaccination and eculizumab administration, the patient should receive the meningococcal vaccine as soon as possible. Although vaccination decreases

the risk of meningococcal infection, it does not reduce the risk to zero.[1] The risk remains high throughout treatment and for a minimum of two half-lives following the final dose of the drug.[1] It is important to educate parents regarding the signs and symptoms of meningococcal infections and to prepare a safety card for them.[6]

INFECTIONS WITH MICROORGANISMS OTHER THAN MENINGOCOCCUS *SPPS.* DURING ECULIZUMAB THERAPY

Neisseria gonorrhoea

Disseminated gonococcal infection caused by *Neisseria gonorrhea* has been reported as a side effect of eculizumab treatment in adult patients. This infection can lead to conditions such as tenosynovitis, septic arthritis, meningitis, endocarditis, and shock.[3] While this infection may not be a major concern in the pediatric age group, physicians should still be aware of the possibility of infection in adolescents with high-risk sexual behaviors. It is recommended to screen for sexually transmitted diseases in high-risk patients who are starting or currently receiving eculizumab therapy.[3]

Streptococcus spp.

Okusa *et al.* reported streptococcal infections including toxic shock syndrome, sepsis, meningitis, septic arthritis, urinary tract infection, cellulitis, erysipelas and pharyngitis following eculizumab treatment. Group B Streptococcus, alpha and Beta hemolytic streptococcus and *Streptococcus pneumoniae* are reported in this study.[10] Infections caused by encapsulated organisms other than Neisseria spp. in patients receiving eculizumab need close attention.[10] However, the encapsulated bacterial organisms that can mainly be prevented by opsonization are less affected by terminal complement inhibition. Therefore, invasive infections with *Streptococcus pneumoniae* or *Haemophilus influenza* are rare.[3]

Pseudomonas, Klebsiella and *Moraxella Spp.*

There are some case reports of infection with gram negative organisms such as *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, and *Moraxella lacunata* in patients on eculizumab not only in adults but also in children.[3,11-13] The number of available articles is scarce and the cause-and-effect relationship is not completely confirmed due to several risk factors for bacterial infections in these patients. However, there is a case report of recurrent *Pseudomonas* infection in a bone marrow transplant patient treated with eculizumab suggesting a probable cause- and- effect relationship.[13] If this relationship is confirmed in the future, the importance of the terminal complement in effectively killing these bacteria might have been underestimated.[3]

Viruses

Meanwhile the complement system plays a role in the regulation of T-cell activation and effector functions, eculizumab may increase the risk of viral infections.[3] However, there is limited evidence indicating that patients on eculizumab may be at greater risk for infections such as herpes simplex 1[14] and severe COVID- 19.[15] There are limited and conflicting data that suggest a potential role for eculizumab as a complement blockade agent in the treatment of severe COVID -19 during pregnancy and the postpartum period.[16]

Currently, according to available guidelines, there are no contraindications for administering live vaccines to patients on eculizumab.[7]

Aspergillus Spp. and *Cryptococcus Neoformans*

Animal studies have shown an increased susceptibility to disseminated invasive aspergillosis due to C5 deficiency.[17] However, there are few reports that support these findings in practice.[3,18]

Available reports suggest that patients receiving eculizumab are more susceptible to infection with encapsulated bacteria and encapsulated yeast such as *Cryptococcus neoformans*.[19] There is a case report of disseminated *Cryptococcus neoformans* following eculizumab therapy.[19]

Parasites

There is currently no published research on the status of parasitic infections during eculizumab treatment. The interaction between parasites and the complement system typically leads to ineffective protection against the parasite due to evasion mechanisms and biological characteristics of the parasite.[20] Therefore, eculizumab treatment is unlikely to have a significant impact on the prevalence or severity of parasitic infections. However, future studies are needed to confirm this.

Eculizumab in Pregnancy and *Lactation*

Many diseases treated with eculizumab may

worsen during pregnancy, making it necessary to start or continue eculizumab treatment. Available studies indicate that the concentration of eculizumab in umbilical cord blood is insufficient to impact complement level or activity in the fetus or newborn.[21,22]

Burwick and colleagues used eculizumab for the treatment of severe COVID- 19 in an open label, multicenter, Expanded Access Program. Six pregnant patients participated in this study. No significant eculizumab-related adverse events were reported in either the mothers or the neonates at three months.[16] Furthermore, eculizumab is not excreted in breast milk, indicating its probable safety in breastfeeding,[21,23] unless future research suggests otherwise.

It should be noted that there is limited data on the use of eculizumab in pregnancy and the risks for both the mother and fetus cannot be guaranteed.[21] The available studies are mainly case series and the level of evidence should be upgraded with more comprehensive studies in the future.

SOME IMPORTANT VACCINES WHICH SHOULD BE USED IN PATIENTS ON ECULIZUMAB

Meningococcal Vaccine

The exact incidence of meningococcal serotypes in Iran is unclear. However, according to recommendations worldwide, immunization against four serotypes (A, C, Y and W135), as well as serotype B of meningococcus in patients using eculizumab is emphasized.[7] Two recombinant serogroup B vaccines are available: MenB-FHbp, administered as a three-dose series at 0, 2, and 6 months, and MenB-4C, administered as a two-dose series at 0, and 2 months[3] (with at least 1 month apart).[1] A booster dose of MenB vaccine is recommended 1 year after completing the series followed by additional doses every two to three years for the duration of eculizumab therapy.[24] Currently, B serotype meningococcal vaccines are not available in Iran. Therefore, only a 4-valent conjugate meningococcal vaccine can be recommended.

Presently, the meningococcal vaccine is not included in Iran's NIP for the general population.[7] However, there are three types of meningococcal conjugate vaccines available in Iran: Menveo®, and Menactra®.[25]

Menveo® protects against meningococcal groups A, C, W, and Y and is licensed for use from two months through 55 years of age. It is administered in four doses at two, four, six, and 12 months of age. If the vaccine is started between seven and 23 months of age, a 2-dose series, is recommended with the second dose given in the second year of life and at least three months after the first dose.[26]

For patients two years of age and older, who have not previously received the vaccine, two doses are administered 8–12 weeks apart. Patients between two months and six years of age require an additional dose after primary immunization three years after the last dose. For patients seven years of age and older, an additional dose is needed, five years after the last dose of the vaccine.[26]

Menactra® protects against meningococcal serogroups A, C, W, and Y and is recommended for individuals aged nine months through 55 years. It can be given as a 2-dose series at nine and 12 months (three months apart) for those under two years old. For patients aged two years and older, two doses are administered 8-12 weeks apart. Children aged between nine months and six years old require an additional dose three years after the primary immunization while those aged seven years and older, need an extra dose five years after the last vaccine dose.[26]

Both types of vaccines should be repeated every five years if the immunodeficiency condition persists.[26] Therefore, the MenACWY vaccine requires a booster dose every five years, during eculizumab therapy.[3]

Pneumococcal Vaccine

Children on eculizumab are at risk of pneumococcal infections, although this risk seems to be lower than the risk of meningococcal infection.[3]

Several studies have attempted to define the most prevalent serotypes in Iran.[27,28] The pneumococcal vaccine was added to Iran's NIP in 2024 and currently the 10-valent pneumococcal polysaccharide conjugate vaccine (Pneumosil®) is being administered in the country. Ideally, patients should receive the vaccine at least two weeks before starting treatment with eculizumab. If this is not possible, they should be vaccinated as soon as possible after beginning eculizumab treatment. Patients with complement disorders are considered a part of the clinical risk groups

that should receive the 23- valent polysaccharide pneumococcal vaccine. However, specific C5 inhibition therapy is not currently a reason to administer this vaccine.[7]

Haemophilus Influenza Vaccine

According to the EPI of Iran, the Haemophilus influenza vaccine is currently administered as part of the pentavalent vaccine at two, four, and six months of age. If a patient has not received this vaccine at the proper time or has not completed the full course, they should receive the vaccine as soon as possible.[7]

ANTIBIOTIC PROPHYLAXIS

Unfortunately, patients receiving eculizumab may still be at risk for infections related to it, despite being fully vaccinated. Reports have shown that these patients can develop meningococcal disease primarily caused by non-groupable *Neisseria meningitidis* despite receiving meningococcal vaccination.[2,29] It is important to note that current meningococcal vaccines do not provide protection against non-groupable *Neisseria meningitidis* and cross protection is not guaranteed.[25] Consequently, the most reliable approach to infection prevention for this group of patients is a combination of immunization and antibiotic prophylaxis.

Penicillin V is the recommended antibiotic for prophylaxis.[7] The antibiotic should be initiated promptly upon the introduction of eculizumab and continued not only during the treatment but also for two half-lives (four weeks) of the drug after discontinuation.[3]

If the patient is allergic or intolerant to beta lactams, macrolides (e.g., azithromycin or erythromycin) serve as alternative agents.[7,9] Depending on local sensitivity reports, ciprofloxacin, and rifampin, can also be used for prophylaxis in these cases.[9]

FUTURE PERSPECTIVES OF ECULIZUMAB USAGE

It is likely that the number of diseases that eculizumab can effectively treat will increase in the future. There are some articles suggesting that complement-targeted therapies may play a role in the treatment of severe COVID-19[16] or dengue fever.[30] An important inquiry for future research is whether disparities exist in the incidence and type of infections across various diseases for which eculizumab is prescribed. In addition, as the use of this drug becomes more widespread, a broader range of infections may be discovered in the future. It is recommended that a multi-center study be conducted in Iran to determine the incidence and type of infections in children receiving eculizumab despite vaccination and antibiotic prophylaxis.

AUTHORSHIP CONTRIBUTIONS

Shirin Sayyahfar designed the study; searched the database, wrote the first draft, revised and finalized the manuscript and is the guarantor.

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CONFLICTS OF INTEREST

The author declares no conflict of interest.

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REFERENCES

1. Eculizumab (including biosimilars): Drug information. [Date cited 2024-July-15]. Available from: https://medilib.ir/uptodate/show/8836.
2. Crew PE, McNamara L, Waldron PE, McCulley L, Jones SC, Bersoff-Matcha SJ. Antibiotic prophylaxis in vaccinated eculizumab recipients who developed meningococcal disease. J Infect. 2020; 80: 350–71.
3. Benamu E, Montoya JG. Infections associated with the use of eculizumab: recommendations for prevention and prophylaxis. Curr Opin Infect Dis.2016; 29:319-29.
4. Eculizumab. [Date cited 2024-January-15]. Available from: https://go.drugbank.com/drugs/DB01257.
5. Winthrop KL, Mariette X, Silva JT, Benamu E, Calabrese LH, Dumusc A, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors). Clin Microbiol Infect. 2018;24 Suppl 2: S21-S40.
6. Engel ER, Walter JE. Rituximab and eculizumab when treatin nonmalignant hematologic disorders: infection risk, immunization recommendations, and antimicrobial prophylaxis needs. Hematology Am Soc Hematol Educ Program. 2020; 2020:312-18.
7. Maville C, Johnson S, Malina M. Available from: Vaccination guideline for patients under 18 years of age treated with eculizumab or ravulizumab. [Date cited 2024-January-15]. Available from: https://www.atypicalhus.

co.uk/wp-content/uploads/2022/12/Vaccination-guideline-for-18-years-and-under-on-eculizumab-or-ravulizumab-FINAL-WEBSITE.pdf.

8. National Immunization technical advisory group of the Ministry of Health and Medical Education of Iran. Schedule and Guideline of Immunization. Iran: Unicef; 2015 [Cited 2023-Augost-05]. Available from: https://goums.ac.ir/files/aghala/files/4(2).pdf.pdf [In Persian].
9. Malpica L, van Duin D, Moll S. Preventing infectious complications when treating non-malignant immune-mediated hematologic disorders. Am J Hematol. 2019; 94:1396-412.
10. Okusa S, Takizawa T, Imai S, Oyama M, Ishizuchi K, Nakahara J, et al. Serious Bacterial Infections Associated with Eculizumab: A Pharmacovigilance Study. Intern Med. 2024;63:1061-6.
11. Kawakami T, Nakazawa H, Kurasawa Y, Sakai H, Nishina S, Senoo N, et al. Severe Infection of Pseudomonas aeruginosa during Eculizumab Therapy for Paroxysmal Nocturnal Hemoglobinuria. Intern Med. 2018; 57:127-30
12. Bicoll PS, Goyal A, Blatt NB, Freij BJ. Eculizumab-Associated Moraxella lacunata Bacteremia and Systemic Inflammatory Response Syndrome in a Toddler with Atypical Hemolytic Uremic Syndrome. Clin Med Insights Pediatr. 2021 8; 15:1179556521992367.
13. Webb BJ, Healy R, Child B, Majers J, Anand S, Gouw L. Recurrent infection with Pseudomonas aeruginosa during eculizumab therapy in an allogeneic hematopoietic stem cell transplant recipient. Transpl Infect Dis. 2016; 18: 312–4.
14. Borhan WM, Dababo MA, Thompson LDR, et al. Acute necrotizing herpetic tonsillitis: a report of two cases. Head Neck Pathol. 2015; 9:119–22.
15. Genthon A, Chiarabini T, Baylac P, Valin N, Urbina T, Pacanowski J, et al. Severe COVID-19 infection in a patient with paroxysmal nocturnal hemoglobinuria on eculizumab therapy. Leuk Lymphoma. 2021; 62:1502-5.
16. Burwick R M, Dellapiana G, Newman R A, Smithson S D, Naqvi M, Williams J, et al. Complement blockade with eculizumab for treatment of severe Coronavirus Disease 2019 in pregnancy: A case series. Am J Reprod Immunol. 2022; 88: e13559.
17. Hector RF, Yee E, Collins MS. Use of DBA/2N mice in models of systemic candidiasis and pulmonary and systemic aspergillosis. Infect Immun. 1990; 58:1476–8.
18. Rondeau E, Cataland SR, Al-Dakkak I, Miller B, Webb NJA, Landau D. Eculizumab safety: five-year experience from the global atypical hemolytic uremic syndrome registry. Kidney Int Rep.2019; 4:1568-76.
19. Lortholary O, El-Sissy C, Leporrier J, Wong S S W, Dannaoui E, Fremeaux-Bacchi V, Aimanianda V.Disseminated Cryptococcosis Following Eculizumab Therapy: Insight Into Pathogenesis. Open Forum Infect Dis.2023; 24; 10:1-4.
20. Goto H, Sanchez MCA. Does the complement work for or against the host during parasite infections? Int Trends Immun. 2013; 1:11-23.
21. Sarno L, Tufano A, Maruotti G M, Martinelli P, Balletta M M, Russo D. Eculizumab in pregnancy: a narrative overview. J Nephrol. 2019; 32:17-25.
22. Lorenzo RD, Ramirez GA, Punzo D, Lorioli L, Rovelli R, Canti V, Barera G, Rovere-Querini P. Neonatal outcomes of children born to mothers on biological agents during pregnancy: state of the art and perspective. Pharmacol Res.2020; 152:104583.
23. Karimi A, Rafiei Tabatabaei S, Mahmoudi S, Rajabnejad M. Blue Book of Vaccination, A supplement to the program and the country's immunization guide. first edition.2019.
24. Managing the Risk of Meningococcal Disease among Patients Who Receive Complement Inhibitor Therapy. [Date cited 2024-January-15]. Available from: https://www.cdc.gov/meningococcal/clinical/eculizumab.html.
25. Sayyahfar S, Mohkam M, Hooman N, Faress F. General Principles of Vaccination of Pediatric Candidates of Kidney Transplant in Iran. Iran J Kid dis. 2023; 17 :285-93.
26. American Academy of Pediatrics. [Meningococcal Infections] In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. Red Book: 2021 Report of the Committee on Infectious Diseases. Itasca, IL: American Academy of Pediatrics: 2021[510-532]
27. Esteghamati A, Nazari-Alam A, Badamchi A, Faramarzi M, Alipoor M, Baradaran Moghaddam A, et al. Determination of Streptococcus pneumonia Serotypes Isolated from Clinical Specimens: A Step Toward the Production of a Native Vaccine in Iran. Arch Clin Infect Dis. 2021;16: e112897.
28. Alizadeh Chamkhaleh M, Esteghamati A, Sayyahfar S, Gandomi-Mohammadabadi A, Balasi J, Abdiaei H, Moradi Y, Moradi-Lakeh M. Correction to: Serotype distribution of Streptococcus pneumoniae among healthy carriers and clinical patients: a systematic review from Iran. Eur J Clin Microbiol Infect Dis. 2020; 39:2257-67.
29. Üçkardeş D, Göknar N, Kasap N, Keleşoğlu E, Arga M, Candan C. Meningococcemia in a vaccinated child receiving eculizumab and review of the literature. Turk J Pediatr. 2023; 65:129-34.
30. Carr JM, Cabezas-Falcon S, Dubowsky JG, Hulme-Jones J, Gordon DL. Dengue virus and the complement alternative pathway. FEBS Lett. 2020; 594:2543-55.

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