HHS Public Access

Author manuscript

Clin Infect Dis. Author manuscript; available in PMC 2020 May 12.

Disseminated Gonococcal Infections in Patients Receiving Eculizumab: A Case Series

Page E. Crew[1], **Winston E. Abara**[2], **Lynda McCulley**[1], **Peter E. Waldron**[1], **Robert D. Kirkcaldy**[2], **Emily J. Weston**[2], **Kyle T. Bernstein**[2], **S. Christopher Jones**[1], **Susan J. Bersoff-Matcha**[1]

[1]Division of Pharmacovigilance, Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, United States Food and Drug Administration, Silver Spring, Maryland; [2]Division of Sexually Transmitted Disease (STD) Prevention, National Center for Human Immunodeficiency Virus (HIV)/AIDS, Viral Hepatitis, STD and Tuberculosis Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia

Abstract

Background.—Gonorrhea is the second most commonly reported notifiable condition in the United States. Infrequently, *Neisseria gonorrhoeae* can cause disseminated gonococcal infection (DGI). Eculizumab, a monoclonal antibody, inhibits terminal complement activation, which impairs the ability of the immune system to respond effectively to *Neisseria* infections. This series describes cases of *N. gonorrhoeae* infection among patients receiving eculizumab.

Methods.—Pre- and postmarketing safety reports of *N. gonorrhoeae* infection in patients receiving eculizumab worldwide were obtained from US Food and Drug Administration safety databases and the medical literature, including reports from the start of pivotal clinical trials in 2004 through 31 December 2017. Included patients had at least 1 eculizumab dose within the 3 months prior to *N. gonorrhoeae* infection.

Results.—Nine cases of *N. gonorrhoeae* infection were identified; 8 were classified as disseminated (89%). Of the disseminated cases, 8 patients required hospitalization, 7 had positive blood cultures, and 2 required vasopressor support. One patient required mechanical ventilation. *Neisseria gonorrhoeae* may have contributed to complications prior to death in 1 patient; however, the fatality was attributed to underlying disease per the reporter.

Conclusions.—Patients receiving eculizumab may be at higher risk for DGI than the general population. Prescribers are encouraged to educate patients receiving eculizumab on their risk for serious gonococcal infections and perform screening for sexually transmitted diseases (STDs) per the Centers for Disease Control and Prevention STD treatment guidelines or in suspected cases. If

Correspondence: P. E. Crew, Center for Drug Evaluation and Research, US Food and Drug Administration, 10903 New Hampshire Ave, White Oak Bldg 22, Rm 3413, Silver Spring, MD 20993 (page.crew@fda.hhs.gov).

Disclaimer. The views expressed are those of the authors and do not necessarily represent those of, nor imply endorsement from, the US Food and Drug Administration, the US Centers for Disease Control and Prevention, or the United States government.

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

antimicrobial prophylaxis is used during eculizumab therapy, prescribers should consider trends in gonococcal antimicrobial susceptibility due to emerging resistance concerns.

Keywords

eculizumab; gonorrhea; disseminated gonococcal infection

Gonococcal infections caused by the bacterium *Neisseria gonorrhoeae* are the second most commonly reported notifiable condition in the United States [1]. In 2016, >460 000 cases of gonorrhea were reported to the US Centers for Disease Control and Prevention (CDC) [2]. Although urethral gonorrhea often causes profuse discharge and painful urination, gonococcal infections of the cervix, pharynx, and rectum are often asymptomatic [1]. Infrequently, *N. gonorrhoeae* can enter the bloodstream and cause disseminated gonococcal infection (DGI), which is thought to occur in approximately 0.5%–3% of gonorrhea cases, though recent data are limited [3]. Risk factors for dissemination include female sex, menstruation, pregnancy, terminal complement deficiency, and infection with strains that are resistant to bactericidal activity of human serum [1, 4–6].

DGI can present with skin lesions (ranging from papules and small macules to pustules, bullae, and erythema nodosum), tenosynovitis, polyarthralgia, or septic arthritis [1, 4]. Even more rarely, life-threatening gonococcemia, endocarditis, or meningitis may develop [1]. Positive blood cultures are observed in up to 50% of DGI presentations characterized by tenosynovitis or polyarthralgia, whereas bacteremia is rarely detected in patients with septic arthritis [4]. Although most patients with DGI do not report symptoms of gonorrhea at mucosal sites, approximately 70%–80% of patients with DGI (or their sex partners) are ultimately found to have genital, anorectal, or pharyngeal gonorrhea infection [4].

Eculizumab is a US Food and Drug Administration (FDA)–approved treatment for diseases with dysregulation of complement activation such as paroxysmal nocturnal hemoglobinuria (PNH, approved 2007), atypical hemolytic uremic syndrome (approved 2011), and anti-acetylcholine receptor antibody–positive generalized myasthenia gravis (approved 2017) [7, 8]. It is a monoclonal antibody that inhibits terminal complement activation by binding to complement protein C5 and preventing cleavage into C5a and C5b [8]. Without C5b, the membrane attack complex is not formed, thereby severely limiting complement activity [9]. Complement blockade at C5 inhibits the ability of the immune system to respond effectively to acquired *Neisseria* infections, due to the lack of adequate serum bactericidal activity and to the diminished upregulation of opsonophagocytic killing [9]. In the United States, eculizumab therapy is associated with an estimated 1000- to 2000-fold increased risk of meningococcal disease [9, 10]. Although there are a few case reports of DGIs in patients receiving eculizumab in the published literature [11–13], there is a growing need for an improved understanding of the risk for *N. gonorrhoeae* infections, particularly disseminated infections, in patients receiving eculizumab. The purpose of this case series is to describe cases of *N. gonorrhoeae* infection among patients receiving eculizumab, with a focus on disseminated infections.

METHODS

The FDA conducted a comprehensive search to identify reports received by the agency of *N. gonorrhoeae* infection in patients receiving eculizumab worldwide. Pre- and post-marketing safety reports that were reported to the FDA's MedWatch Program and housed in either the FDA Adverse Event Reporting System (FAERS) or as part of the safety submission under the investigational new drug (IND) application were reviewed. The FAERS database is a postmarketing pharmacovigilance tool for surveillance of adverse events voluntarily reported by consumers, caregivers, and healthcare professionals, and has been described in detail elsewhere [14]. Drug sponsors are required to submit adverse event reports to the FDA (through FAERS and under an IND). Additionally, the medical literature was queried using PubMed and Embase for case reports. Searches were not limited by start date in an effort to capture all safety reports and literature from the start of eculizumab pivotal clinical trials in 2004 to 31 December 2017.

To be included in the case series, a patient must have received at least 1 eculizumab dose within the 3 months prior to a reported mucosal or DGI (due to the 270- to 375-hour half-life of eculizumab [8]). Cases were included in the series if a diagnosis of gonorrhea (disseminated or mucosal) was reported or if microbiological evidence of *N. gonorrhoeae* was reported. Microbiological evidence of *N. gonorrhoeae* was not required for inclusion because FAERS cases often contain incomplete information and reporters frequently do not provide laboratory results. However, available microbiological evidence, where reported, is presented in the results. Reporter classification of the gonococcal infection, as mucosal or disseminated, was also noted. Duplicate reports were excluded.

RESULTS

The FDA safety report search identified a total of 12 pre- and postmarketing safety reports of *N. gonorrhoeae* infection. After case review, 3 FAERS reports were excluded as duplicates. The 9 remaining FAERS cases included 3 cases that were also published in the literature. No additional published literature cases were identified outside of safety reports already submitted to FDA.

The case series differs markedly from the general population with *N. gonorrhoeae* infection (Table 1). Eight of 9 patients in our series were classified as disseminated (89%), all of whom were hospitalized (89%). As part of their diagnostic workup, 3 patients had cerebrospinal fluid sampling but none were diagnosed with meningitis. One patient had a transthoracic echo-cardiogram (case 2), which was negative for valvular vegetation. Two patients appeared to have experienced septic shock, as they required vasopressor support during the acute period of their illness (cases 6 and 8), 1 of whom also required mechanical ventilation (case 6). There was no comment on vasopressor use in the other 7 cases.

Most patients were female and <30 years of age, and 3 of 9 cases in the series were from outside the United States. Of the 8 disseminated cases, 7 had positive blood culture results (78%). One patient (case 5) had a positive cervical culture and subsequent joint pain, which led to a diagnosis of DGI (see Table 1 for additional description of this case). For the patient

whose infection was not described as disseminated, microbiological details regarding the reported anatomic site of *N. gonorrhoeae* infection were not provided, precluding further determination as to whether the infection was local vs disseminated.

Six patients reportedly took concomitant medications; 3 patients did not report this information. Of these 6, 3 patients took antibiotic prophylaxis. The antibiotic and duration of prophylaxis was not specified for case 4; 2 other patients (cases 3 and 9) had taken penicillin. Case 3 received 2 weeks of oral penicillin as antibiotic prophylaxis at the time of eculizumab therapy initiation but was not on prophylaxis at the time of *N. gonorrhoeae* infection, and case 9 reported oral penicillin therapy as "ongoing" (presumably long-term). The definitive antibiotic regimen used to treat the *N. gonorrhoeae* infection was reported in 6 cases (Table 1): ceftriaxone and single-dose azithromycin (cases 2 and 3), ceftriaxone (cases 8 and 9), meropenem (case 6), and ciprofloxacin (case 7).

Eculizumab disposition following the *N. gonorrhoeae* infection was included for 8 patients. Seven patients continued (or intended to continue) eculizumab therapy, while 1 discontinued. All gonococcal infections reportedly resolved, except in case 5. This patient subsequently developed endocarditis (pathogen not specified) and thrombotic complications, and ultimately died. The patient had a past medical history of PNH with aplastic anemia, and she initially presented with a positive cervical culture for *N. gonorrhoeae*. She then developed joint pain that was diagnosed by an infectious diseases specialist as DGI (no arthrocentesis performed), and a 4-week course of antibiotic therapy was planned. Her hospital course was complicated by endocarditis and cerebral thrombosis with hemorrhage requiring a craniotomy. Her death, which occurred approximately 2 months after diagnosis of DGI, was attributed to complications from PNH by the reporter.

DISCUSSION

Although DGI accounts for few gonorrhea cases in the general US population [3], nearly all of the cases in our series (8 of 9 cases) were DGIs. Our series illustrates that *N. gonorrhoeae* infection in patients receiving eculizumab can cause a severe, invasive, and life-threatening infection. Similar to meningococcal disease risk, we suspect that patients receiving eculizumab may be at higher risk for DGI relative to the general population. However, spontaneously reported data cannot prove this hypothesis. It is also possible that the impaired complement immunity imparted by eculizumab increases the risk for dissemination of *N. gonorrhoeae*, similar to patients with terminal complement deficiencies [4]. In addition, recent data published by the CDC suggest that nongroupable strains of *Neisseria meningitidis* are capable of producing invasive meningococcal disease in patients receiving eculizumab, even though nongroupable *N. meningitidis* strains are rarely pathogenic in healthy patients [10]. Thus, the strains of *N. gonorrhoeae* that are capable of successful dissemination in the bloodstream may differ in patients receiving eculizumab because of impaired bactericidal and opsonophagocytic killing of *Neisseria* species [9], though our current data do not provide insight on this hypothesis. Further research could better define the epidemiology of *N. gonorrhoeae* infections and the risk for dissemination in patients receiving eculizumab.

Awareness of the risk of invasive gonococcal infection in patients receiving eculizumab is critical for implementing appropriate infection prevention measures. Prescribers are encouraged to obtain sexual histories from patients receiving eculizumab, including ascertainment of the number and gender of sex partners and the type of sexual contact that the patient has had; this information will guide appropriate screening recommendations. Prescribers are also encouraged to educate patients on their risk for gonorrhea and DGI, and encourage safer sex practices, such as correct and consistent condom use during sex. At this time, screening recommendations for gonorrhea in patients receiving eculizumab do not differ from those for the general population. CDC recommends annual gonorrhea and chlamydia screening in sexually active women <25 years of age, and older women who are at increased risk for infection [1]. CDC also recommends that sexually active gay, bisexual, and other men who have sex with men be screened for gonorrhea and chlamydia at least annually at potentially exposed anatomic sites, with more frequent screening if risk behaviors persist [1]. Given the high proportion of patients in the series with disseminated infection, and the concern for life-threatening outcomes due to DGI, healthcare professionals are encouraged to evaluate all patients receiving eculizumab who have *N. gonorrhoeae* infection for signs and symptoms of disseminated infection. The risk for invasive gonococcal infection likely persists throughout the duration of eculizumab therapy. In addition, eculizumab exposure persists for approximately 3 months after therapy discontinuation due to the prolonged eculizumab half-life [8]; therefore, the risk for disseminated infection likely continues during this time.

For patients diagnosed with uncomplicated gonococcal infection of the cervix, urethra, rectum, or pharynx, prescribers are strongly encouraged to treat with the CDC-recommended regimen of intramuscular 250 mg ceftriaxone in a single dose and 1 g oral azithromycin in a single dose [1]. Those diagnosed with DGI (presenting as arthritis or arthritis-dermatitis syndrome) should be treated with 1 g intramuscular or intravenous ceftriaxone daily and 1 g oral azithromycin as a 1-time dose; providers can switch to an oral agent guided by antimicrobial susceptibility testing 24–48 hours after substantial clinical improvement, for a total treatment course of at least 7 days [1]. Treatment of DGI presenting as gonococcal meningitis or endocarditis should be treated with intravenous ceftriaxone 1–2 g every 12–24 hours and 1 g oral azithromycin as a 1-time dose [1]. Parenteral treatment for meningitis should be continued for 10–14 days; parenteral therapy for endocarditis should be administered for at least 4 weeks [1].

Antimicrobial resistance to *N. gonorrhoeae* is a challenge, and the risk for *N. gonorrhoeae* in patients receiving eculizumab adds complexity to decisions regarding the use of antimicrobial prophylaxis to prevent meningococcal infection. In July 2017, CDC advised prescribers to consider antibiotic prophylaxis for the duration of eculizumab therapy, but preferred antibiotic agents have not been defined [10]. In recent years, a growing body of evidence has demonstrated declining azithromycin susceptibility in *N. gonorrhoeae* and increasing macrolide resistance [15, 16]. Consequently, prolonged azithromycin prophylaxis for meningococcal infection in eculizumab patients might facilitate the development of drug-resistant *N. gonorrhoeae* and diminish the effectiveness of the only recommended treatment regimen. Because eculizumab patients may be at an elevated risk for severe infection due to gonorrhea, infection with antimicrobial-resistant *N. gonorrhoeae* can complicate their

clinical outcomes. Therefore, healthcare professionals are discouraged from using macrolide antimicrobials as meningococcal prophylaxis in patients receiving eculizumab who may also be at risk for *N. gonorrhoeae*. However, we recognize that patients receiving eculizumab are medically complex and there may be circumstances where macrolides need to be considered, guided by expert medical judgement.

There are several important limitations to consider when interpreting this case series data. Most of the data presented here are case reports from the FAERS database, which often lack complete data for a patient case. Also, the FAERS database contains spontaneously reported data, so it is impossible to estimate the incidence of mucosal *N. gonorrhoeae* infection or DGI in patients receiving eculizumab due to the lack of a reliable numerator or denominator. The case count undoubtedly reflects underreporting to the FDA for this infection. Although we would like to be able to estimate the absolute risk for DGI in patients receiving eculizumab, it is not possible with the available data. A reporting rate calculation for DGI in patients receiving eculizumab may lack validity due to uncertainty in estimated cumulative patient-year exposure data for eculizumab in the United States and probable underascertainment of cases from the small sample size of spontaneously reported events in patients receiving eculizumab. In addition, there may be bias toward reporting DGI over uncomplicated mucosal *N. gonorrhoeae* infections, as drug-associated adverse events. Further, we recognize the case series contains 5 patients aged <25 years; young adults have a baseline high risk for *N. gonorrhoeae* infections regardless of eculizumab therapy [1].

To our knowledge, this is the first case series of *N. gonorrhoeae* infections in patients receiving eculizumab. All health-care professionals who encounter patients receiving eculizumab should be aware of the risk of meningococcal infections as well as DGI. Healthcare professionals are encouraged to follow CDC sexually transmitted disease treatment guidelines' recommendations for gonorrhea screening, educate patients receiving eculizumab about their increased risk for severe infections, and include DGI in the differential diagnosis of patients receiving eculizumab who present with a gram-negative diplococcal infection, especially with joint or skin involvement. Finally, healthcare professionals are encouraged to report suspected adverse events, including infections, to FDA's MedWatch program [17] for continued safety surveillance.

References

1. Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep 2015; 64:1–137.
2. Centers for Disease Control and Prevention. Sexually transmitted diseases surveillance, 2016 Available at: https://www.cdc.gov/std/stats16/CDC_2016_STDS_Report-for508WebSep21_2017_1644.pdf. Accessed 20 February 2018.
3. Hook EW, Handsfield HH. Gonococcal infections in the adult In: Holmes KK, Starling PF, Stamm WE, et al., eds. Sexually transmitted diseases. 4th ed. New York: McGraw-Hill Medical, 2008:627–45.
4. Rice PA. Gonococcal arthritis (disseminated gonococcal infection). Infect Dis Clin North Am 2005; 19:853–61. [PubMed: 16297736]
5. Bleich AT, Sheffield JS, Wendel GD Jr, Sigman A, Cunningham FG. Disseminated gonococcal infection in women. Obstet Gynecol 2012; 119:597–602. [PubMed: 22353959]

6. Lee MH, Byun J, Jung M, et al. Disseminated gonococcal infection presenting as bacteremia and liver abscesses in a healthy adult. Infect Chemother 2015; 47:60–3. [PubMed: 25844265]
7. US Food and Drug Administration. Drugs@FDA: Soliris (BLA 125166). 2018 Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process. Accessed 14 March 2018.
8. Soliris (eculizumab) [package insert]. Cheshire, CT: Alexion Pharmaceuticals, 2018 Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125166s426lbl.pdf. Accessed 13 April 2018.
9. Konar M, Granoff DM. Eculizumab treatment and impaired opsonophagocytic killing of meningococci by whole blood from immunized adults. Blood 2017; 130:891–9. [PubMed: 28630122]
10. McNamara LA, Topaz N, Wang X, Hariri S, Fox L, MacNeil JR. High risk for invasive meningococcal disease among patients receiving eculizumab (Soliris) despite receipt of meningococcal vaccine. MMWR Morb Mortal Wkly Rep 2017; 66:734–7. [PubMed: 28704351]
11. Gleesing J, Chiwane S, Rongkavilit C. Gonococcal septic shock associated with eculizumab treatment. Pediatr Infect Dis J 2012; 31:543. [PubMed: 22511000]
12. Hublikar S, Maher WE, Bazan JA. Disseminated gonococcal infection and eculizumab—a “high risk” connection? Sex Transm Dis 2014; 41:747–8. [PubMed: 25581812]
13. Khandelwal A, Wright JK, Pavenski K, Taggart LR. Risks of novel therapeutics: gonococcemia in an immune-suppressed patient receiving eculizumab. CMAJ 2017; 189:E1558–60. [PubMed: 29255100]
14. US Food and Drug Administration. Questions and answers on FDA’s adverse event reporting system (FAERS). Available at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/. Accessed 22 March 2018.
15. Kirkcaldy RD, Harvey A, Papp JR, et al. *Neisseria gonorrhoeae* antimicrobial susceptibility surveillance—the gonococcal isolate surveillance project, 27 sites, United States, 2014. MMWR Surveill Summ 2016; 65:1–19.
16. Papp JR, Abrams AJ, Nash E, et al. Azithromycin resistance and decreased ceftriaxone susceptibility in *Neisseria gonorrhoeae*, Hawaii, USA. Emerg Infect Dis 2017; 23:830–2. [PubMed: 28418303]
17. US Food and Drug Administration. MedWatch: the FDA safety information and adverse event reporting program. 2018 Available at: https://www.fda.gov/Safety/MedWatch/default.htm. Accessed 21 March 2018.

Table 1.

Patient Characteristics and Treatment Outcome of 9 Cases of Gonococcal Infection in Patients Receiving Eculizumab

Case	Age, Sex, Country	Eculizumab Indication	Infection Classification, per Reporter or Culture Results	Culture Results, Where Reported	Infection Details	TTO	Antibiotic(s) Received	Outcome of Infection
1	22, F US	PNH	DGI	Blood cultures positive	NR	NR	NR	NR
2, literature [12]	28, F US	PNH	DGI	Blood cultures positive, urogenital NAAT positive, LP performed (negative cultures), transthoracic echocardiogram performed (negative)	Fever 103.1 °F, chills, headache, swollen/warm left index finger, no skin lesions	~16 mo	Vancomycin and ceftriaxone, then ceftriaxone and single-dose azithromycin	Resolved
3, literature [13]	23, F Canada	aHUS	DGI	Blood cultures positive; cervical swab for *Neisseria gonorrhoeae*. negative NAAT; urine for *N. gonorrhoeae*. negative NAAT; throat swab for *N. gonorrhoeae*. negative culture; rectal swab: negative culture	1 d of fever and rigors, no localized symptoms, CNS symptoms, joint pain/ swelling, skin rashes, or genitourinary symptoms. Sex partner diagnosed with gonorrhea at time of patients DGI diagnosis	46 d	Piperacillin-tazobactam and vancomycin, then ceftriaxone and single-dose azithromycin	Resolved
4	18, F US	aHUS	NR	NR	Possibly pregnant at time of infection	NR	NR	Resolved
5	19, F US	PNH	DGI	Cervical culture positive	After cervical culture complained of joint pain, ID consult diagnosed DGI, no arthrocentesis performed	NR	NR	Diagnosed with endocarditis (pathogen NR), thrombotic spleen, intracranial bleed, cerebral thrombosis, then death approximately 2 mo following DGI diagnosis
6, literature [11]	19, F US	PNH	DGI	Blood cultures positive, LP "unsuccessful," DNA amplification tests/cultures from rectal and genital swabs negative (after 3 d of antibiotics)	Fever 39.4°C, vomiting, RUQ abdominal pain, light-headed, hypotension, WBC 4400/mm^3, no arthralgia or rash or genital lesions or discharge (but currently menstruating)	788 d	Vancomycin and ceftriaxone then meropenem	Developed respiratory failure and required mechanical ventilation and ICU care; ultimately resolved
7	42, M Netherlands	PNH	DGI	Blood cultures positive	Fever 39°C, skin eruption on wrists, knees, ankles, abdomen, no other localizing symptoms, 2 d after antibiotic therapy WBC 5.5 (no units)	1613 d	Ciprofloxacin	Resolved
8	44, F US	PNH	DGI	Blood cultures positive	Reported trauma to right middle finger 3 d prior to admission, presented with fever 104.5°F, fatigue, body aches, hypotension, WBC 4900 (no units),	NR	Cefepime, vancomycin, and levofloxacin, then ceftriaxone	Required ICU care, ultimately resolved

Case	Age, Sex, Country	Eculizumab Indication	Infection Classification, per Reporter or Culture Results	Culture Results, Where Reported	Infection Details	TTO	Antibiotic(s) Received	Outcome of Infection
					pelvic ultrasound “ruled out tubal ovarian abscess”			
9	28, F France	aHUS	DGI	1 of 3 blood cultures positive, PCR of endocervix negative for gonorrhea, LP performed (reported as “negative for meningococcal”), skin biopsy negative for meningococcus and varicella	Fever 40°C, headache, vomiting, shivering, 2 small papular eruptions later described as maculopapular rash which spread, and macular lesions on arms and thighs, “no articular sign,” examined by gynecologist who noted “no particular sign was observed”	613d	Ceftriaxone	Resolved

Abbreviations: aHUS, atypical hemolytic uremic syndrome; CNS, central nervous system; DGI, disseminated gonococcal infection; ICU, intensive care unit; ID, infectious diseases; LP, lumbar puncture; NAAT, nucleic acid amplification test; NR, not reported; PCR, polymerase chain reaction; PNH, paroxysmal nocturnal hemoglobinuria; RUQ, right upper quadrant; TTO, time to onset from start of eculizumab therapy; WBC, white blood cell count.