Blood Reviews xxx (xxxx) xxx

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/issn/0268960X

Review

Management of infection in PNH patients treated with eculizumab or other complement inhibitors: Unmet clinical needs☆

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ARTICLE INFO

Keywords:
Eculizumab
Complement inhibitors
Paroxysmal nocturnal hemoglobinuria
Infections
Vaccination
Chemoprophylaxis

ABSTRACT

This article presents the results of group discussion among an *ad hoc* constituted panel of experts aimed at identifying and addressing unmet clinical needs (UCNs) in the management of infectious risk associated with eculizumab or new terminal complement inhibitors (CIs) in paroxysmal nocturnal hemoglobinuria (PNH). With the Delphi technique, the most clinically relevant UCNs in PNH patients candidate to or on terminal CI were selected. They resulted to be: optimizing the infection prevention measures; developing non pharmacological infectious risk-mitigation strategies; improving the management of disease exacerbation during infectious complications. For each of these issues consensus opinions were provided and, when appropriate, proposals for advancement in clinical practice were addressed. The hope is that this comprehensive overview will serve to improve the practice of CIs therapy and inform the design and implementation of new studies in the field.

1. Introduction

Eculizumab, a monoclonal antibody that targets C5 complement and prevents the formation of C5a and C5b-9, thereby blocking complement-activated hemolysis, has been approved for managing paroxysmal nocturnal hemoglobinuria (PNH) and other diseases, including atypical hemolytic uremic syndrome, generalized myasthenia gravis, and neuromyelitis optica spectrum disorders.

In PNH, the approval of eculizumab in 2007 introduced a paradigm shift in the treatment of the disease with improvement of the chronic hemolytic process and reduction of the thrombotic rate, with improvement of patients' quality of life and survival [1]. However, despite this beneficial impact on disease outcomes, the use of the drug was associated with a 1000- to 2000-fold increased incidence of infection, notably with encapsulated bacteria and in particular with *Neisseria meningitidis* [2]. Anti-meningococcal vaccination was made compulsory since eculizumab was introduced. At the same time, since cases of meningococcal infection have been observed even in vaccinated individuals, antibiotic prophylaxis during treatment with eculizumab, or with other recently approved complement inhibitors (CIs: *e.g.* ravulizumab), has been

☆ *A consensus-based position paper fostered by the* Associazione Italiana Emoglobinuria Parossistica Notturna (AIEPN).

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https://doi.org/10.1016/j.blre.2022.101013

Available online 6 September 2022

recommended [3].

Despite the clinical relevance of anti meningococcal prophylaxis for the health of PNH patients, the concepts that govern anti-infectious strategies have been translated from a limited number of interventional clinical studies. Data from patients with hereditary complement deficiencies may be considered, however, while confirming an increased risk of infections by encapsulated organisms, they do not allow the definition of clear anti-infective strategies that can be translated as such to patients with PNH [4]. As a consequence, unmet clinical needs (UCNs) continue to challenge the clinical practice of physicians who care for PNH patient treated with CIs. In particular, concerns have emerged on the timing of the use of the anti-meningococcal vaccine in PNH due to the risk of vaccine-dependent complement activation and consequent enhanced hemolysis [5]. Moreover, antibiotic prophylaxis is not widely shared both for the difficulty of a lifelong prophylaxis and for the emergence of penicillin resistant strains. Finally, there is no evidence of wide use of the US Food and Drug Administration recommended non-pharmacological risk mitigation strategies [6].

The same community of Italian patients affected by PNH expressed some concerns regarding the lack of knowledge of the above reported issues by the local health services and requested an intervention for a disclosure of the problem. Therefore, the Scientific Committee of the Italian PNH Association (Associazione Italiana Emoglobinuria Parossistica Notturna, AIEPN), a non-profit association of patients with PNH and their families, agreeing with patients' concerns decided to foster the development of a position paper aimed to define UCNs of the management of infections in PNH patients candidate to be treated or during treatment with eculizumab or new CIs, and to produce recommendations for the management of the most relevant UCNs.

2. Methods

Two chairmen (AR and CG) appointed an Expert Panel (hereafter referred to as the Panel) of 10 members, selected for having previously published and/or expressed an interest in infectious complications in PNH. Most of the Panel members are on the Scientific Committee of the AIEPN. A clinician with expertise in clinical epidemiology (GB) assured the methodological correctness of the process. During an initial meeting on June 2021, the outline of the project was discussed and the topics that form the structure of the present document were decided. The key UCNs were selected through a series of questionnaires according to the Delphi technique [7]. Chairmen reviewed evidence on selected unmet clinical needs by PubMed searches of English-language literature (2007 to December 2021). Additionally, the proceedings of the latest international annual meetings were searched for relevant unpublished evidence. Afterwards, panelists drafted statements that addressed one identified UCN, while the remaining panelists scored their agreement with those statements and provided suggestions for modifications. Finally, the Panel convened for a consensus conference in February 2022. In this conference, final proposals were given: participants were first asked to comment in round-robin fashion their disagreements with the proposed issues and to vote for a final statement.

3. Unmet clinical needs

Although numerous UCNs in the domain of infectious risk of patients with PNH were issued by the Panel (Table 1), this review focuses only on some of the major outstanding challenges voted as the most relevant and urgent by the panelists.

3.1. Optimizing infection prevention in PNH patients candidate to or on complement inhibitors

A narrative review of the epidemiology of infections in patients with PNH treated with eculizumab, ravulizumab and other CIs is reported in the Supplemental Material I.

Table 1
Candidate unmet clinical needs in the management of infectious risk of subjects under complement inhibitors.

1. Acquiring new evidence on infectious complications (incidence, signs and symptoms, risk factors, predictors, mortality) in PNH patients treated with complement inhibitors
2. Optimizing the infection prevention measures in PNH patients candidates to or on complement inhibitors (type and timing of the vaccine, antibiotic prophylaxis). Providing precise indications regarding vaccination for COVID-19 in patients treated with anti-complement therapy and monitoring strategies
3. Improving the knowledge on disease exacerbation during infections complications in PNH on anti complement treatment (hemolysis) and on their appropriate treatments
4. Improving the education of newly diagnosed patients on complement inhibitors (about early signs and symptoms of infection to promptly alert the medical team)
5. Improving the awareness on the risk of infections of the relatives and caregivers of subjects with PNH treated with anti complement therapy
6. Developing other risk-mitigation strategies for PNH patients on anti-complement treatment, not limited to pharmaceutical interventions. Specify the role of peripheral centers and the referral center in a network work as funding-point of improving the knowledge on infectious risk of patients treated with anticomplement therapy in the non-specialist doctors. Implementing a readily accessible and qualified information source for the management of infectious risk in subjects with PNH and eculizumab therapy
7. Improving the management of disease exacerbation during infectious complications in PNH on CI treatment.
8. Identifying safety issues which are not necessarily covered by standard "pharmacovigilance" (eg, not related to the treatment, or not leading to formal treatment emergent adverse events)

Most literature data on CIs related infectious complications regard eculizumab; few data are available on ravulizumab and even less on other investigational CIs. Until more information is available, the Panel agrees that the following recommendations should apply to patients being treated with any type of CI.

3.1.1. Anti-meningococcal vaccination

Since eculizumab was approved to treat adult patients with PNH in the US and Europe, US FDA provided a black box warning about meningococcal infections [6]. The product monograph recommended vaccination with quadrivalent MenACWY (*i.e.* against serogroups A, C, W, and Y) and MenB (against serogroup B) vaccines at least 14 days before treatment, unless the risk of delaying eculizumab out-weighted infectious risk. For patients in whom CI therapy was deemed to be so urgent that meningococcal vaccinations could not be given two or more weeks before starting eculizumab, antibiotic prophylaxis was recommended. In addition, the US Advisory Commission on Immunization Practice (ACIP) recommends MenACWY booster doses for previously vaccinated persons who remained at increased risk of infections [8]. The Center of Disease Control recommends administer a booster dose of MenACWY vaccine every 5 years for the duration of eculizumab therapy [9]. Considering that plausible duration of protection of MenB vaccine is thought to be 18 months following a 2 dose primary course and 36 months following the additional booster dose [10] a booster dose of MenB vaccine 1 year after series completion and then every 2 to 3 years thereafter, for the duration of eculizumab therapy is recommended [9]. Some concerns have been raised about the risk-benefit ratio of MenB vaccination [11]. Health Canada's safety review in 2016 reported a risk of anemia and hemolysis when patients already on eculizumab were vaccinated with MenB-4C, particularly when the vaccine was given several days after eculizumab dose [5]. To minimize the risk of hemolysis, the manufacturer recommended that in patients on eculizumab MenB-4C vaccine shoud be administered within one week from a prior eculizumab infusion, when the drug concentration in the blood can be presumed to be relatively high. Considering that not only MenB can induce hemolysis in PNH patients, these rules of vaccination timing in patients already being treated with a CI should reasonably be respected for all types of vaccines. However, it should be noted that the Canadian document did not report information on vaccine-related haemolytic

events when the vaccine was administered prior to initiation of CI treatment. This is an important issue as the literature does not quantify the risk and the severity of post-vaccine haemolytic events in patients not yet treated with CI and the question remains as to when it is best to administer the first dose of vaccine, whether before the start of CI treatment or after.

Despite *Men*ACWY vaccination and, when available, MenB vaccination have become worldwide implementation practice in eculizumab and ravulizumab recipients, both pharmacovigilance [12–14] and individual case reports [15–27] have documented that CIs recipients remain at risk for meningococcal disease even after receipt of appropriate meningococcal vaccines. In particular, the review of pharmacovigilance studies documented that 14 of the 16 meningococcal disease cases reported by Mc Namara and co-workers [2] had documentation of receipt of MenACWY before disease onset. Moreover, almost all 67 cases of meningococcal infection reported by Socie and co-workers occurred in patients with previous confirmed meningococcal vaccination [12], and all 47 patients reported by Crew and co-workers received ≥1 dose of a meningococcal vaccine [28]. Fatal meningococcal infection was uncommon (for details see Supplemental material 1).

Table 2 reports serogroups of meningococcal infection in 63 PNH patients treated with eculizumab in which the infecting germ had been studied. Although most cases of invasive meningococcal disease in immunocompetent people are caused by encapsulated serogroup B, C, W, or Y strains, several infections in eculizumab treated patients were caused by meningococcal serotypes not covered by the two vaccines, in particular by strains of non-groupable meningococcus that do not normally cause serious infections in immunocompetent subjects. Also several infections by serogroup B strains have been documented during eculizumab treatment. Considering that only few information on previous MenB vaccination is available for these cases it is difficult to define the risk of breakthrough MenB infections after MenB vaccination.

The evidence of meningococcal disease in eculizumab recipients vaccinated against the infecting serogroup, together with the susceptibility of these persons to non-groupable meningococcal strains, suggested that eculizumab therapy would interfere with the ability of antimeningococcal antibodies to provide protection against invasive disease. In support to this hypothesis, *ex vivo* data have shown that vaccination may not fully suppress the risk of meningococcal infection due to inhibition by eculizumab of the opsonophagocytic activity and complement-dependent cytotoxicity required for eradication of *Neisseria* [29].

Health care providers have measured response titers to vaccination as a correlate of protection [14,30,31]. These studies showed a variable serological response for different serotypes and found a decrease in protective serum bactericidal titer over time starting at 6 months after vaccination. On the basis of these results, monitoring serologic response to meningococcal vaccination at various timepoints after vaccination in order to re-vaccinate patients with non-protective titers was suggested [14,30]. However, these recommendations were criticized given that antibodies require a functional terminal complement pathway to kill the meningococci efficiently. Thus, in the last version of ACIP no evaluation of antibody titer against meningococcal serogroups for the purposes of establishing immunity or the need for re-vaccination was recommended [8].

Table 2
Cases of meningococcal infection with identified serogroup in PNH patients treated with Eculizumab reported in the literature (ref 2, 10, 14–26).

Serogroup	N. of cases	Comments
B	21	Few information on previous Men B vaccination
C	8	All cases in patients who had received meningococcus C vaccination.
W	5	1 patient had not been vaccinated, 2 patients had been vaccinated with Men ACWY but antibody levels against W were suboptimal. No information for the other cases.
X	2	Vaccination does not cover X serogroup.
Y	11	Almost all had received one or two doses of Men ACWY
E	1	Vaccination does not cover E serogroup.
Z	1	Vaccination does not cover Z serogroup.
Non groupable	15	Most of cases in patients vaccinated with Men ACWY and, in part, with MenB. Vaccines are not active against non-groupable strains.
Total	63	

Recommendations

- According to the international guidelines the first dose of Men-ACWY and Men-B vaccines should be administered at least two weeks before start of CI treatment. However, in view of the reported risk of vaccine triggered hemolysis particularly with MenB vaccine and mostly in patients not yet being treated with CI, the Panel discussed the appropriateness of postponing the start of anti-meningococcal vaccination to some weeks after CI treatment start, when CI blood levels are adequate (under appropriate antibiotic prophylaxis). This option has been already the practice by some experts of this Panel. However, this cannot be now recommended in the absence of evidence. The Panel agreed that it is urgent to obtain further data on the risk of enhanced hemolysis in patients vaccinated before CI therapy. Retrospective regional or national registry data analysis may be an appropriate source of evidence.
- The second dose of Men-ACWY should be administered 8 weeks after the first dose and the second dose of Men-B one month after the first dose.
- A booster dose of Men-ACWY is recommended every 5 years.
- A booster dose of MenB is recommended one year after completion of the primary series, followed by a booster dose of MenB every 3 years thereafter.
- When eculizumab needs to be started as an emergency measure, or when there may be a high risk of vaccine-triggered hemolysis, pharmacological anti-Men prophylaxis must be given and the first dose of vaccine can be given after CI treatment is started.
- As a general rule, in view of possible vaccine-triggered hemolysis, in patients already on CI treatment it is reasonable to assume that each vaccine should preferably be administered in the first half of the course of CI therapy (i.e. during the first week after eculizumab or during the first four weeks after ravulizumab), when the drug concentration in the blood is high. In the week after vaccination the patient should be carefully monitored.
- In order to avoid the risk of more intense vaccine reactions potentially responsible for hemolytic events when multiple vaccines are co-administered, in any PNH patient only one vaccine should be preferably administered at a time. This especially in patients with a history of vaccine reactions.
- No evaluation of antibody titer against meningococcal serogroups for the purposes of establishing immunity or the need for vaccination is recommended

3.1.2. *Anti-meningococcal chemoprophylaxis*

Since patients on eculizumab remain at risk for meningococcal disease even when vaccinated against meningococcus, some health care providers in the United States as well as public health agencies in other countries recommend antimicrobial prophylaxis for the duration of eculizumab treatment [3,6]. Some clinicians have also advocated lifelong antibiotic chemoprophylaxis [32–34].

Recently, Patriquin and co-workers [11] analyzed the data from the international PNH registry to assess meningococcal infections rates in PNH patients who received eculizumab with or without prophylactic antibiotic. Overall, 501 patients who received prophylactic antibiotics were compared to 730 patients who did not. In total, 3 and 4 patients in the two groups experienced a meningococcal infection during the study period. The estimated rates of meningococcal infection per 100 patient-years were 0.1 in both groups. A drawback of this study was represented

by the limited details of antibiotic prophylaxis use reported in the registry, in particular, it is not clear whether the patients were still on antibiotic prophylaxis or had already stopped it at the time of meningococcal infection.

An important issue for penicillin prophylaxis is decreased susceptibility and emergence of penicillin-resistant meningococcal strains that can vary depending on local sensitivity reports [35].

Looking at the more recent practices or recommendations, subtle differences in antimeningococcal chemoprophylaxis strategies emerged. Beneamu and Montoya (2016) recommended chemoprophylaxis with penicillin V potassium, 250 mg every 12 h or ciprofloxacin 500 mg daily for at least 4 weeks after complete immunization or until protective titers are decreased [36]. Lebel and co-workers (2018) [15] suggested that those found to be carriers of *Neisseria meningitidis* should be offered a targeted, susceptibility-based antibiotic course, in addition to the routine penicillin prophylactic treatment. They provided the alternative approach of administering patients with oral 750 mg ciprofloxacin, coupled with comprehensive explanation to use it when symptoms compatible with meningococcal infection occur, while seeking immediate medical evaluation. In 2018, the European Society of Clinical Microbiology and Infectious Diseases recommended prophylactic antibiotics for 4 weeks following vaccination [37]. In 2020, Langereis and co-workers [31] advised to offer antibiotic prophylaxis for 2 weeks according to the US FDA recommendation and prescribe antibiotics for immediate administration at home upon start of fever. In 2021, Brodsky [38] recommended penicillin prophylaxis (500 mg twice a day) in addition to vaccination for patients younger than 45 years old. The British PNH National Service strongly advised patients to take daily prophylactic antibiotics, either penicillin V 500 mg twice daily (or erythromycin 500 mg twice daily if allergic to penicillin) [39].

With regard to *Neisseria gonorrhoeae* infections, literature data shows that most cases were observed in young women presumably being secondary to genital infection. Considering the anecdotal cases of these sexually transmitted infections and the generally favourable evolution, guidelines do not suggest any prevention strategy other than attention to lifestyle.

Recommendations

- Prophylaxis of meningococcal infections with antibiotics (penicillin 500 mg twice daily or amoxicillin 500 mg twice daily, in alternative erythromycin 500 mg twice daily or ciprofloxacin 500 mg twice daily) is in general recommended before immunization has occurred. Prophylaxis should be given from the start of complement inhibitor therapy and until 15 days from the second meningococcal vaccines administration.
- Long-term antibiotic prophylaxis has been implemented in some countries, but determining its desirable duration is an UCN that requires more data. The panel agreed that treatment with a CI per se does not require lifelong antibiotic prophylaxis, unless because of other medical conditions, or because early management of suspected infections can be ensured.
- The panel agreed that country-specific data on the epidemiology of Neisseria meningitidis infection and on determinants of infection are needed to better manage chemoprophylaxis for infectious complications. Retrospective registry data analysis may be useful in this respect.
- With regard to novel CIs (in particular C3 and factor D inhibitors), considering the scarce information on the time-dependent infectious risk and on determinants of infections, while waiting for more data, the Panel agreed that a cautious approach is advised and the above antibiotic prophylaxis strategy should be adopted.

3.1.3. Anti-COVID-19 vaccination

A review of literature on COVID-19-infection in CIs recipients is reported in **Supplemental material II** [40–44]. Although the above data do not seem to suggest a significantly increased risk or a poorer outcome of SARS CoV 2 infection in PNH patients compared with the general population, anti-COVID-19 vaccination schedule for high risk subjects is indicated regardless of CIs treatment. However, reports of hemolytic exacerbations following SARS-CoV-2 vaccines have been reported in PNH despite CI treatment [45–50]. A systematic survey to evaluate complications and hemolytic flares in PNH patients who received SARS-CoV-2 vaccinations has been conducted among 8 Italian reference centers [49]. Eighty-seven PNH patients who received SARS-CoV-2 vaccination between January 2021 and January 2022 were included in the analysis. A total of 240 vaccine doses were administered and 66 (76%) patients received three doses at the time of the analysis. During the observation period, 13 hemolytic exacerbations were observed in 12 patients (13.8%) three of whom requiring supportive therapy and hospitalization. The remaining 10 episodes were mild. Most events ($N = 10$) occurred after the second/third dose, generally within 24–48 h. Anti-spike protein antibodies were available for 18 patients, of whom 16 on anti-complement treatment. Fifteen showed protective titers (median 838 U/mL, range 26;7500 U/mL), whilst 3 had a titer <80 U/mL (1 with an associated bone marrow failure, and 2 on CIs). Anti-complement treatment was not associated with impaired antibody response to vaccine ($p = 0.31$). In a large study from the Leeds Center 171 patients with PNH and aplastic anemia were compared to 45 healthy volunteers to assess antibody response to COVID-19 vaccination [50]. After one vaccination, patients had a substantially reduced seroconversion rate of 63% compared with 95% of healthy volunteers, with 2.4-fold lower antibody response than healthy volunteers. After second vaccination, seropositivity improved and was equivalent to healthy volunteers (99% *vs* 98%), with no difference in antibody levels. The reason for the difference in response between patients and healthy volunteers after one vaccination but not two vaccinations is unclear.

Recommendations

- Vaccination for COVID-19 is recommended. Even if the post-vaccination inflammatory reaction may cause breakthrough hemolysis, the risk-benefit ratio remains in favor of the vaccination.
- In order to reduce the risk of vaccine-triggered hemolysis, administration of COVID-19 vaccine should be performed as close as possible to the CI treatment (during the first week after eculizumab and during the first four weeks after ravulizumab). Furthermore, considering that most flares occur within few days after vaccine administration, close clinical monitoring and patient education particularly in the first week following vaccine is recommended.

3.1.4. Vaccination and chemoprophylaxis against other infections

Epidemiological data on infections other than meningococcus and SARS CoV-2 in patients with PNH treated with CIs are reported in the Supplemental Material I.

Recommendations

- Treatment with eculizumab and other CIs does not represent per se an indication to vaccination against pathogens other than N. meningitidis (S. pneumoniae, H. influenzae, influenza virus). The panel recommends these vaccines when additional risk factors are present (i.e. splenectomy, advanced age, co-morbidities) according to the following schedule:
  - o pneumococcal vaccination: 13-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal polysaccharide vaccine 8 weeks later. Revaccinate with a single dose of 23-valent pneumococcal polysaccharide vaccine after 5 years.
  - o Haemophilus influenzae type b: one single dose
  - o Influenza (injectable): A single dose annually
- Antibiotic prophylaxis of Neisseria gonorrhoeae infection is not required during CI treatment. Lifestyle habits and attention to signs and symptoms of genital infection must be the main preventive measures of this uncommon disease.

3.2. Developing other risk-mitigation strategies for PNH patients on anti-complement inhibitors, not limited to pharmaceutical interventions

This issue is particularly felt by patients who complain of a non-homogeneous knowledge of PNH by local health system in relation to the characteristics of the disease and the implications related to its treatment. To mitigate the occurrence of and morbidity associated with meningococcal infections, since the first guiding document on the eculizumab use, FDA recommended a risk evaluation and mitigation strategy to educate health care providers and patients about the risk for and early signs of possible meningococcal infection and the need for immediate medical evaluation of signs and symptoms consistent with possible meningococcal infection [6]. However, PNH is a rare disease characterized by dispersed organization of health care and the risk of inappropriate management, when incident clinical problems are not managed by the referral centers, can represent a serious problem. In Italy, as in many of European countries, management of PNH patients is distributed across many centers, including academic or research hospitals, and local hematology units. With this organizational background, the clinical management of PNH patients requires an integrated care approach [51]. Integrated care is a term that reflects a concern to improve patient experience and achieve greater efficiency and value from health delivery systems. The aim is to facilitate the appropriate delivery of health care services and overcome fragmentation between providers considering the peculiarity of PNH patients. In Italy, this functional network has received a structural recognition by the National Network of Rare Diseases, established in 2001 (https://www.salute.gov.it/portale/temi/p2_6.jsp?lingua=italiano&id=707&area=Malattie%20rare&menu=vuoto).

Considering the experience gained in the organization of this network the Panel suggests the following.

Recommendations

- For an integrated care of patients with PNH, a limited number of regional referral centre(s) should be identified on the basis of indisputable clinical experience. Regional referral centres should be coordinated by an above parts national institution.
- In order to facilitate an appropriate and timely approach to complications in PNH patients, in particular infections, the same patients and their care givers should be instructed to provide useful information. This is particularly important when patients go to centers other than their reference. Patient safety can be improved by technical means (e.g. patient cards, information booklets, dedicated websites), but the role of reference PNH expert doctor appears irreplaceable to ensure the proper awareness in the patient and in his family members and support peripheral health structures. Each patient should be able to provide direct contact of the referring hematology team (telephone number, email address). This not only for advice on the management of a complication but also for indications on the continuation of treatment with the CI.
- Contact with the reference centre (which can also be implemented by means such as telemedicine) is even more necessary in view of the introduction of new treatments, where the compliance of the patient could be critical in ensuring the optimal result and in preventing possible serious reactions.
- All patients on CIs treatment and their care givers should be instructed in the careful evaluation of possible infectious signs (i.e. having a raised temperature, above 38 °C) and in the early intake of an antibiotic treatment (amoxicillin-clavulanate 2 g followed by 1 g every 8 h or ciprofloxacin 500 mg every 12 h) if there is a delay in receiving medical care / advice. This should not replace contacting a healthcare professional for advice and assessment.

3.3. Improving the management of disease exacerbation during infectious complications in PNH on CI treatment

That disease exacerbations may occur in PNH is semantically implied in its own name; indeed, it is well know that paroxysms appear in any condition triggering the complement cascade [52,53]. Infections are the most obvious events leading to hemolytic crises in PNH, as well known by treating physicians, and patients themselves.

Systematic investigations of infectious events and possible consequences on hemolysis in PNH on anti-complement treatment are missing, even if information may be drawn from prospective trials [54–58] as well as from retrospective studies. Indeed, the re-appearance of hemolysis during anti-complement treatment is referred as “breakthrough hemolysis”, which is a discrete endpoint included in most PNH studies.

While the most typical breakthrough hemolysis is due to subtherapeutic level of eculizumab [59], in case of infectious events the cause of hemolysis is due to some hyper-activation of the complement cascade (in addition to the spontaneous C3-tickover) which likely generate C3-rich C5 convertases which may better compete with eculizumab for their C5 substrate [60,61]. These two conditions can be described as pharmacokinetic and pharmacodynamic breakthrough, respectively [62–64].

In the recent literature, pharmacodynamic breakthrough can be found also as breakthrough hemolysis associated with complement-amplifying conditions [65], a definition which highlights the fact that in most cases it occurs in absence of meaningful plasma level of free C5 [66]. Indeed, infectious events often result in exacerbations of hemolysis despite CI treatment; in most cases these hemolytic episodes are self-limiting and transient, since they resolve once the underlying condition triggering the complement cascade has disappeared (or mitigated).

While hemolytic exacerbations during anti-C5 treatment are quite well described, less is known about disease exacerbations occuring in PNH patients receiving the more recent proximal CIs [67–70]. Clinically speaking, the fact that the outstanding hematological benefit of these compounds is associated with extremely high proportions of PNH erythrocytes (even >90%) justifies some fear for possible dramatic hemolytic events [71]. Nevertheless, so far these severe hemolytic crises have been rarely described with the anti-C3 pegcetacoplan [72–74], less with the anti-factor D Danicopan [68], and never with the anti-factor B iptacopan [69].

Recommendations

- In patients with PNH experiencing an infectious complication, anti-complement treatment must not be discontinued
- In most cases extra-dose of eculizumab (or other anti-C5 agents) are not indicated, because supra-therapeutic, concentrations of anti-C5 do not overcome a pharmacodynamic breakthrough.
- Extra-doses of eculizumab may be considered when a sub-therapeutic plasma level of the anti-C5 is suspected or confirmed
- In the absence of this knowledge, the Panel recommended to follow the recommendations issued in the clinical trials protocols. Accordingly, in case of clinically meaningful events rescue treatment with anti-C5 agents should be taken in high consideration without discontinuing the proximal inhibitor.

4. Conclusions and future directions

A main aim of the Italian PNH Association is to optimize the care of patients with PNH. Consonant with this aim and solicited by the patients themselves, the Scientific Committee of the Association has undertaken this review focused on the risk of infection in patients treated with eculizumab or with new CIs. Despite the paucity of high-level evidence on several important clinical issues, the panel of experts was able to reach a high degree of consensus on some issues and to identify UCNs for which further evidence is needed. This consensus is a valid basis for

clinical implementation of the recommendations given and for the design of new studies that may guide therapeutic decisions. The Panel identified aspects that deserve further study by indicating the clinical research methodology useful for acquiring new knowledge and guiding future infection prevention strategies in PNH patients.

Practice points

- Prevention strategy of meningococcal infections based on vaccination and chemoprophylaxis is the standard of care of PNH patients on CIs treatment.
- However, the timing of vaccination and the duration of chemoprophylaxis are still debated issues.
- Although CIs treatment does not seem to significantly increase the risk of infections other than meningococcal (*i.e.* SARS CoV-2 infection, pneumococcus infection, influenza), the vaccination against these pathogens should also be considered.
- Until more information is available, the eculizumab targeted recommendations should also apply to patients being treated with other CIs.
- To mitigate the occurrence of and morbidity associated with meningococcal diseases, education of health care providers and patients about the risk for and early signs of possible infection should be implemented.

Research agenda

- Continuous investigation on epidemiology and risk assessment of infections is required to detect the risk profile of infections in PNH patients treated with old and new CIs.
- Information is particularly required on infectious risk related to the use of new CIs in order to assess whether the infectious risk and related preventive measures are comparable to those observed during eculizumab treatment.
- Implementation of such information in retrospective regional or national registry data and clinical trials is highly recommended.

Funding

Alexion Pharma, Italy provided financial support for this project but had no role in identifying statements, abstracting data, synthesizing results, grading evidence, or preparing the manuscript or in the decision to submit the manuscript for publication.

Declaration of Competing Interest

C. Girmenia has received honoraria from Gilead Sciences, MSD, Pfizer Pharmaceuticals, Celgene, Novartis, Janssen, Takeda, Amgen, GSK, Biotest and Alexion Pharmaceuticals.

W. Barcellini has received honoraria from Agios, Alexion, Apellis, Biocryst, Incyte, Janssen, Momenta, Novartis, Sanofi, SOBI and Alexion Pharmaceuticals.

P. Bianchi has received honoraria from Agios Pharmaceuticals, Rocket Pharmaceuticals and Alexion Pharmaceuticals.

E. Di Bona has received honoraria from Alexion Pharmaceuticals a.

A.P. Iori has received honoraria from Novartis, Takeda, Amgen, JAZZ and Alexion Pharmaceuticals.

R. Notaro has received honoraria from BioCryst, SOBI Pharmaceuticals and Alexion Pharmaceuticals.

S. Sica: has received honoraria from Amgen Jazz, Pfizer, Astellas, Sobi and Alexion Pharmaceuticals.

A. Zanella has received honoraria from Agios e Rocket Pharma. and Alexion Pharmaceuticals.

A. De Vivo has received honoraria from Takeda Italia, Sobi Italia and Alexion Pharmaceuticals.

G.Barosi has received honoraria from Alexion Pharmaceuticals.

A. Risitano has received honoraria from Apellis, Sobi, Novartis, Roche, Samsung, Pfizer and Alexion Pharmaceuticals.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.blre.2022.101013.

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