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Serologic response to meningococcal vaccination in patients with cold agglutinin disease (CAD) in the novel era of complement inhibition

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ABSTRACT

Cold agglutinin disease (CAD) is a rare, potentially life-threatening acquired autoimmune hemolytic anemia characterized by hemagglutination and hemolysis due to immunoglobulin-mediated (usually IgMκ) classic complement pathway activation. Complement inhibition (CI) represents a novel treatment option to control hemolysis. Due to CI patients (pts) are susceptible to encapsulated bacteria e.g. *N. meningitidis*. Therefore, meningococcal vaccination on CI is mandatory. In this study serologic response to the tetravalent conjugate vaccine Menveo® was analyzed in CAD pts on eculizumab treatment (DECADE trial) using rabbit serum as complement source (rSBA). Protective rSBA titers varied for meningococcal serogroups and over time reflecting an early decline to even non-protective rSBA titers. These data highlight the importance of serologic analyses under chronic CI. Currently, re-vaccination with a tetravalent meningococcal conjugate vaccine every 3 years is recommended on chronic CI. However, re-vaccination on CI might further rely on serologic analyses, implying even early booster vaccinations similar to adults with (functional) asplenia.

1. Introduction

Cold agglutinin disease (CAD) is an ultra-rare, acquired autoimmune hemolytic anemia (AIHA) with an estimated prevalence of 16 cases per million, representing 13–32% of all AIHAs [1,2]. Primary CAD is distinct from secondary cold agglutinin syndrome (CAS) and thought to be caused by a low-grade clonal lymphoproliferative B-cell bone marrow disorder. CAD is mediated by cold agglutinin-induced (CA) complement-mediated extra- and intravascular hemolysis and hemagglutination aggravated by exposure to cold environmental temperatures, inflammation, or infections. Cold agglutinins are predominantly monoclonal immunoglobulin (Ig) M kappa (κ) light chain restricted autoantibodies (IgMκ) that demonstrate an inherent affinity for the carbohydrate I antigen on the cell surface of erythrocytes. This is of special importance. During passage of erythrocytes through acral parts of the body, as blood is cooled, hemagglutination is caused by binding of CAs to the erythrocyte carbohydrate I antigen, which in turn is followed by classic complement pathway initiation as the antigen-bound IgM-CAs bind complement protein 1q (C1q). In addition, C3b plays a substantial role of continuous extravascular hemolysis in even stable disease states via supporting phagocytosis of C3b-coated erythrocytes in the liver as C3b remains attached to erythrocytes despite the detachment of CAs from erythrocytes in

Abbreviations: AchR, anti-acetylcholine receptor; ANC, absolute neutrophil count; CAs, cold agglutinins; CAD, cold agglutinin disease; CAS, cold agglutinin syndrome; CI, complement inhibition; CMV, cytomegalovirus; DAT, direct antiglobulin test; EBV, Epstein-Barr virus; EC, European Commission; EU, European Union; gMG, generalized myasthenia gravis; GMT, geometric mean titer; Hib, Haemophilus influenzae serotype b; Ig, immunoglobulin; IMD, invasive meningococcal disease; LDH, lactate dehydrogenase; mAb, monoclonal antibody; MAC, membrane attack complex; N. meningitidis, Neissera meningitidis; PNH, paroxysmal nocturnal hemoglobinuria; RKI, Robert Koch Institute; rSBA, serum bactericidal antibody (SBA) assay using baby rabbit serum as external complement source; STIKO, Standing Vaccination Committee; S. pneumoniae, Streptococcus pneumoniae.

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the central circulation as blood is warmed to 37 °C, allowing agglutinated erythrocytes to separate. In severe hemolytic patients or during an acute hemolytic exacerbation, intravascular hemolysis is primarily mediated by C5 [3].

Although not all patients require a specific pharmacological therapy, and treatment is dependent on disease severity, the lack of effective treatment options to control hemolysis in CAD results in high treatment failure rates, low median response durations in treatment responders, and high relapse rates. This, in turn raises the need for multiple treatment lines, increasing the potential risk of long-term toxicity. By now, conventional treatment approaches based upon IgM suppression in addition to supportive red blood cell transfusions are considered the mainstay in CAD management, even though, they do not address complement, representing the key driver of immune hemolysis in these patients [4].

Complement-directed approaches (*eculizumab-C5*, *sutimlimab-C1s* (*BIVV009*), and *APL-2-C3*) consequently resemble a promising therapeutic alternative in CAD. Due to inhibition of the complement cascade, patients are susceptible to infections caused by encapsulated bacteria, e.g. *Neisseria meningitidis (N. meningitidis)* in addition to *Streptococcus pneumoniae (S. pneumoniae)*, and *Haemophilus influenzae serotype b (Hib)* in patients under treatment directed upstream complement component C5, e.g. at the level of C3. Therefore, effective vaccination is urgently needed and mandatory on CI in order to reduce the risk of infection. This especially accounts for *N. meningitidis*, as the prevalence of meningococcal infections varies among the different serogroups with serogroup B and C being responsible for the majority of disease cases in Europe [5]. However, the individual risk for an invasive meningococcal disease (IMD) in the presence of an acquired complement defect, as seen in patients subject to targeted CI, is less clear [6]. In addition, these patients might further be at risk for contracting a serious meningococcal infection by uncommon serogroups such as Y, W, and X or even unencapsulated strains, despite their low prevalence [7].

2. Primary objective and study definitions

The prospective phase II, non-randomized, bicentric DECADE trial performed at the University Hospital of Essen and Ulm was assigned to evaluate the efficacy and safety of the terminal complement inhibitor eculizumab in symptomatic or transfusion-dependent treatment-naïve or refractory hemolytic CAD patients [8].

The primary objective of this current subanalysis of the DECADE trial was to evaluate serologic response in these patients following vaccination with the tetravalent meningococcal conjugate vaccine Menveo® (GlaxoSmithKline Biologicals, Inc.) under CI in order to evaluate the efficacy of meningococcal vaccines by measuring serum bactericidal antibody titers using baby rabbit serum as source of external complement (rSBA) against meningococcal serogroups A, C, W, and Y pre- and post vaccination at two distinct time intervals.

The serum bactericidal assay antibody (SBA) is a widely accepted surrogate to monitor sero-response to meningococcal vaccines, serving as an immunological correlate of protection. Using rSBA is justified by the fact that in this specialized population treatment is directed to inhibit complement and eculizumab is highly species specific and not known to inhibit rabbit complement [9]. SBA titers for each serogroup were expressed as the reciprocal of the last dilution that led to ≥50% killing of the meningococci after one hour. By definition, sero-response in this cohort – as it is generally defined for the purpose of meningococcal vaccine licensure – was defined by a post-vaccination rSBA titer ≥1:8 in patients with a baseline rSBA titer ≤1:4 or, at least a four-fold rise in patients with a pre-vaccination rSBA titer ≥1:4 [10]. This accounts especially in patients with a baseline rSBA titer ≥1:8-1:64 pre-vaccination [11].

3. Patients and methods

Of the overall 13 CAD patients enrolled in the DECADE trial, rSBA titers prior to meningococcal vaccination were assessed in nine patients and thus, found to be eligible for further evaluation according to the above defined study criteria. Baseline clinical- and pre-treatment characteristics are shown in Table 1. In these patients rSBA titers were monitored and documented post-vaccination under terminal CI with eculizumab at two distinct time intervals (visit 6 (fourth treatment week) and 17 (26th treatment week)), with the first interval being as closely related to other vaccine studies evaluating immune response to meningococcal vaccines post-vaccination. The second interval (visit 17) was designed to monitor the rSBA titer course over time. In the remaining four patients rSBA titers were not measured prior to vaccination in three patients, including one patient with acute CAD who was treated with prednisone and in whom immediate treatment with eculizumab was mandatory due to severe hemolytic exacerbation. In another patient, no rSBA titers were determined during treatment phase. Hence, protective rSBA titers or a specific titer increase indicating immune response after vaccination could in general not be excluded. None of the patients had a history of IMD before trial enrollment or developed active signs or symptoms being suspicious for IMD during the observation period. None of the patients were vaccinated with a meningococcal vaccine prior to trial enrollment.

CAD was defined by the combination of hemolysis/hemolytic anemia in association with a cold agglutinin titer (IgM or IgA) ≥1:64 at 4 °C and a positive direct antiglobulin test (DAT) with strong positivity for anti-C3d and negativity (or weakly positivity) for anti-IgG. All patients were at least 18 years of age. Patients requiring treatment with rituximab, alkylating agents, human immunoglobulins, or plasmapheresis four weeks before screening were not allowed to participate. Other important exclusion criteria were the presence of an active bacterial or viral infection, such as hepatitis B or C, or prior bone marrow/stem cell transplantation. Each patient was monitored for a minimum period of 34 weeks. According to the trial protocol, recommendations and national guidelines for patients under CI with eculizumab at that time, all patients were vaccinated with a single dose of the tetravalent meningococcal conjugate vaccine (Menveo®) administrated by intramuscular injection 14 days prior to treatment initiation.

By the time of eculizumab initiation, all patients were provided with an appropriate antibiotic prophylaxis, if necessary, usually ciprofloxacin, depending on additional circumstances for a minimum duration of two weeks starting from eculizumab treatment initiation and meningococcal vaccination. In the twelve patients with chronic CAD, prior therapeutic regimens included the use of cyclophosphamide (5 patients), prednisone (4 patients), azathioprine, rituximab (3 patients each), chlorambucil, bendamustine, fludarabine and human immunoglobulins (1 patient each) [8].

Informed consent for measurement of SBAs was obtained in all patients. Determination of rSBA titers were performed at the Reference Centre for Meningococci and Haemophilus influenzae at the University of Würzburg, Germany, as described preciously [12]. This analysis as part of the DECADE trial was conducted in accordance with the Declaration of Helsinki.

The study was conducted at the Department of Hematology at the University Hospital Essen and at the Department of Internal Medicine III at the University Hospital Ulm. Analyses and use of data were approved by the Ethical Committees of the Faculty of

Table 1
Baseline clinical- and pre-treatment characteristics (n = 9).

Pat.	Pat. ID	Age (yrs.)	Gender	Ethnicity	BMI (kg/m^2)	Hb at baseline (g/dL)	LDH at baseline (U/L)	No. of prior therapies	IgG levels prior to eculizumab therapy (g/L)	Meningococcal vaccine
1	10-001	77	Female	CAU	30.78	10.8	545	0	11.8	Menveo®
2	10-003	72	Male	CAU	25.88	9	572	0	12.7	Menveo®
3	10-004	73	Female	CAU	21.87	8.8	625	3	5.1	Menveo®
4	10-006	75	Female	CAU	20.55	11.6	797	2	7	Menveo®
5	10-007	80	Female	CAU	22.74	8.3	685	5	4	Menveo®
6	10-012	74	Female	CAU	22.86	8.3	514	0	9.8	Menveo®
7	10-013	64	Female	CAU	22.32	10.8	638	0	5.2	Menveo®
8	12-010	69	Female	CAU	24.22	9.5	566	0	9.9	Menveo®
9	12-015	76	Female	CAU	24.86	9.2	453	0	11	Menveo®
Median (range)		74 (64–80)			22.86 (20.55–30.78)	9.2 (8.3–11.6)	572 (453–797)	0 (0–5)	7 (4–12.7)	

Abbreviations: BMI, body mass index; CAU, Caucasian; Hb, hemoglobin; IgG, immunoglobulin G (normal range: 7–16 g/L); LDH, lactate dehydrogenase; Pat. ID, patient identifaction; yrs, years.

Medicine at the University Hospital of Duisburg-Essen (Eudra-CT: #2009-016966-97) and the Faculty of Medicine at the University Hospital of Ulm, Department of Internal Medicine III.

4. Results

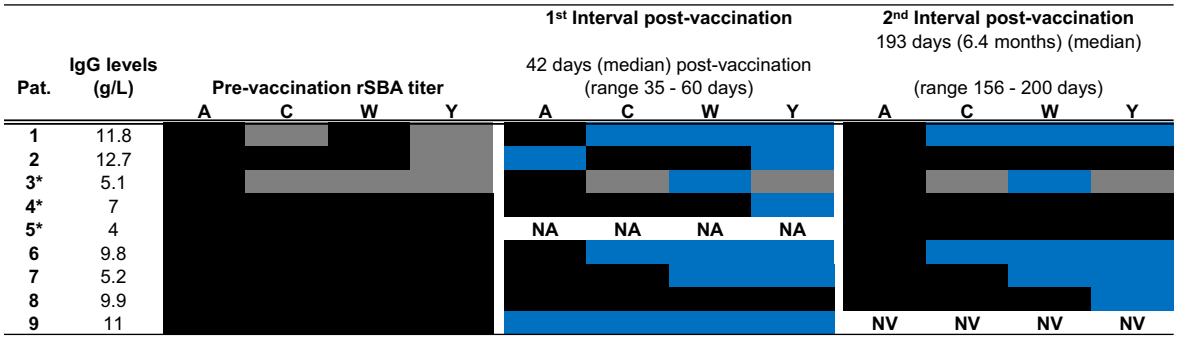
Sero-response measured by SBAs using baby rabbit serum (rSBA) as source of exogenous complement varied in the evaluated CAD patients for the different meningococcal serogroups A, C, W, and Y following vaccination with Menveo® throughout the observation time. With regard to baseline rSBA titers measured prior to meningococcal vaccination, rSBA titers were assessed at a median of 42 days (fourth treatment week) post-vaccination (range 35–60 days) in eight of the nine eligible patients. In patient 5, the SBA was not assessable at the first observation period. Nevertheless, in this patient rSBA titers remained ≤1:4 at the second end-point, being suggestive that a protective immune response in terms of protective rSBA titers was further not evident at the first observation period. Protective bactericidal antibody titers were detected in 75% (6/8) of the patients against serogroup Y followed by 62.5% (5/8) against serogroup W. By contrast, in only 37.5% (3/8) of the patients was a protective immune response to serogroup C evident with lowest immune response against serogroup A (25% (2/8)). Only in one patient (patient 9) a full immune response was documented on day 37 following vaccination with Menveo®. In patient 3, rSBA titers were ≥1:8 prior to vaccination for serogroup C and Y. However, at the first observation period in this patient, no four-fold titer increase from baseline was observed, so that a protective immune response could not be assumed.

At a median of 6.4 months of observation, rSBA titers were determined in eight out of the nine CAD patients showing that in five patients protective bactericidal titers according to the defined criteria following vaccination with Menveo® could be documented. In patient 8, sero-conversion to protective SBA titers was evident for meningococcal serogroup Y following 6.7 months after initial vaccination. Overall immune response analyses in the studied CAD patients are depicted in Table 2. Furthermore, in two patients (patient 2 and 4) a decrease in rSBA titers to non-protective titers was observed during the observation period, despite the fact, that in all patients with rSBA titer follow-up, an expected decline in rSBA titers at 6.4 months following vaccination was evident (Fig. 1).

In the three immunosuppressive pre-treated CAD patients (patient 3, 4, and 5) a protective sero-response to vaccination could not be observed against three meningococcal serogroups in two of the patients (patient 3 and 4) at the first observation period. In the third patient (patient 5), rSBA titers were not assessable at that time. However, in this patient non-protective rSBA titers could still not be observed at 6.4 months post vaccination. Of note, in two of three immunosuppressive pre-treated patients, implying the use of rituximab or related immunosuppressive agents, a concomitant immunoglobulin G (IgG) depletion was observed prior to eculizumab therapy (patient 3: IgG 5.1 g/L and patient 4: 4 g/L). Furthermore, an associated IgG deficiency (IgG 5.2 g/L) prior to study enrollment was observed in one of the treatment-naïve patients (patient 7) (Table 2).

Due to the small sample size with a nearly uniform age and BMI distribution, an age- and BMI-related stratification was omitted.

Table 2
Immune response to meningococcal vaccination with Menveo® in CAD patients (n = 9).



Abbreviations: Black boxes: rSBA titer ≤1:4, grey boxes: rSBA titer ≥1:8-1:64, blue boxes: immune response defined as a post vaccination rSBA titer ≥1:8 in patients with a baseline rSBA ≤1:4 or, at least a four-fold higher than baseline titer in patients with a pre-vaccination rSBA titer ≥1:4; IgG, immunoglobulin G baseline levels (normal range: 7–16 g/L); NA, not assessable; NV: no value; Pat., patient; * pre-treated patients.

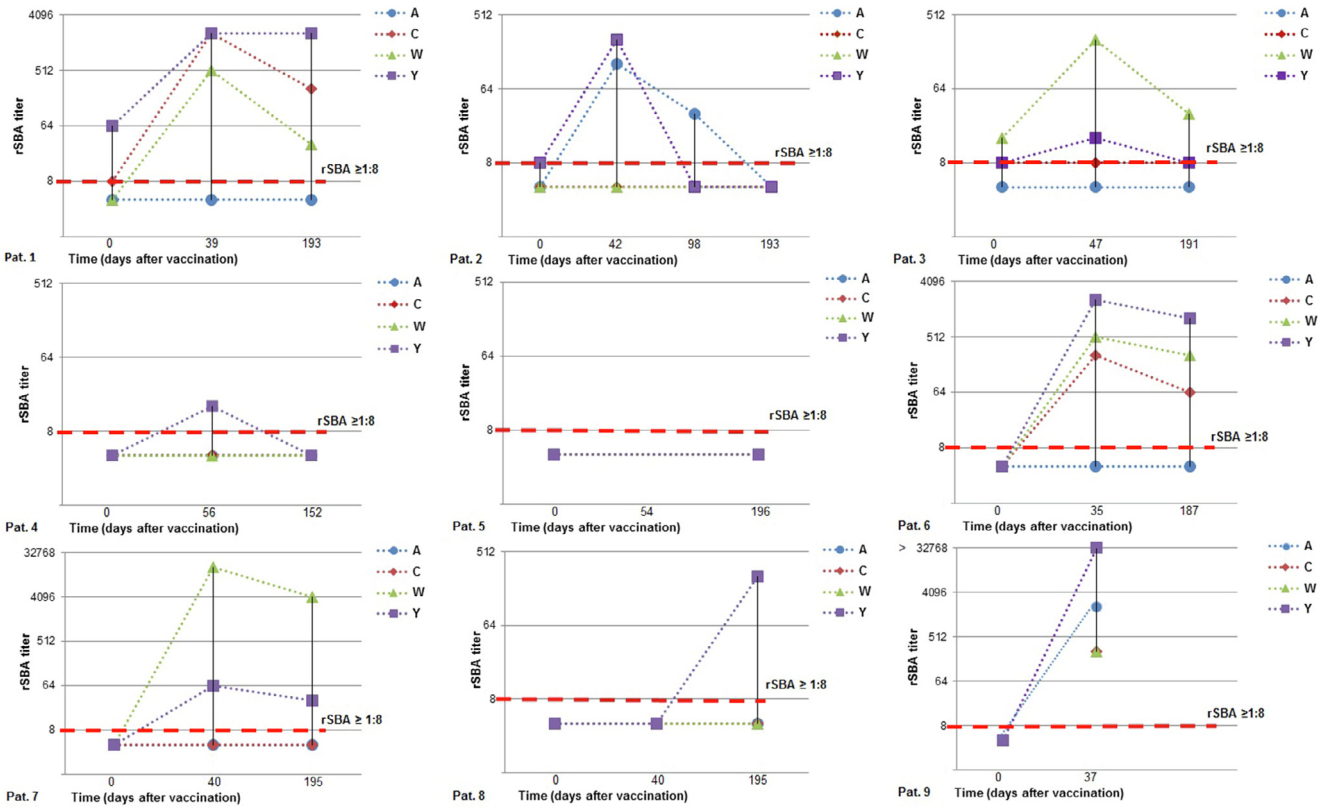


Fig. 1. rSBA titer course over time to meningococcal serogroups A, C, W, and Y following vaccination with Menveo® in eculizumab-treated CAD patients (n = 9).

Similarly, a correlation between serologic responses following meningococcal vaccination in the setting of prior immunosuppressive treatment could not be determined due to the small sample size.

5. Discussion

Complement-directed therapies in patients with symptomatic primary CAD represent a novel and promising therapeutic alternative to the current standard of care. The driving mechanism responsible for immune-mediated hemolysis in CAD is entirely complement-dependent due to classic complement pathway initiation by CAs and subsequent phagocytosis of erythrocytes opsonized with complement protein C3b in addition to downstream cleavage of C5b with activation of the membrane attack complex (MAC), resulting in intra- and extravascular hemolysis [3]. Therefore, this approach is especially feasible for patients who are ineligible for or not responding to B-cell-directed therapies.

Attempts to efficiently inhibit complement by blocking regulatory proteins undoubtedly are critical to its function and regulation, and the associated risks with long-term CI are presently unknown, resulting in predictable or even unpredictable defects in complement-dependent functions by interfering with complement's physiological role in host defense, exposing patients to danger of infections with encapsulated bacteria (*N. meningitidis*, *S. pneumoniae*, and *H. influenzae* serotype b (Hib)). This highlights the importance and need for adequate prophylactic vaccination and clinical monitoring of patients under (chronic) CI, especially for *N. meningitidis*, as complement deficiencies affecting the alternative pathway, C3, and the terminal complement components (C5-C9; MAC), all of which being currently under investigation in CAD patients, are associated with an increased risk of contracting an IMD [13,14]. Moreover, meningococcal serogroups may differ from one another due to differences concerning their binding affinity to certain complement regulatory proteins [15].

This analysis, as part of the DECADE trial, is the first study in this highly specialized population evaluating serologic response against meningococcal serogroups A, C, W, and Y prior to and under therapy with the terminal complement inhibitor eculizumab following vaccination with the quadrivalent meningococcal polysaccharide conjugate vaccine Menveo® by measuring serum bactericidal antibody titers using baby rabbit serum as source of complement (rSBA). None of the patients was vaccinated with a meningococcal vaccine prior to actual trial enrollment, as documented by non-protective rSBA titers. Furthermore, in none of the patients a meningococcal infection was observed during the observation period and none of them developed clinical signs or symptoms being consistent for IMD throughout observation. Taking into account that the DECADE trial was conducted between January 2011 and September 2014, none of the patients at that time were vaccinated against meningococcal serogroup B. 4CMenB (Bexsero®, GlaxoSmithKline Biologicals, Inc.) received a marketing authorization valid throughout the European Union (EU) on 14 January 2013 and was recommended in August 2015 by the German Standing Vaccination Committee (STIKO) – Robert Koch Institute (RKI) for patients under eculizumab therapy. Whereas, MenB-FHbp (Trumenba®, Pfizer, Inc.) received marketing authorization valid by the European Commission (EC) in May 2017 for active immunization and prevention of IMD in adolescents and young adults 10 years of age and older [16,17].

In eculizumab-treated CAD patients, serologic protection differed for the individual serogroups, showing a poor immune response following meningococcal vaccination with Menveo® at a median of 42 days (range 35–60 days) with protective rSBA titers being evident in only 25% (2/8) against serogroup A and 37.5% (3/8) against serogroup C. Sero-conversion to protective rSBA titers was

highest against serogroup W (62.5% (5/8)) and Y (75% (6/8)). However, at a median of 6.4 months (range 156–200 days) of observation, a decline to even non-protective rSBA titers was seen in three patients for serogroup A and Y. These data are consistent with previously published studies by Alashkar et al. (2017) and Gäckler et al. (2018) evaluating serologic response to meningococcal vaccines in eculizumab-treated patients. Despite the fact that in both studies rSBA titers prior to vaccination were not obtained, a four-fold rSBA titer rise in patients with a baseline rSBA titer $\geq$1:4 indicating serologic protection could in general not be assumed [18,7].

The findings reinforce the hypothesis of an increased risk for contracting a serious meningococcal infection under CI with eculizumab, as eculizumab blocks not only the assembly of the membrane attack complex (MAC), it consequently blocks upstream the formation of C5 convertase and thereby cleavage into C5a and C5b, with C5a being a potent anaphylatoxin and chemoattractant that is essential for effective opsonophagocytosis via upregulating FcγR and activating neutrophils [19]. As a result, one might conclude, that even in the presence of protective antibody titers in eculizumab-treated CAD patients the ability to mount an infection might be reduced. In addition, the frequent use of immunosuppressive B-cell-directed therapies in CAD patients represents an additional risk factor for lower rates of protective immune responses following vaccination as described by Nazi et al. (2013), further resulting in an associated overall higher risk of contracting a meningococcal infection [20]. Unfortunately, a detailed analysis with regard to IgG subclasses in addition to B-cell counts was not possible as these parameters were not routinely documented prior to treatment.

The SBA assay using either human or baby rabbit serum as source of complement represents the gold standard in clinical trials in order to measure the bactericidal activity of an individual's serum towards *N. meningitidis* serving as a surrogate marker for determining the efficacy of meningococcal vaccines [21]. Serum bactericidal antibody titers are defined as the reciprocal of the serum dilution where $\geq$50% bacterial growth is inhibited in comparison to controls. As eculizumab is highly species specific and has no appreciable activity against rabbit complement, serologic analysis in patients under CI with eculizumab should be evaluated by using baby rabbit serum as source of complement [9,7]. In addition, in none of the investigatory meningococcal vaccine trials eculizumab-treated patients were included.

When correlating our data with past studies evaluating the immunogenicity of Menveo® in healthy adults aged 56–65 years one month post-vaccination, a decreased immune response to Menveo® in the studied CAD patients was observed. However, immune response analyses following vaccination with Menveo® in adults >65 years of age have not been established, thus limited knowledge in older patients concerning immune responses to vaccines exist, which especially accounts for our patient cohort (median age 74 years (range 64–80 years)).

In the observer-blind, randomized phase III multicenter V56P17 study evaluating immunogenicity to a single dose of Menveo® within 28–42 days following vaccination in healthy adults between 56 and 65 years of age for meningococcal serogroups the proportion of subjects who achieved a hSBA $\geq$1:8 were as follows: A: 87% (n = 83; 95% confidence interval 78–93), C: 90% (n = 84; 95% confidence interval 82–96), W: 94% (n = 82; 95% confidence interval 86–98), and Y: 88% (n = 84; 95% confidence interval 79–94) [22]. Notwithstanding the fact, that in this current analysis baby rabbit serum instead of pooled human serum was used as the source of complement as eculizumab has no appreciable activity against rabbit complement, and the fact that seroresponse determined with rabbit and human complement poorly correlate, baby rabbit serum is currently more frequently used in trials evaluating the efficacy to meningococcal vaccines. This is because it lacks endogenous bactericidal activity compared to human serum, with human serum lacking bactericidal antibodies against meningococci being difficult to obtain [23]. The poor correlation between serum bactericidal activity against the different meningococcal serogroups is not fully understood and might be related to various interactions between antibody subclasses and the complement source being used in addition to species-specific interaction of *N. meningitidis* with complement regulators. However, Jones (2016) provided further important insights in the understanding of antibody responses to meningococcal vaccines by showing that in individuals with large IgM responses to vaccination, rSBAs produce higher titers compared to hSBAs in humans with high IgM responses, as polysaccharide-specific IgM contributes more to bactericidal titers in rSBAs, whereas the concentration of polysaccharide-specific IgG1 antibody correlated most with hSBA titers [24].

Vaccination against meningococcal serogroups A, B, C, W, and Y in addition to vaccination against *S. pneumoniae* and *H. influenzae* serotype B (Hib) is further implicated in the currently recruiting complement-directed investigatory APL-2 and sutimlimab trials in CAD patients. Sutimlimab (Bioverativ Therapeutics Inc.) is a humanized monoclonal antibody (mAb) directed against C1s ((*Cardinal Trial* (NCT03347396) and *Cadenza Trial* (NCT03347422)), whereas APL-2 is a cyclic peptide inhibitor of C3 (Apellis Pharmaceuticals, Inc. (NCT03226678)) [14]. By specifically binding C1s via sutimlimab, the alternative and lectin pathway remain functionally intact in addition to C1q, whereas APL-2 as a potent C3 inhibitor effectively blocks all three distinct complement pathways with particularly high potency against the alternative pathway and is thought to prevent both, C3-mediated extravascular and MAC-mediated intravascular hemolysis. By targeting complement in CAD, immediate cessation of hemolysis with rapid correction of anemia and symptomatic improvement of disease-related symptoms is expected.

In summary, the results of this analysis, in accordance with prior analyses such as Alashkar et al. (2017) indicate that serological analyses in patients under chronic CI are useful to monitor immune responses to vaccines in these special patients and should further be implemented in current guidelines as these patients are at an increased risk for contracting an IMD [17,7]. Similar to vaccination recommendations in asplenic and hyposplenic patients, a booster-vaccination with a tetravalent meningococcal conjugate vaccine following 8–12 weeks apart from the first vaccination might be indicative in order to reduce the risk of infection, inducing a more potent immune response. This especially accounts for patients with a poor immune response following the first vaccine dose, as short-term protection, reflected by SBAs, is more meaningful than immunologic memory [25]. In patients with a sub-optimal serologic response seen after the booster-vaccination no further vaccination should be given, as the geometric mean titer (GMT) required for long-term immune response is presently unknown [10]. The implementation of vaccination against *S. pneumoniae* and *H. influenzae* serotype B (Hib), in addition to *N. meningitidis* serogroups A, C, W, and Y in the present complement-modulating CAD trials, might further reduce the risk of infectious complications. However, as different complement pathways are being targeted, the ability of vaccine-induced antibodies conferring protection in these settings is poorly understood and serious meningococcal infections have already been observed in vaccinated patients under CI, with most cases so far being described in eculizumab-treated patients. Thus, it is important not to fully rely on the efficacy of a meningococcal vaccine in patients under (chronic) CI. Physicians and patients must be aware and vigilant for meningococcal disease at all times. Therefore, we recommend a stand-by treatment (e.g. 750 mg of ciprofloxacin) be given immediately in the case of signs

or symptoms suspicious of meningococcal infection (e.g. fever) with further medical evaluation and treatment without any delay [26,27].

Contribution

F.A. wrote the first draft of the manuscript and designed the figures and tables; U.V. measured rSBA titers; A.R., A.H., A.T., C.V., C.S., M.B., U.D., U.V. reviewed the draft; A.R., M.B., A.H., D.H.-T., and U.D. directed the clinical activities at the participating study centers; and all authors contributed to data interpretation, reviewed the draft, and approved the final version of this report.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Disclosures: A.R. and U.D. received honoraria from Alexion Pharmaceuticals and Roche Pharma. The remaining authors declare no competing financial interests.].

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.09.033.

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