Safety of vaccinations in patients with cryopyrin-associated periodic syndromes: a prospective registry based study

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Running header: Safety of vaccinations in CAPS

ABSTRACT

Objectives: Pneumococcal, tetanus and influenza vaccinations are recommended for patients with Cryopyrin-Associated Periodic Syndromes (CAPS) when treated with immunosuppressive medication. The aim of this publication is to report the safety of pneumococcal and other vaccinations in CAPS patients.

Methods: All CAPS patients followed in the β-CONFIDENT (Clinical Outcomes and Safety Registry study of Ilaris patients) registry were analysed if they had received a vaccination. The β-CONFIDENT registry is a global, long-term, prospective, observational registry, capturing and monitoring patients treated with canakinumab.

Results: 68 CAPS patients had received a total of 159 vaccine injections, 107 injections against influenza, 19 pneumococcal vaccinations, 12 against tetanus/diphtheria antigens and 21 other vaccinations. 14% of injections had elicited at least one vaccine reaction. All five vaccine related serious adverse events were associated with pneumococcal vaccination. Vaccine reactions were observed in 70% of pneumococcal vaccinations, compared to 7% in influenza and 17% in tetanus/diphtheria vaccinations. The odds ratios to react to the pneumococcal vaccines compared to influenza and tetanus/diphtheria vaccines were 31.0 (95%CI8-119) and 10.8 (95%CI 2-74). Vaccine reactions after pneumococcal vaccinations were more severe and lasted significantly longer (up to 3 weeks) compared to other vaccinations. In two patients, pneumococcal vaccination also elicited symptoms consistent with systemic inflammation due to CAPS reactivation.

Conclusion: Pneumococcal vaccines, unlike other vaccines, frequently trigger severe local and systemic inflammation in CAPS patients. Clinicians must balance potential benefits of pneumococcal immunisation against safety concerns. The 13-valent pneumococcal conjugate vaccine might be favourable over the polysaccharide vaccine in CAPS patients.

Keywords: cryopyrin-associated periodic syndromes, CAPS, vaccinations, safety

KEY MESSAGES

In cryopyrin-associated periodic syndromes patients, pneumococcal vaccines unlike other vaccinations frequently induced local inflammation.

In cryopyrin-associated periodic syndromes, pneumococcal vaccines reactions were more severe, longer-lasting and at times systemic.

INTRODUCTION

Cryopyrin-Associated Periodic Syndromes (CAPS), specifically Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS), and Neonatal Onset Multisystem Inflammatory Disease (NOMID) are autoinflammatory periodic fever syndromes caused by mutations of the *NLRP3* gene which elicit a constitutive activation of the NLRP3 inflammasome and enhance the synthesis of active IL-1β after the detection of danger signals by toll-like receptors (TLR) [1,2]. Canakinumab, a human IgG1/k monoclonal antibody that selectively blocks human IL-1β has been licensed for the treatment of CAPS [3].

Patients with CAPS, like other patients with immune related disorders on immunosuppressive treatments, may have an increased susceptibility to pneumococcal pneumonia [4] which even in the general population represents a significant cause of morbidity and mortality [5,6].

The European League Against Rheumatism (EULAR) and the Advisory Committee on Immunisation Practices to the Center for Disease Control and Prevention (CDC) therefore recommend pneumococcal vaccination, tetanus and influenza vaccines, among other immunisations in patients with periodic fever syndromes treated with immunosuppressive medication [5,7].

Our early recognition of unusually severe local and/or systemic inflammatory adverse reactions led us to publish information in a case series of seven CAPS patients, consecutively vaccinated with pneumococcal vaccines [8]. Six of the seven patients reported in the case series are also included in this analysis as they were followed in the β-CONFIDENT (Clinical Outcomes and Safety Registry study of Ilaris patients) registry, a long-term prospective observational study of patients treated with canakinumab. Following up on the findings of the case series [8], we prospectively

investigated the safety of pneumococcal and other vaccines within the entire β-CONFIDENT registry.

METHODS

Study population and design

This study analysed the vaccination safety data of the β-CONFIDENT registry, registered in ClinicalTrials.gov (NCT01213641). Each centre contributing to the β-CONFIDENT registry obtained ethical approval by its local ethics committees or institutional review boards; informed consent according to the declaration of Helsinki was required from each patient/guardian prior in compliance with local regulations. No additional approval was required for this study analyzing the vaccination safety data.

The β-CONFIDENT registry is a global, multicentre, 5 year, prospective, observational registry, capturing long-term safety and effectiveness data of adult and paediatric patients treated with canakinumab [9]. As this was a non-interventional study, patients were treated according to the local prescribing information, and routine medical practice. Data collection was in compliance with Good Medical Practice and Good Pharmacovigilance Practice.

Given the observational nature of this study the protocol did not mandate any specific schedule of vaccination or follow-up and vaccinations were administered as part of regular medical care according to the independent recommendations of treating physicians.

Collection of vaccination data in the registry started in July 2010, and ended in December 2015. For the purpose of this analysis, patients treated with canakinumab for conditions other than definite CAPS were excluded, as were patients without information of the presence or absence of any vaccination reactions.

Statistical analysis

Categorical variables were calculated as frequencies and percentages and continuous variables were calculated as means with standard deviations (SD) and

medians with interquartile ranges (IQRs). Mann-Whitney-U tests were applied for across group comparisons. Odds ratios and their corresponding 95% confidence intervals (CIs) were obtained using univariate logistic regression analysis taking the clustering of vaccine injections within one patient into account. All statistical analyses were performed with Stata/IC 13.1 (StataCorp, College Station, Texas, USA).

RESULTS

The β-CONFIDENT registry followed 285 patients, 68 of whom fulfilled the inclusion criteria (Figure 1). The 68 included patients received 159 vaccine injections and were followed in 14 centres in nine countries. The majority of patients (81%) had been vaccinated against influenza, 26% of patients had received a pneumococcal vaccination, 18% of patients had received vaccinations with tetanus and diphtheria antigens and 16% of patients had received at least one vaccine directed against other pathogens (Figure 1). During the observation period, 43 CAPS patients (63%) had received more than one vaccine injection. Due to the inclusion criteria of the β-CONFIDENT registry, all patients were concomitantly treated with canakinumab at enrolment into the registry. The demographic and disease characteristics of the patients are provided in Table 1.

Of the total of 159 vaccine injections administered to the 68 CAPS patients, there were 22 injections in 18 patients that elicited at least one vaccine reaction (Table 2). The majority of vaccine reactions (n=13) occurred in 12 patients receiving pneumococcal vaccines. Twelve of the 15 pneumococcal polysaccharide vaccine (PPV) injections (80%) elicited a vaccine reaction and none of the two patients who were administered a pneumococcal conjugate vaccine (PCV). In two pneumococcal vaccinations, one of which elicited a reaction, the exact vaccine type was unknown. The high frequency of pneumococcal vaccine reactions contrasted with that of reactions to other vaccine types; only 17% and 7% of the tetanus/diphtheria and influenza vaccinations elicited a vaccine reaction, respectively. The odds ratio to react to any of the pneumococcal vaccines compared to influenza vaccines was 31.0 (95%CI 8-119) and compared to tetanus/diphtheria vaccines was 10.8 (95%CI 2-74). Considering only PPV reactions, the odds ratio compared to influenza vaccinations

was 57.1 (95%CI 13-252) and compared to tetanus/diphtheria vaccinations was 12.2 (95%CI 1-102).

The severity of the vaccine reactions, as assessed by the number and intensity of different inflammatory symptoms (fever, swelling, erythema, and pain) was also increased after PPV vaccination compared to other vaccines (Table 2). Fever was elicited by almost half of all PPV injections. All symptoms after pneumococcal vaccination were observed very rapidly, usually within hours. Unlike the symptoms observed after influenza, tetanus or diphtheria vaccination, which resolved rapidly, the symptoms related to PPV were much more prolonged and in some cases lasted more than three weeks.

In two MWS patients, PPV exposure was also associated with symptoms attributable to CAPS reactivation. One patient developed meningitis and the C-reactive protein was reported to be elevated one day after PPV injection. The events resolved after a period of 10 to 18 days.

During the entire observation period, there were a total of five patients experiencing vaccine related serious adverse events (SAEs). Four events were observed in MWS patients and one in a NOMID patient; all were observed after PPV injections. The SAEs required hospital treatment in three cases. In one patient, a hospital consultation was necessary due to fever and local inflammation one day after PPV. Hospitalisation was required in two patients, four days after PPV due to meningitis and cellulitis at the injected arm in one patient and seven days after PPV due to progressive cellulitis at the injected arm in another patient. A fourth patient also developed local inflammation immediately after the injection. Over the next three days, this patient worsened and developed a swollen, hot erythematous arm, as well as nausea, headache and fever. A fifth patient developed local inflammation and fever one day after the PPV injection.

In all five patients, the vaccine related SAEs resolved after a period of 10-28 days.

Two patients had been vaccinated twice with pneumococcal vaccine. One patient first received PCV followed by PPV two months later and did not experience any vaccine reactions. The second patient received two PPV vaccines 1.8 years apart. This patient experienced only pain at the first vaccination, but developed pain, fever, and erythema which lasted for 12 days after the second PPV injection.

Nine of the 12 patients who had reacted to pneumococcal vaccines had been previously (n=7) or subsequently (n=5) vaccinated with other vaccines (18 influenza vaccine injections and two vaccinations against tetanus/diphtheria). In these nine patients, none of the other vaccine injections had elicited a vaccine reaction.

Comparing the pneumococcal vaccine reactions among the different CAPS phenotypes, patients with NOMID had a higher nominal proportion of different injection site symptoms than patients with MWS or FCAS and a higher incidence of fever (Table 3). Patients who reacted to pneumococcal vaccines also tended to be younger than those who did not react. The former also had a slightly shorter time since the last administration of canakinumab, but had received lower canakinumab doses (Table 4). There was also no association between the time from the last canakinumab administration, or the canakinumab dose and the number of reaction symptoms (p=0.57, p=0.17, respectively).

Antibody titre measurements following vaccination were recorded in a total of four patients, all of whom had received PPV. In these four patients, PPV had resulted in titres considered to be protective.

DISCUSSION

This prospective observational study demonstrates that in CAPS patients, pneumococcal vaccines are associated with adverse events that are more frequent, more severe, and longer lasting than comparator vaccines such as tetanus, diphtheria and influenza. Pneumococcal vaccination was also associated with a high rate of serious events. The events associated in this study with pneumococcal vaccinations also appear more frequent and more intense than those previously reported after pneumococcal immunisation in healthy persons [10] and in patients with other rheumatic diseases [11]. Of note, there was a strikingly higher incidence of serious post pneumococcal vaccine reactions which also appeared more severe than those previously reported in healthy persons and in patients with other rheumatic diseases [10].

Some cases in this study also suggested that pneumococcal vaccines can trigger systemic inflammation and even CAPS flares. Our early recognition of these findings

led us to publish information about six patients from the registry and an additional patient not treated with canakinumab [8]. The present study confirms, extends, and puts the findings from the previous case series into perspective. One hypothesis that could explain the adverse events following pneumococcal vaccination is that pneumococcal antigens contain TLR2 and TLR4-ligands which trigger the rapid onset and systemic symptoms in patients who are genetically prone to inflammasome overactivation, i.e. in CAPS patients [8]. The observation that patients with the more severe CAPS phenotype (NOMID) appeared to have more frequent and more severe events than CAPS patients with the less severe phenotype (FCAS), also supports a role of inflammasome hyperactivation in this adverse reaction. PPV commonly utilizes purified polysaccharides from 23 pneumococcal serotypes; immunity is induced primarily through stimulation of IgM secreting B-cells without the assistance of T cells. Since there is no immunoglobulin type switch, the PPV vaccine does not elicit IgA antibodies and mucosal immunity; immunisation is not life-long [12]. PCV contains capsular polysaccharides covalently bound to diphtheria toxoid, but employs antigens of fewer pneumococcal serotypes than PPV. In contrast to PPV, PCV elicits long lasting T-helper cell dependent immune responses, immunoglobulin type switching, mucosal immunity, and immunologic memory [12]. Interestingly, all of the adverse events described in this study after pneumococcal vaccinations were associated with PPV, though numbers are too small to warrant any conclusion about a potential difference between the two. Both vaccines however contain TLR2 and 4 ligands and vaccine reactions to PCV have been also observed in a 24 year old woman with FCAS not followed in this registry (HMH unpublished observation) as well as another CAPS case [8], suggesting that the inflammatory reaction is not restricted to the PPV vaccine subtype.

Moreover, familial Mediterranean fever is a condition associated with increased inflammasome activation [13]. The β-CONFIDENT registry also followed a boy with familial Mediterranean fever. This boy (not included in this analysis of the registry) was vaccinated with PPV at the age of 13. Within less than one day, the boy experienced severe pain and massive swelling at the injection site. These symptoms lasted for seven days. Further support for the permissive role of the inflammasome for the pneumococcal vaccine reactions stems from similar events reported in patient with Behçet’s disease [14], a condition also associated with aberrant inflammasome activation [13,15].

It is intriguing that not all patients receiving pneumococcal vaccines in the β-CONFIDENT registry appear to have reacted to pneumococcal vaccines. We cannot fully rule out recall deficits or incomplete data capture as a possible explanation. On the other hand, canakinumab may be expected to mitigate symptoms by counteracting an enhanced IL-1 β activation. We however failed to identify a protective effect of canakinumab in our CAPS patients as there was no association between the presence or severity of the vaccine reactions with canakinumab dose or timing. Local vaccine reactions could however also be explained by insufficient canakinumab concentrations. The lack of a protective effect of canakinumab may however also result from the involvement of proinflammatory pathways other than IL-1β, as the activated inflammasome can also activate preforms of IL-18, induce inflammatory cell death known as pyroptosis, and enhance eicosanoid production [13,14].

The risk of adverse vaccine reactions must be clearly weighed against the risk of pneumococcal infections. Mice with dysfunctional NLRP3 signalling are more susceptible to pneumococcal pneumonia [4,14], providing an argument in favour of continued vaccination. In the absence of more robust data it is unclear if both types of pneumococcal vaccines elicit inflammatory symptoms to a similar degree. The authors tend to favour the 13-valent PCV over PPV in CAPS patients, also for the immunologic advantages of PCV discussed above.

The NLRP3 inflammasome plays an important role in the generation of pneumococcal antibodies following vaccination and is also required for the effects of aluminium and other vaccine adjuvants raising the possibility of an impaired vaccine efficacy [15–17]. We did not detect an impaired antibody production in the few patients treated with canakinumab that had pneumococcal antibody titre measurements. Future research should consider systematic measurements of antibody titres and could also investigate if pneumococcal vaccine side effects could be mitigated by employing reduced antigen doses, or by concomitantly administering anti-inflammatory medications such as cyclooxygenase inhibitors and glucocorticosteroids [13,18].

In conclusion, pneumococcal vaccines, unlike other vaccines, trigger severe local and systemic inflammation in CAPS. Clinicians must weigh potential benefits of pneumococcal immunisation against safety concerns.

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Figure 1. Flow chart of patients included and excluded in the analysis

* Five patients received more than one vaccine injection against different pathogens.

Table 1. Demographics and disease characteristics of cryopyrin-associated periodic syndromes patients at their first vaccination

Vaccine[a]	Influenza	Tetanus + diphtheria[b]	Pneumococcus			Other
Pneumococcal vaccine subtype	-	-	PCV	PPV	Unknown	-
Patients who received a vaccination, n	55	12	2	14	2	11
Age						
Mean years (SD)	36 (18)	24 (13)	31 (30)	41 (17)	31 (18)	26 (16)
Median years (IQR)	37 (18-51)	23 (16-30)	31 (10-52)	47 (24-54)	31 (18-43)	25 (15-45)
Patients <16 years, n (%)	9 (16)	3 (25)	1 (50)	1 (7)	0 (0)	4 (36)
Female sex, n (%)	30 (55)	6 (50)	2 (100)	10 (71)	2 (100)	4 (36)
CAPS symptom duration						
Mean years (SD)	30 (19)	19 (12)	30 (31)	36 (21)	25 (26)	22 (17)
Median years (IQR)	32 (15-44)	16 (15-23)	30 (8-51)	40 (19-54)	25 (6-43)	15 (14-28)
CAPS phenotype						
NOMID n (%)	4 (7)	0 (0)	1 (50)	2 (14)	0 (0)	1 (10)
MWS n (%)	34 (62)	7 (58)	0 (0)	11 (79)	1 (50)	5 (45)
FCAS n (%)	17 (31)	5 (42)	1 (50)	1 (7)	1 (50)	5 (45)
Known NLRP3 mutation, n (%)	52 (95)	11 (92)	2 (100)	14 (100)	2 (100)	11 (100)

[a]Vaccines containing tetanus and diphtheria antigens: Tetanus/diphtheria (5 patients), Diphtheria/tetanus/pertussis (5 patients), Diphtheria/tetanus/pertussis/polio (1 patient), Diphtheria/tetanus/haemophilus influenzae type b (1 patient). [b]Other vaccines: hepatitis B (6 patients), hepatitis A (5 patients), typhoid, (3 patients), tick borne encephalitis (2 patients), polio (1 patient), mumps, measles, rubella (1 patient), human papillomavirus (1 patient), lyme disease (1 patient) and cholera (1 patient). FCAS: familial cold autoinflammatory syndrome; MWS: Muckle-Wells Syndrome; NLRP3: nucleotide-binding domain, leucine-rich family pyrin domain containing protein 3; NOMID: neonatal onset multisystem inflammatory disease; PCV: pneumococcal conjugate vaccine; PPV: pneumococcal polysaccharide vaccine.

Table 2. Canakinumab exposure of cryopyrin-associated periodic syndromes patients and vaccination reactions according to the vaccine type

Vaccine	Influenza	Tetanus + diphtheria[a]	Pneumococcus			Other[b]
Pneumococcal vaccine subtype	-	-	PCV	PPV	Unknown	
Injections, n	107	12	2	15	2	21
Time since last canakinumab						
Mean days (SD)	56 (138)	88 (123)	10 (7)	22 (18)	37 (28)	99 (140)
Median days (IQR)	36 (17-50)	38 (31-59)	10 (6-14)	22 (2-41)	37 (17-57)	42 (30-79)
≤30 days; n (%)	44 (41)	2 (17)	2 (100)	10 (67)	1 (50)	6 (29)
Last canakinumab dose						
Mean mg/kg (SD)	2.6 (1.2)	3.1 (1.2)	7.9 (8.3)	2.7 (1.3)	1.8 (0.1)	3.2 (1.7)
Median mg/kg (IQR)	2.1 (1.8-2.7)	2.7 (2.3-4.1)	7.9 (2.0-13.8)	2.2 (1.9-2.5)	1.8 (1.7-1.8)	2.4 (2.1-4.4)
Patients receiving ≤2 mg/kg, n (%)	43 (41)	1 (8)	0 (0)	4 (27)	2 (100)	3 (14)
Injections eliciting any vaccine reaction, n (%)	7 (7)	2 (17)	0 (0)	12 (80)	1 (50)	0 (0)
Injections eliciting no reaction, n (%)	100 (93)	10 (83)	2 (100)	3 (20)	1 (50)	21 (100)
Injections with one reaction feature[c], n (%)	2 (2)	0 (0)	0 (0)	1 (7)	1 (50)	0 (0)
Injections with two reaction feature, n (%)	3 (3)	0 (0)	0 (0)	1 (7)	0 (0)	0 (0)
Injections with three reaction features, n (%)	2 (2)	2 (17)	0 (0)	4 (26)	0 (0)	0 (0)
Injections with four reaction features, n (%)	0 (0)	0 (0)	0 (0)	6 (40)	0 (0)	0 (0)

Fever, n injections (%)	2 (2)	0 (0)	0 (0)	7 (47)	0 (0)	0 (0)
Time to fever onset, days, median (IQR)	2 (1-3)	na	na	1 (1-1)	na	na
Duration of fever, days, median (IQR)	0.5 (0-1)	na	na	17 (9.5-22)	na	na
Fever maximum, °C, median (IQR)	38.2	na	na	39.3 (39.0-39.6)	na	na
Swelling, n injections (%)	4 (4)	2 (17)	0 (0)	9 (60)	0 (0)	0 (0)
Time to swelling onset, days, median (IQR)	0 (0-1)	1	na	1 (0-1)	na	na
Swelling duration, days, median (IQR)	2 (1-7)	unknown	na	8 (4-22)	na	na
Erythema, n injections (%)	4 (4)	2 (17)	0 (0)	11 (73)	1 (50)	0 (0)
Time to erythema onset, days, median (IQR)	0 (0-0)	0.5 (0-1)	na	1 (0-3)	0	na
Erythema duration, days, median (IQR)	1 (1-9)	unknown	na	9.5 (5.5-17)	unknown	na
Pain, n injections (%)	3 (3)	2 (17)	0 (0)	12 (80)	0 (0)	0 (0)
Time to pain onset, days, median (IQR)	1	1	na	0 (0-3)	na	na
Pain duration, days, median (IQR)	7	unknown	na	9 (4-22)	na	na
SAE, n patients (%)	0 (0)	0 (0)	0 (0)	5 (33.3)	0 (0)	0 (0)

Unless otherwise stated, the numbers and percentages presented are based on vaccine injections, not patients. [a]Vaccines containing tetanus and diphtheria antigens: Tetanus/diphtheria (5 patients), Diphtheria/tetanus/pertussis (5 patients), Diphtheria/tetanus/pertussis/polio (1 patient), Diphtheria/tetanus/haemophilus influenzae type b (1 patient). [b]Other vaccines: hepatitis B (6 patients), hepatitis A (5 patients), typhoid, (3 patients), tick borne encephalitis (2 patients), polio (1 patient), mumps, measles, rubella (1 patient), human papillomavirus (1 patient), lyme disease (1 patient) and cholera (1 patient). [c]Vaccine reaction features systematically asked for in the registry consist of fever, swelling, erythema and pain. FCAS: familial cold autoinflammatory syndrome; MWS: Muckle-Wells Syndrome; NOMID: Neonatal onset multisystem inflammatory disease; na: not applicable; PCV: Pneumococcal conjugate vaccine; PPV: Pneumococcal polysaccharide vaccine; SAE: serious adverse event.

Table 3. Vaccine reactions after pneumococcal vaccine injections, stratified by cryopyrin-associated periodic syndromes phenotype

	NOMID	MWS	FCAS
Pneumococcal vaccinations, n	3	13	3
Injections eliciting a vaccine reaction, n (%)	2 (67)	10 (77)	1 (33)
Injections eliciting no reaction, n (%)	1 (33)	3 (23)	2 (67)
Injections with one reaction feature, n (%)	0 (0)	1 (8)	1 (30)
Injections with two reaction feature, n (%)	0 (0)	1 (8)	0 (0)
Injections with three reaction features, n (%)	0 (0)	4 (31)	0 (0)
Injections with four reaction features, n (%)	2 (67)	4 (30)	0 (0)
Fever, n (%)	2 (67)	5 (38)	0 (0)
Time to fever onset, days, median (IQR)	unknown	1 (1-1)	na
Duration of fever, days, median (IQR)	unknown	17 (10-22)	na
Swelling, n (%)	2 (67)	7 (54)	0 (0)
Time to swelling onset, days, median (IQR)	1 (1-1)	1 (0-1)	na
Duration of swelling, days, median (IQR)	unknown	8 (4-22)	na
Erythema, n (%)	2 (67)	9 (69)	1 (33)
Time to erythema onset, days, median (IQR)	0.5 (0-1)	1 (0-1)	0 (0)
Duration of erythema, days, median (IQR)	unknown	10 (6-17)	unknown
Pain, n (%)	2 (67)	10 (77)	0 (0)

Time to pain onset, days, median (IQR)	0 (0-0)	0 (0-1)	na
Duration of pain; median days (IQR)	unknown	9 (6-17)	na
SAE; n patients (%)	1 (33)	4 (31)	0 (0)

Unless otherwise stated, the numbers and percentages presented are based on vaccine injections, not patients. FCAS: familial cold autoinflammatory syndrome; MWS: Muckle-Wells syndrome; na: not applicable; NOMID: neonatal onset multisystem inflammatory disease; SAE: serious adverse event.

Table 4. Comparison of demographic and treatment characteristics of cryopyrin-associated periodic syndromes patients recieving pneumococcal vaccine injections

	No reaction	**Any reaction**
Pneumococcal vaccine injections, n (%)	6	13
Age		
Mean years (SD)	46 (19)	36 (16)
Median years (IQR)	52 (43-54)	42 (20-50)
Patients <16 years, n (%)	1 (17)	1 (8)
Female sex, n vaccine injections (%)	6 (100)	8 (62)
CAPS symptom duration		
Mean years (SD)	45 (20)	29 (19)
Median years (IQR)	52 (43-54)	26 (15-42)
NLRP3 mutation, n (%)	6 (100)	13 (100)
Time since last canakinumab		
Mean days (SD)	29 (24)	19 (16)
Median days (IQR)	26 (6-56)	18 (2-37)
≤30 days, n (%)	3 (50)	10 (77)
>30 days, n (%)	3 (50)	3 (23)
Last canakinumab dose		
Mean mg/kg (SD)	4.0 (4.8)	2.7 (1.4)

Median mg/kg (IQR)	2.0 (2.0-2.3)	2.2 (1.9-2.5)
Patients receiving ≤2 mg/kg, n (%)	1 (17)	5 (38)
Patients receiving >2 mg/kg, n (%)	3 (83)	8 (62)

The numbers and percentages presented are based on vaccine injections, not patients. NLRP3: nucleotide-binding domain, leucine-rich family pyrin domain containing 3.