

Severe inflammation following vaccination against *Streptococcus pneumoniae* in patients with cryopyrin-associated periodic syndromes (CAPS)

Ulrich A. Walker¹, Hal M. Hoffman², Rene Williams³, Jasmin Kuemmerle-Deschner^{4*} and Philip N. Hawkins^{3*}

* contributed equally

¹ Unispital Basel, Dept. of Rheumatology, Basel, Switzerland

² University of California at San Diego, San Diego, USA

³ University College London, United Kingdom

⁴ University Hospital Tübingen, Germany

Correspondence

Ulrich A. Walker, M.D.

Unispital Basel

Dept. of Rheumatology

Petersgraben 4

CH 4037 Basel

Switzerland

Tel.: +41-61-2652525

Fax: +41-61-2659021

e-mail: ulrich.walker@usb.ch

Disclosures

UAW, HMH, JKD and PNH are members of the steering committee of the β -confident registry that prospectively follows children and adult CAPS patients treated with canakinumab. The authors however report their observations as individual clinicians who followed current immunisation guidelines.

Abstract

Objectives: Pneumococcal vaccination is recommended for patients requiring treatment with immunosuppressive drugs. The aim of this report is to describe unusually severe adverse reactions to pneumococcal vaccination in each of seven consecutive patients with cryopyrin associated periodic syndromes (CAPS).

Methods: Seven consecutive patients with CAPS were vaccinated with pneumococcal polysaccharide or conjugate vaccines. Clinical information was collected retrospectively.

Results: Within a few hours after the vaccination, all seven patients developed severe local reactions at the injection site. Two patients had to be hospitalized for systemic reactions including fever. All symptoms resolved in a period of 3 to 17 days.

Conclusion: Pneumococcal vaccines can trigger a severe local and systemic inflammatory reaction in patients with CAPS and possibly patients with other autoinflammatory diseases. Careful consideration is warranted when implicating current EULAR immunization guidelines in this patient population.

Cryopyrin-Associated Periodic Syndromes (CAPS), specifically Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS), and Neonatal Onset Multisystem Inflammatory Disease (NOMID) are a group of rare hereditary autoinflammatory periodic fever syndromes associated with mutations in the *NLRP3* gene, whose encoded product interacts with other intracellular proteins to form the NLRP3 inflammasome (1;2). Mutations in the *NLRP3* gene cause a constitutive activation of the NLRP3 inflammasome. Toll-like receptors (TLR) detect intracellular and extracellular pathogens and danger signals and their signalling enhances the synthesis of pro-interleukin-1 β (IL-1 β). Abnormally enhanced activation of the inflammasome in CAPS results in the cleavage of pro-IL-1 β and thus in the overproduction of active IL-1 β . Following the identification of the genetic basis for CAPS and the common pathway of IL-1 β activation, new approaches to treat these conditions have been licensed. Among these is canakinumab, a monoclonal antibody that specifically blocks IL-1 β (3).

Infections with *Streptococcus pneumoniae* represent a significant cause of morbidity and mortality (4;5). The European League Against Rheumatism (EULAR) therefore strongly recommends consideration of the 23-valent polysaccharide pneumococcal vaccine (23-PPV) in patients with periodic fever syndromes (6). Similarly, the Advisory Committee on Immunization Practices to the Center for Disease Control and Prevention (CDC) recommends pneumococcal vaccination to patients with diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids (4).

Patients and Methods

The authors followed these recommendations and consecutively vaccinated seven CAPS patients with pneumococcal vaccines. All seven patients developed unusually severe local and/or systemic inflammatory adverse reactions. The purpose of this manuscript is to report and interpret these events.

Results

All cases are summarized in the Table. Case 1 is that of a 43 year old female with MWS who received a Pneumovax II vaccination in January 2014, the same day as her next canakinumab injection of 150mg was due. Within a few hours of having the vaccination she experienced local injection site symptoms of swelling, redness and pain. On the subsequent day, she developed fever, profuse shivering and sweating, nausea and vomiting. By the fourth day she had developed a severe headache associated with neck stiffness and photophobia, and continued to have fever along with a florid red rash covering much of the arm where the vaccine had been administered. The patient was admitted to her local hospital that evening with a diagnosis of presumed viral meningitis. Lumbar puncture revealed elevated white cells (96 per cubic millimetre, neutrophils 84%), normal glucose 2.3 mmol/L and elevated protein at 0.79 g/L in the CSF. Her CRP taken on admission was 63mg/L. She remained hospitalized for 18 days, during which the symptoms gradually improved; rash on the arm was still present at discharge.

Case 2 is that of a 20 year old female with NOMID who received a Pneumovax II vaccination on the same day as case 1, along with her next scheduled 300 mg canakinumab injection. Within hours of having the vaccination, she experienced injection site symptoms of slight swelling, a rash just below the injection site and pain. Over the next few days the rash spread down her left arm and became more painful. She began experiencing fever. On the eighth day after the vaccination, the patient was admitted to her local hospital with cellulitis involving the vaccinated left arm. She was discharged from hospital at day 13, describing her rash as 'dramatically improved', with residual discoloration, no redness but some itch at times.

The authors subsequently vaccinated five additional CAPS patients, all of which developed severe local inflammation. Cases 1 to 6 were in stable remission while receiving canakinumab, whereas case 7 had daily flares and had not received any immunosuppression at the time of vaccination. The local adverse reaction to the 23-PPV was similar in all patients and developed a few hours after the injection with pain, redness and local swelling; urticarial lesions were not reported.

Several aspects are remarkable. The reaction occurred with pneumococcal vaccines from three different manufacturers and in patients with different CAPS phenotypes. Four vaccination reactions occurred in temporal association with concomitant co-injections of canakinumab, two other vaccination reactions were separated by 15 days from last canakinumab dose, but in case 7, a similar event was also observed prior to any canakinumab therapy. Lastly it should be noted, that some patients had been vaccinated with a variety of other vaccines without complications.

Discussion

We report unusually severe adverse reactions in each of seven consecutive patients with CAPS who received pneumococcal vaccination, requiring hospitalization in two cases. The safety of pneumococcal vaccination has previously been established in a number of autoimmune diseases, including rheumatoid arthritis, juvenile arthritis, and systemic lupus erythematosus (7). Local or systemic adverse events and disease flares were reported at only a low frequency (8). Of note, fever ($>37.8^{\circ}\text{C}$) was reported in less than 3% of vaccinated normal subjects (8). In healthy subjects, cellulitis-like reactions were only rarely reported post marketing (9). When approximately 43 million doses were distributed, the annual reporting rate of cellulitis-like reactions was 2.5/100'000 doses, and the median hospitalisation time was two days after vaccine administration (9). Our observations suggest that the frequency and intensity of vaccine reactions may be greater in CAPS than in populations of patients without this hereditary periodic fever syndrome.

We noted vaccine reactions with preparations from three different manufacturers. Some of these (Pneumovax 23 and Pneumovax II) contain phenol as a preservative. Phenol however has only low immunogenic properties and is also used in the influenza and *Haemophilus influenzae* vaccines. Our subjects had however previously reported to have tolerated the latter vaccines well and phenol is not a component of Prevenar (Pevnar) 13, a vaccine to which one of our cases reacted. Aluminum is another frequently used vaccine constituent in which it is used as an adjuvant. The *NLRP3* inflammasome plays a crucial role in the immunostimulatory property of aluminium (10). Although Prevenar does contain aluminium, Pneumovax 23 and Pneumovax II do not. Four subjects have received canakinumab in conjunction with the pneumococcal vaccine. It is however unlikely that the observed reactions are caused by canakinumab co-administration because an adverse reaction was also observed in two patients 15 days after the last canakinumab injection and in one patient who had had no exposure to canakinumab (case 7). In summary, the adverse reactions cannot be explained by the presence of a preservative, the presence of an adjuvant, or the preparation/ batch of a particular manufacturer. Thus the vaccine reaction appears to be specific for pneumococcal antigens.

Pneumococcal polysaccharides (present in Pneumovax 23 and Pneumovax II) and pneumococcal conjugates (present in Prevenar) can activate inflammatory gene transcription by stimulating TLR2 and TLR4 (5;11). Enhanced TLR triggering by pneumococcal vaccine components with subsequent inflammasome hyperactivation in CAPS patients with *NLRP3* mutations may best explain the high incidence rate of this adverse event, its rapid onset, severity, and the systemic nature of the reaction. It is interesting in this context that case 1

had developed meningitis, a complication that may reflect activation of the underlying CAPS. Severe local and systemic reactions to consecutive applications of Pneumovax have also been described in patients with Behçets disease (BD) (12), a condition that has also been proposed to result from aberrant activation of the inflammasome (13). In some of these BD patients who had reacted to pneumococcal vaccination (12), the vaccine had elicited pseudofolliculitis (unpublished observation of the corresponding author, documented in Figure 1 of the online supplement). Thus, it seems that pneumococcal vaccines can trigger flares of the autoinflammatory disease, which then could also contribute to the observed systemic inflammation.

If pneumococcal TLR agonists enhance IL-1 β cleavage in patients predisposed to hyperactivation of the inflammasome, why does then canakinumab not completely block the clinical manifestation of the resulting inflammation? One hypothesis is, that the activated inflammasome can mediate proinflammatory pathways independent of IL-1 β cleavage in terms of IL-18, pyroptosis and eicosanoid production (14), and that the vaccine reaction is mediated by these IL-1 β -independent pathways. Alternatively, local vaccine reactions could be explained by insufficient canakinumab concentrations at the injection site of the vaccine.

The risk of adverse vaccine reactions must clearly be weighed against the risk of pneumococcal infections (15). Mice with dysfunctional NLRP3 signalling are more susceptible to pneumococcal pneumonia (16) and a functional inflammasome is important for the generation of protective antibodies against pneumococci (17;18). Intact IL-1 signalling is also important in the normal host response to pneumococcal infection, which is illustrated in patients with IRAK4 deficiency who have increased risk of streptococcal infection, presumably due to aberrant IL-1 receptor responses. The implications of the inflammasome in the clinical protection against pneumococci in people however remain unclear (5). Although vaccination protocols for immunosuppressed persons mostly result in titers that are considered protective, a clinical protection of pneumococcal vaccines in persons treated with biological agents has not yet been demonstrated. By balancing the observed vaccine reactions against the known benefits of pneumococcal vaccines, the authors have momentarily stopped to routinely vaccinate CAPS patients against pneumococci in their clinics until further data become available.

This case series suggests that the safety of pneumococcal vaccinations in CAPS patients be further investigated and those patients be more closely monitored after vaccination. The observational, non-experimental nature of this case series also accounts for the lack of systematic and detailed follow-up.

The β -confident registry is an open-label, multi-centre, long-term, prospective, observational study (CTN: NCT01213641) that includes CAPS patients treated with canakinumab. The registry has completed enrolment in December 2014 and will complete up to six years of follow up, with a minimum of one year follow up, in December 2015. The full analysis of this registry data is expected to include analyses of prior and concurrent immunisation experience.

In conclusion, pneumococcal vaccines can trigger severe local and systemic inflammatory reaction in CAPS patients, and possibly patients with other autoinflammatory diseases. Until further data become available, the potential benefits of pneumococcal vaccines should be carefully balanced against their safety concerns.

Table 1. Clinical characteristics of CAPS patients who developed severe inflammation after pneumococcal vaccination

Case Nr. Age, gender	Clinical presen- tation	<i>NLRP3</i> Mutation	CAPS duration	CAPS treatment	Vaccine/ manufacturer	Previous uneventful vaccines	Days since last canakinumab	Days until onset	Local symptoms	Systemic reaction	Treatment of vaccine reaction	Days until resolution
Case 1 43 years, female	MWS	T348M	43 years	Canakinumab 150 mg every 8 weeks	Pneumovax II / Sanofi Pasteur	Nil	New canakinumab dose given on day of vaccination (63 days since previous dose)	0	Swelling, rubor, dolor, calor	Fever, nausea, headache, stiff neck	Antibiotics (i.v.) Prednisolone Paracetamol	17
Case 2 20 years, female	NOMID	L632F	20 years	Canakinumab 300 mg every 8 weeks	Pneumovax II/ Sanofi Pasteur	Influenza	New canakinumab dose given on day of vaccination (56 days since previous dose)	0	Swelling, rubor, dolor, calor	Fever	Ibuprofen	12
Case 3 26 years, female	NOMID	A352T	26 years	Canakinumab 300 mg every 8 weeks	Pneumovax II/ Sanofi Pasteur	Nil	New canakinumab dose given on day of vaccination (49 days since previous dose)	0	Swelling, rubor, dolor, calor	Not known	Antibiotics (i.v., oral) Local therapy	14
Case 4 43 years, male	MWS	T348M	43 years	Canakinumab 150 mg every 8 weeks	Pneumovax II/ Sanofi Pasteur	Influenza	New canakinumab dose given on day of vaccination (63 days since previous dose)	0	dolor	None	Nonsteroidal anti- inflammatory drugs Local therapy	4
Case 5 24 years, female	MWS	E311K	10 years	Canakinumab 150 mg every 8 weeks	Pneumovax 23/ Merck	Influenza, HiB	Canakinumab was given 15 days prior to vaccination	0	Swelling, rubor, dolor, calor	None	Local therapy	3
Case 6 52 years, female	MWS	E 311K	51 years	Canakinumab 300 mg every 8 weeks	Pneumovax 23/ Merck	Influenza	Canakinumab was given 15 days prior to vaccination	0	Swelling, rubor, dolor, calor	None	Local therapy	10
Case 7 7 years, female	FCAS	No known mutation	7 years	None	Prevenar 13/ Wyeth	Diphtheria Polio Tetanus	No prior or concomitant canakinumab	0	Swelling, rubor, dolor, calor	None	Local therapy	4

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