bijwerkingen centrumlareb

Meningococcal ACWY vaccine (Nimenrix®) and urticaria

Introduction

Meningococcal disease refers to conditions that are caused by infection with *Neisseria meningitidis* (meningococcus). Among others, these bacteria can lead to sepsis and meningitis which are potentially life-threatening. Since 2015, an increase is seen in the number of Dutch patients that become ill due to infection with meningococcus serotype W. Because of this, the Dutch government decided to adjust the National Immunisation Programme by replacing the meningococcal type C vaccine, that children receive at the age of 14 months, with the meningococcal type ACWY vaccine. This adjustment was carried out in May 2018. Because teenagers in the age group of 13 to 18 years are also considered more at risk for meningococcal infection, the vaccine was also offered to this group through vaccination campaigns in 2018 and [1,2]. In the Netherlands, the meningococcal ACWY vaccine 'Nimenrix®' is used in the National Immunisation Programme and the vaccination campaign [3].

Nimenrix® is a non-adjuvanted quadrivalent meningococcal ACWY tetanus toxoid conjugated polysaccharide vaccine. Because this vaccine does not contain live pathogens, it cannot cause the diseases to which it offers protection. Before Nimenrix® was approved for use, it has been investigated thoroughly in clinical trials. In these trials the most frequently reported adverse events were pyrexia, fatigue, syncope and headache, and swelling, erythema and pain at the injection site [4].

Up to the first of May 2019, Pharmacovigilance Centre Lareb has received 699 reports of adverse events following immunisation (AEFIs) with Nimenrix®. 14 Reports were reported via marketing authorisation holders and the remaining 685 were directly reported to Lareb.

Urticaria are raised, erythematous, itchy plaques, which are well circumscribed and vary in size and shape. Some common causes of urticaria are allergic reactions (e.g. to medications, insect bites/stings, food (additives)), bacterial, viral and parasitic infections, and direct mast cell activation due to a non-allergic mechanism. Other, less common causes are physical stimuli (e.g. temperature, exercise), serum sickness and hormone associated disorders [5].

Reports

Between June 22th 2018 and May 1st 2019 the Netherlands Pharmacovigilance Centre Lareb received 17 reports of urticaria following vaccination with Nimenrix®.

Table 1: Overview of the received reports of urticaria following vaccination with Nimenrix®

Number, Sex, Age, Reporter	Suspect vaccine	Concomitant medication	Reaction	Time to onset, Outcome
A: NL-LRB-00289267, male, 1-2 years, Consumer	menACWY (Nimenrix®) measles/mumps/rubella (MMRVAXPRO®)		urticaria	within 1 day, not recovered 2.5 weeks after onset of the reaction
B: NL-LRB-00297376, male, 1-2 years, Consumer	menACWY (Nimenrix®) measles/mumps/rubella (MMRVAXPRO®)		allergic urticaria	1 day, recovering 4 days after onset of the reaction
C: NL-LRB-00294393, male, 1-2 years, Consumer	menACWY (Nimenrix®) measles/mumps/rubella (MMRVAXPRO®)		urticaria	6 days, recovering within 1 day after onset of the reaction
D: NL-LRB-00299874, female, 2-4 years,	menACWY (Nimenrix®)		urticaria, swelling of limbs (including hands and feet)	3 days, recovering 1 month after onset of the reaction

Consumer				
E: NL-LRB-00301197, male, 2-4 years, Consumer	menACWY (Nimenrix®)		urticaria, fatigue	1 day, recovering 1 day after onset of the reaction
F: NL-LRB-00298490, male, 1-2 years, Consumer	menACWY (Nimenrix®) measles/mumps/rubella (MMRVAXPRO®)		urticaria, injection site swelling	within 1 day, recovered after 4 days
G: NL-LRB-00304737, female, 2-4 years, Consumer	menACWY (Nimenrix®) measles/mumps/rubella (MMRVAXPRO®)		urticarial rash, pyrexia, vomiting, abdominal pain	11 days, not recovered the day of onset
H: NL-LRB-00301960, female, 10-20 years, Consumer	menACWY (Nimenrix®)		urticarial rash	within 1 day, recovering 2 days after onset of the reaction
I: NL-LRB-00307844, female, 10-20 years, Physician	menACWY (Nimenrix®)		urticaria	5 days, recovering 2 days after onset of the reaction
J: NL-LRB-00308046, female, 10-20 years, Consumer	menACWY (Nimenrix®)		urticaria	2 days, recovered after 7 days
K: NL-LRB-00308552, male, 10-20 years, Consumer	menACWY (Nimenrix®)		urticaria, dyspnoea	4 days, recovering 2 days after onset of the reaction
L: NL-LRB-00324327, male, 4-7 years, Consumer	menACWY (Nimenrix®)		urticaria, swollen eyes	2 days, unknown
M: NL-LRB-00322779, male, 1-2 years, Consumer	menACWY (Nimenrix®) measles/mumps/rubella (MMRVAXPRO®)		urticaria	8 hours, not recovered 1 day after onset of the reaction
N: NL-LRB-00323075, male, 1-2 years, Consumer	menACWY (Nimenrix®) measles/mumps/rubella (MMRVAXPRO®)		urticaria	5 days, recovered after 10 days
O: NL-LRB-00323658, male, 10-20 years, Consumer	menACWY (Nimenrix®)	levodopa/carbidopa	urticaria	5 days, recovering 3 days after onset of the reaction

P: NL-LRB-00325546, male, 10-20 years, Consumer	menACWY (Nimenrix®)	methylphenidate	urticaria, localised rash	3 days, recovered
Q: NL-LRB-00328479, male, 10-20 years, Consumer	menACWY (Nimenrix®)	non specified acne medication	urticaria, swelling face, lip swelling, peripheral swelling	3 days, recovered after 5 days

Additional information on cases

Nine reports described that the patient visited their GP. In addition, one report was reported by a general practitioner which suggests that the urticaria in this patient were confirmed. Besides, 6 reports included a photograph of the skin.
Of twelve patients it is known that they were treated with antihistamines, cooling ointment/menthol gel, paracetamol and/or other unknown medication.

For patient D, the general practitioner mentioned that the reaction could also be caused by a food allergy.

For patient L, other possible circumstances which may have caused or aggravated the reaction were known allergies for house dust mite, cats and rabbits, although the patient had had no complaints for months. In the past, the patient had swollen eyes before, 2 days after administration of the measles/mumps/rubella vaccine (MMRVAXPRO®). Later, the patient also got swollen eyes, urticaria and pruritus 2 days after vaccination with the diphtheria/poliomyelitis/tetanus vaccine.

In patient O the lesions occurred after touching the skin and after change of temperature (e.g. after showering).

Other sources of information

SmPC

Urticaria is not mentioned in the Dutch SmPC of Nimenrix® as adverse event [6]. Urticaria is a known adverse event of other vaccines, like the mumps-measles-rubella virus vaccine (MMRVaxPro®), diphtheria-acellular pertussis-poliomyelitis-tetanus-vaccine (Boostrix-polio®), pneumococcal vaccine (Synflorix®) and the meningococcal group C (NeisVac-C®) and meningococcal group B vaccine (Bexsero®) [7-11].

Literature

In 2000, the Advisory Committee on Immunization Practices (ACIP) published an update of the recommendations concerning prevention and control of meningococcal disease. This report mentioned that: 'severe reactions to polysaccharide meningococcal vaccine are uncommon. Most studies report the rate of systemic allergic reactions (e.g. urticaria, wheezing and rash) as 0.0-0.1 per 100,000 vaccine doses. Anaphylaxis has been documented in <0.1 per 100,000 vaccine doses' [12].

In 2001, Ball et al. published safety data on the meningococcal polysaccharide vaccine using the Vaccine Adverse Event Reporting System (VAERS). Between July 1990 and October 31th 1999, 110 adverse events were reported after receipt of meningococcal vaccine alone. Urticaria was with 12% among the most common reported events. The time to onset was not specified for the reports concerning urticaria. However, the median time to onset for all reported events was less than 1 day (range 0-367 days) after vaccination with the meningococcal vaccine alone [13].

Databases

Table 2. Reports of urticaria associated with Nimenrix®, in the Lareb and WHO [14, 15] database on 19 June 2019.

Database	MedDRA PT	Number of reports	ROR (95% CI)
Lareb	Urticaria	20[#]	1,2 (0.8-2.0)*
WHO	Urticaria	100	**

* The Reporting Odds Ratio was not calculated based on the complete database, but on the fraction of vaccine reports in the Lareb database (ATC J07).# ROR included all received reports till June 19th 2019.
** Lareb is not able to determine disproportionality for Nimenrix® specifically, this can only be calculated on substance level by Lareb.

Prescription data

According to data from Stichting Farmaceutische Kengetallen (SFK) 75660 Nimenrix® vaccines were issued from January 2018 to May 2019 from public Pharmacies, with a peak in September 2018 (20809 vaccines) and 3118 in May. These vaccines are probably given by the general practitioner. These were issued for all age groups, but the large majority was given to children (0-18 years). SFK has also published on meningococcal vaccines issued in earlier years [16].

From 1 May 2018 the Men C vaccination in the National Immunisation Programme was replaced by a Men ACWY vaccination (Nimenrix®. The RIVM published on the vaccination rate for children of the birth cohort 2016; 1.4% were found to have had a Men ACWY vaccination and 91.2% a Men C vaccination. Data for later birth cohorts are not yet published [17].

In the last months of 2018, adolescents born between 1 May and 31 December 2004 were offered a Men ACWY vaccination. The provisional vaccination rate for this group is 87.1%; in 2019 they will receive another reminder call. In 2019, the rest of the birth cohort 2004 and the cohorts 2001, 2002, 2003 and 2005 (catch-up campaign) will be offered a ACWY vaccination. Only then can the final vaccination rate for 2004 birth cohort be calculated [17].

Mechanism

Urticarial lesions are mediated by cutaneous mast cells and according to Ying et al basophils were also identified in biopsies from patients with chronic idiopathic urticaria [5,18]. After activation, mast cells and basophils release several mediators including histamine and vasodilatory mediators causing e.g. pruritus and localised swelling of the upper layers of the skin [5]. Activation of mast cells can be caused by IgE mediated type I allergic reactions and non-immunologic mechanism [5,19]

Both the active component and the other components in vaccines, can cause hypersensitivity reactions. The majority of acute-onset reactions are type I hypersensitivity reactions mediated by preformed IgE antibodies against a vaccine component. However, many vaccine-associated adverse reactions are not immunologically mediated. Although urticaria is considered a typical manifestation of an immediate-type allergic reaction, they can also occur with delayed reactions. In a delayed reaction this is likely the result of non-IgE mediated processes. In general, the time to onset for delayed reactions is commonly within hours or days after vaccination, although symptoms can even appear after 2 to 3 weeks [19].

Discussion and conclusion

Pharmacovigilance Centre Lareb received 17 reports of urticaria following vaccination with the meningococcal ACWY vaccine Nimenrix®. Only in a few reports other symptoms such as eye or lip swelling are reported. In 7 reports, the patient was simultaneously vaccinated with the measles/mumps/rubella vaccine (MMRVAXPRO®). For MMRVAXPRO®, urticaria is mentioned as adverse event in the SmPC. In the other 10 reports, Nimenrix® was administrated alone. Overall, the time to onset varied from 1 day to 11 days (median 3 days) after vaccination. Concerning the reports where Nimenrix® was given alone, the time to onset varied from 1 day to 5 days (median 3 days) after vaccination. For most reports, the time to onset is longer than what may be expected for an acute hypersensitivity reaction after vaccination. However, according to McNeil et al, urticaria can also be mediated by delayed type reactions.

At least half of the patients went to the general practitioner and many patients were treated for the urticaria. At time of reporting, most patients were recovering (n=8) or recovered (n=5) with a recovery time between 4 days and 10 days. In one patient (D), food allergy was mentioned as other possible cause. Another patient (L) already had a history of allergic reactions for house dust mite and several

animals. This patient, also got urticaria after vaccination with another vaccine. Furthermore, in one patient (O), the urticaria seemed to be provoked by physical stimuli. For the other reports, no relevant information about medical history, past drug therapy and occurrence of similar previous reactions was available. Therefore, in these reports the causality between urticaria and vaccination with Nimenrix® cannot be substantiated.

The occurrence of urticaria can have a variety of causes. Urticaria is a known adverse event for several vaccines, including the meningococcal vaccines for type C (NeisVac-C®) and type B (Bexsero®). Furthermore, literature shows that urticaria can also appear after vaccination with polysaccharide meningococcal vaccines. In conclusion, these data present a signal that urticaria may also be related to vaccination with Nimenrix®.

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This signal has been raised on July 4, 2019. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl