Overview of reports of injection site inflammation after Prevenar13® administered to a selected population of elderly

Introduction

In the autumn of 2008 the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) was performed [i,ii]. It was a double-blind, randomized, placebo-controlled vaccine efficacy trial using Prevenar13®. The study population was 85,000 persons aged 65 and above. In February 2014 the results from the study were presented. They study showed that vaccination with Prevenar13® protected the vaccines against pneumonia [iii]. Because of these results, it was decided that placebo recipients (42,000) would be offered the active vaccine. These placebo recipients were invited for a vaccination. It is expected that about 25,000 persons, now aged above 70, will be vaccinated with Prevenar13® between September 1, 2014 and January 1, 2015.

As the vaccine is now registered for vaccination in the elderly, Adverse Events Following Immunisation (AEFI) from the vaccine administered, will only be collected through spontaneous reporting. Vaccinees are encouraged to report possible AEFIs to the Netherlands Pharmacovigilance Centre Lareb. After vaccination they received a leaflet with information about the importance of reporting AEFIs as well as the website and telephone number where to report.

In the period September 8, 2014 and November 1, 2014 Lareb received 140 reports, with a total of 214 possible AEFIs after vaccination with Prevenar13®. A report may contain multiple AEFIs. Of these reports, we noted a large number of reports of injection site inflammation with an unexpected long latency (time to onset). For this reason, the Netherlands Pharmacovigilance Centre Lareb decided to make an overview of these reports.

Reports

Injection site inflammation is a well-known AEFI and is defined by Lareb as at least two symptoms of inflammation out of swelling, redness, warmth, pain or functio laesa of the arm.

Of the 140 reports received, 68 reports concerned injection site inflammation according to criteria described above. In addition there were 26 reports of other injection site reaction related AEFIs. For an overview of the number and type of AEFIs, see table 1.

Table 1: Overview of injection site reaction related AEFIs

Reported reactions (MedDRA® Lower Level Term)	Number
Injection site inflammation	68
Extensive swelling vaccinated limb	6
Injection site cellulitis	1
Injection site erythema	1
Injection site hematoma	2
Injection site infection	1
Injection site pain	12
Injection site rash	1
Injection site redness	2
Total	**94**

Fifteen persons (22%) reported a time to onset of 1 day or shorter. 40 persons (60%) reported a time to onset of 4-7 days, see figure1. A few persons reported a biphasic duration of the local reactions. First injection site pain or injection site redness with a short time to onset followed by an injection site inflammation after 4-7 days.

Most persons with injection site inflammation have reported symptoms of redness and warmth. Symptoms of induration/swelling are less reported and if reported, the swelling was not very prominent. The duration of the injection site inflammation is unknown as most of the reports were made at the moment that the injection site inflammation was still present.

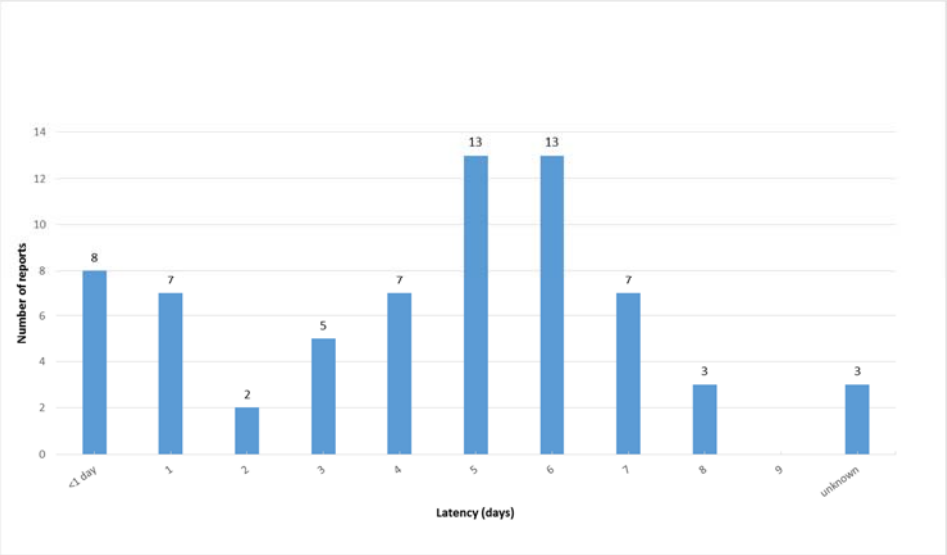

Figure 1. Time to onset of injection site inflammation following immunisation with Prevenar13®

Other sources of information

SmPC
Prevenar13® is an aluminum-phosphate adjuvanted conjugated 13-valent pneumococcal vaccine. The SmPC of Prevenar13® describes injection site erythema; induration/swelling 2.5 cm -7 cm or vaccination pain/tenderness, including impaired movement as a very common AEFI in adults 18 to 39 years. According to the SmPC report adults of 65 years of age or older reported fewer AEFIs compared with adults 18 to 29 years [iv].

Literature
In a study after immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine in adults 70 years of age and older compared with 23-valent pneumococcal polysaccharide vaccine, less local reactions are reported after vaccination with 13-valent pneumococcal conjugate vaccine. Participants reported after vaccination with 13-valent pneumococcal conjugate injections site redness (10.8%), injection site swelling (10.4%), injection site pain (51.7%) and limitation of the arm (10.5%). [v].

Discussion

Before September 2014, Lareb did not received any reports on Prevenar13®. On Prevenar7® which previously was part of the Children's national immunization injection site is a well-known AEFI. In 2011, the last year Prevenar7® was part of the immunization programme, Lareb received 24 reports of injection site inflammation and 1 report of extensive limb swelling. The reported latency for injection site inflammation varies from minutes to 18 hours [vi].

Injection site reactions are the most common AEFI reported to the Netherlands Pharmacovigilance Centre Lareb. Injection site reactions usually manifests as redness, warmth and swelling often in combination with pain and an itching at the injection site. The time to onset is usual 2 hours to 2 days and the duration of the injection site reaction is a few days [vii]. The long time to onset (4-7 days) of injection site inflammation after Prevenar13® in this population is striking. Some persons also report a biphasic duration of the injections site reactions. Also striking is that most persons reported redness and warmth. Swelling/induration are less reported as expected.

The late time to onset of the reported reaction suggests that a secondary cause of inflammation may be induced by the vaccine. It is conceivable that prior immunity to a vaccine constituent may be boostered from immunological memory. Both the polysaccharide antigens and the crm197-diphtheria toxin (*carrier protein) may in theory induce such response.

It is likely that the vaccines, which are used in 2014 belong to another batch than the vaccines used during the study. A batch related problem should also be taken in consideration.

Conclusion

Lareb received, in a period of 8 weeks, 68 reports of injection site inflammation after vaccination with Prevenar13® which was administered to participants who had been given placebo in the CAPiTA trial. Striking with these reports is the unexpected time to onset of 4-7 days and that most reports reported redness and warmth without swelling or with slight swelling.

It could be advisable to further investigate why this atypical time to onset is seen in this population of elderly people. Lareb will continue to monitor AEFI's after vaccination with Prevenar13® and will do a further analysis in January 2015.

Reference

[i]. Bonten MJM, Het CAPiTA-onderzoek in Nederland. Ned.Tijdschrift Med. Microbiologie 2010; 18(1): 10-13.
[ii]. Bonten M, Bolkenbaas M. Huijts S,. Webber C, Gault S, Gruber W, Grobbee D. Community Aqcquired Pneumonia Immunisation Trial in Adults (CAPITA). ISPPD-0541.
[iii]. Persbericht Pfizer Februar 24, 2014: Pfizer Announces Positve Top-Line results of Landmark Community-Acquired Pneumonia Immunization Trial In Adults (CAPiTA) Evaluating Efficacy Of Prevenar 13.
[iv]. Dutch SmPC Prevenar13®. (version date 09 December 2009)
[v]. Jackson LA, Gurtman A, Rice K, Pauksens K, Greenberg RN, Jones TR, Scott DA, Emini EA, Gruber WC, Schmoel-Thoma B. Immunogenicity and safety of 13-valent pneumococcal conjugated vaccine in adults 70 years of age and older previously vaccinated with 23-valent pneumococcal polysaccharide vaccine. Vaccine 2013; 3: 3585-3593
[vi]. Lareb. Meldingen van bijwerkingen Rijksvaccinatieprogramma. Rapportages 2011, www.lareb.nl.
[vii]. Bijwerkingendatabank Nederlands Bijwerkingen Centrum Lareb via http://www.lareb.nl/bijwerkingen/zoekgeneesmiddel.asp (vrij toegankelijk)

This overview was published on March 2015. 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