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Adverse reactions associated with meningococcal group B vaccine (4CMenB) in adults in special situations

Reacciones adversas asociadas a la vacuna del meningococo B (4CMenB) en adultos en situaciones especiales

Abstract
Objective: To know the safety profile of the 4CMenB vaccine in adults in special situations. Method: Security prospective study of phase IV. Inclusion criteria and some vaccination conditions were applied. The adverse reactions described in the data sheet were collected. The adverse reactions evaluation was performed 24 hours after vaccination ("requested") and during the first seven days ("not requested").
Results: 72 patients were included (54.2% men, mean age 52.5 years, 81.9% anatomic asplenia). The frequency of fever > 38 ºC in the first 24 hours of vaccination was higher than the observed in the summary of product characteristics for the group of adults (12.5% vs. not known). More than 75% of the patients reported local pain in the first hours (average of the Analog Visual Scale score 3.22 [95% CI: 2.67-3.76] in the first dose and 3.23 [95% CI: 2.69-3.78] in the second dose). There were no statistically significant differences. 97.22% registered symptoms until 7 days after vaccination.
Conclusions: 4CMenB® shows a good safety profile in adults in special situations. The frequency of fever > 38 ºC is higher than expected. Local pain is the most frequently recorded adverse reactions, but the intensity is low. These results suggest a review of the situation in order to suggest a possible modification of the summary of product characteristics of the vaccine.

KEYWORDS
Postmarketing Drug Surveillance; Adverse effects; Vaccines; 4CMenB; Meningitis; Immuno compromised patients; Meningococcus.

PALABRAS CLAVE
Seguimiento postautorización; Efectos adversos; Vacuna; 4CMenB; Meningitis; Pacientes inmunocomprometidos; Meningococo.
Introducción
Neisseria meningitidis es un exclusivamente humano patógeno, capaz de causar severas infecciones como la meningococcemia. La edad es un factor esencial en la distribución del riesgo asociado con Neisseria meningitidis, y por lo tanto hay un riesgo más alto de infecciones en bebés, aunque hay un alto riesgo de portadores adrede y niños adolescentes comparado con adultos jóvenes.

En 2014, 2760 confirmados de IMD en Europa fueron reportados al European Centre for Disease Prevention and Control, lo que muestra una incidencia anual de 0.5 casos por 100,000 habitantes. De estos casos, 64% fueron causados por un serogrupo B meningococcicos (MenB). Actualmente hay seis vacunas meningocólicas en el mercado en España: tres monovalentes contra el serogrupo C (Menjugate®), Meningitec® y NeisVac-C®, dos tetravalentes contra serogrupos A, C, W y Y (Menvi®) y Nimenrix®, y la vacuna cuatro componentes de FHbp proteína (proteína de unión a factor H), conocida como MenNZ-Hep (Trumemb®). Actualmente, solo la vacuna contra serogrupo C incluye el sistema de vacunación infantil en España, mientras que el MenB vacuna es únicamente recomendado y recomendado bajo algunos casos especiales en el sistema de salud nacional (SNS).

Vacuna y farmacovigilancia son dos elementos clave en cualquier vacunación. Los ensayos clínicos realizados en el 4CMenB vacuna muestran que los principales efectos adversos (AEs) reportados son dolor y el eritema. Además, en el caso de los bebés, temperatura >38 ºC aparece en 14% de los casos y es mayor en niños mayores del 50% de los vacunados, y claramente las figuras más altas se alcanzarán (85%) si se administran conjuntamente con otras vacunas. Es importante resaltar que estos ensayos clínicos fueron realizados especialmente con niños, adolescentes y adultos, pero no hay estudios comparativos con niños de diferentes grupos en edad. Por lo tanto, la vacuna contra el serogrupo C es incluida en el sistema de vacunación infantil en España, mientras que el MenB vacuna es únicamente recomendado y recomendado bajo algunos casos especiales en el sistema de salud nacional (SNS).

Métodos
Tipo de estudio
Un estudio post-marketing para seguir a futuro asociado con seguridad.

Estudio de preparación y programación
El estudio se realizó en la Unidad de Vacunación (VU) de un hospital regional con 1069 camas, desde marzo 2015 hasta marzo 2017.

Inclusión criterios
Los siguientes criterios de inclusión fueron implementados:
1) Pacientes con indicación para vacunación con 4CMenB según el SNS.
   a) Deficiencia complementaria/condición de memoria.
   b) Tratamiento con eculizumab.
   c) Aplasia o déficit de seres leucocíticos.
   d) Historia de un IMD previo.
   e) Lab staff en potencia en contacto con Neisseria meningitidis.
2) Edad >18 años.
3) No específicos contraindicaciones para la administración de la vacuna 4CMenB (Bexsero®) según el producto de especificaciones.
4) Habiendo firmado el Consentado Informe por el VU.

Condiciones de vacunación
Los siguientes criterios de vacunación fueron tomados en cuenta:
1) La vacuna se administró únicamente, sin el consenso de la administración de cualquier otra vacuna en el mismo acto vacunación.
2) La vacunación dosis reglamento para >11 años y adultos se usó, en función de las indicaciones en el producto de especificaciones (PS) para Bexsero®: dos dosis separadas por al menos 30 días. No se estableció una vacunación booster.
3) Hubo un periodo de tiempo al menos de 30 días entre otras vacunas administradas y la dosis de Bexsero®.
4) Hubo un periodo de tiempo al menos de 30 días entre la segunda toma de Bexsero® y cualquier otro tratamiento previo.
5) En pacientes con inmunosupresión o inmunomodulación, hubo un periodo de tiempo al menos de 1 semana y luego de administrar el tratamiento y la vacunación de la dosis de Bexsero®.
6) No se recomendó tomar prophylactic oral paracetamol, a menos que la temperatura corporal del paciente >37,5 ºC después de la primera dosis.
7) No se administró a pacientes con acné, sospechoso incubación periodo, fiebre >38,0 ºC después de la primera toma.

Variables de estudio
Variables sociodemográficas fueron recabadas (edad, género, indicación de vacunación) así como el desarrollo de cualquier efecto adverso descrito en la sección 4.8. Reacciones Adversas de Bexsero®: producto de especificaciones (febrícula, fiebre, dolor en el sitio de inyección, rash cutáneo, somnolencia, irritabilidad, urcoño, vomitando, convulsiones, seco de rana, palidez, fiebre de Kawasaki, dolor muscular-squelitico y general malaise), el tiempo entre la vacunación y el inicio de los síntomas de la reacción adversa, así como las adaptaciones de dichos síntomas.

Procedimiento de recogida de información
La recogida de reacciones adversas se realizó en la misma forma para el primer y segundo dosis de vacuna administrada.

Reportar al Sistema de Vigilancia Farmacovigilancia del Estado
Adverse reaction recording was conducted in the same way for the first and second dose of vaccine administered.

It was structured into two phases: (1) early symptoms (within the first 24 hours), collected through telephone survey by trained nursing staff (‘requested’ adverse reactions), and (2) symptoms appearing within the first seven days after vaccination, collected by the patient through a record sheet designed for this purpose (‘not requested’ adverse reactions), including the clinical sign or symptom, the start date and its duration. Similarly, patients were asked to report if they needed to take paracetamol or any other medication in order to alleviate said symptom.

For evaluation of “pain at the injection site”, each patient was trained on the use of the Analogue Visual Scale (AVS), where 1 means “no pain” and 10 means “unbearable pain”.

Análisis estadístico
El análisis estadístico se hizo mediante el software PASW program (previously in SPSS), version 18, used for paired samples. A Chi square test was used for dichotomous qualitative variables, and Student’s T test for quantitative variables as well as percentages (qualitative variables), and their 95% Confidence Intervals (CI 95%). Bivariate analysis was conducted to find out if the selected study variables were associated or not. Chi square test was used for dichotomous qualitative variables, and Student’s T test was used for paired samples. A p value <0.05 was considered statistically significant. The PASW program (previously known as SPSS), version 18, was used for all this.
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On the other hand, qualitative methodology based on the biographical method was used for the record of adverse reactions conducted by each patient during the first seven days after vaccination.

Ethical aspects

The study received a favourable report by the Clinical Research Ethics Committee (Ref: 119/15), and was classified by the Spanish Agency of Medicines and Medical Devices as a post-marketing study for prospective follow-up (Ref: MFC-BEX2016-01).

Results

In total, the study included 72 patients who met the inclusion criteria. Of these, 54.2% (39) were male and 45.8% (33) were women. Their mean age was 52.5 years, with a ±18.0-year standard deviation.

Regarding the medical indication for vaccination against 4CMenB, the sample was distributed into: 81.9% (59) with anatomic asplenia, 12.5% (9) with previous IMD, 2.8% (2) on treatment with eculizumab, 1.4% (1) with common variable immunodeficiency in a lab staff in contact with N. meningitidis, and 1.4% (1) with functional asplenia due to graft-versus-host disease of haematopoietic progenitors. On the other hand, 80.6% (58) were receiving treatment for some chronic disease at the time of vaccination, while 19.4% (14) were receiving no treatment.

The most frequent adverse reactions, appearing within the first 24 hours after vaccination with the first and second doses of Bexsero® were: local pain [80.6% (58) after the first dose and 77.8% (56) after the second dose], headache [20.8% (15) after the first dose and 18.10% (13) after the second dose] and fever >38ºC [12.5% (9) after the first and second doses]. Figure 1 shows the frequency rate of all adverse reactions described at Bexsero®’s product specifications for the first and second doses of the vaccine. No statistically significant differences were found between any of the variables studied. However, when comparing the adverse reactions identified in this study with those shown in Bexsero®’s PS, some noteworthy differences can be observed. Thus, we can highlight the development of six adverse reactions that are not described in the PS of the vaccine for the >11-year-old and adult group, such as: fever >38°C, somnolence, loss of appetite, irritability, vomiting and paleness (Table 1).

Figure 1. Proportion of requested adverse reactions after the first and second doses of Bexsero®, with their 95% confidence interval, and statistical analysis of the differences between them (p values in italics). The number of patients who presented each one of the adverse reactions is shown in the table below the graph.
Pain at the site of injection was evaluated at 24 hours of vaccination through an AVS on which each patient had been previously trained, 80.6% (58) and 77.8% (56) of patients reported local pain within the first 24 hours after vaccination with the first and second doses. The mean AVS score with the first dose was 3.22 (CI95%: 2.67-3.76) and 3.23 with the second dose (CI95%: 2.69-3.78). There were no statistically significant differences (p=0.979); however, there was a higher frequency of moderate pain with the first dose (AVS score 4-6), and of mild pain with the second dose (AVS score 1-3), as shown in Figure 2. It is worth highlighting that only two patients assigned a value >8 in the AVS to their pain both for the first and the second dose of the vaccine.

Adverse reactions in the first seven days after vaccination (“not requested”) were analyzed with qualitative methodology. Of those 72 persons included in the research, only 2 reported no sign or symptom within the seven days after vaccination. On the contrary, the remaining 70 persons reported some adverse reaction, including local pain [84.72% (61)], general malaise [63.11% (26)] and fever [22.22% (16)] within the first seven days after Bexsero®. The “latency” and “duration” variables could not be analyzed due to lack of record by patients. Table 2 shows the grouped outcomes.

It is worth noting that even though 80.6% of patients in the study were receiving chronic treatment due to their basal condition, the development of both local and systemic adverse reactions was attributed to vaccination, because symptoms were compatible both clinically and epidemiologically, and moreover, these were solved without any treatment interruption.

The only adverse reaction classified as severe, according to the clinically relevant criterion, was reported to the SEV-H (Record No. 600167). This adverse reaction consisted in general malaise with nausea, dizziness, and unspecific abdominal discomfort, it lasted over three days and then disappeared.

**Discussion**

Phase IV studies are essential in order to improve the detection of adverse pharmacological reactions. In most occasions, infrequent adverse reactions, or those appearing in specific patient subpopulations, are not identified in pre-marketing stages, therefore, post-marketing monitoring becomes specially relevant. Many studies have been conducted with the 4CMenB vaccine in paediatric population, but not so many in the adult population, beyond those conducted in specific closed populations, such as university campuses or labs with staff at risk. Therefore, we have a lack of clinical trials, not only in the adult population but specifically for the group of adults in special situations. For this reason, this present research represents a novelty in terms of studying the safety of this vaccine in the adult population in special situations.

The frequency of adverse reactions on the sample under study has been compared with the one stated in the product specifications. It is worth highlighting that the PS states that the frequency rate of fever for the >11-year-old and adult group is unknown, while this study has recorded a frequency >10% for both doses. These results coincide with what other authors have described: they have also found, although with great variability, that the frequency of developing fever is higher than expected.

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**Table 1. Frequency of adverse reactions after the first and second doses in comparison with the frequencies described in the product specifications of Bexsero®**

<table>
<thead>
<tr>
<th>First dose (%)</th>
<th>Second dose (%)</th>
<th>Bexsero® PS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever &gt;38°C</td>
<td>12.50*</td>
<td>12.50*</td>
</tr>
<tr>
<td>Headache</td>
<td>20.80*</td>
<td>18.10*</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>2.80*</td>
<td>0.00*</td>
</tr>
<tr>
<td>Local pain</td>
<td>80.60*</td>
<td>77.80*</td>
</tr>
<tr>
<td>Rash. itching</td>
<td>6.90*</td>
<td>2.80*</td>
</tr>
<tr>
<td>Somnolence</td>
<td>4.20*</td>
<td>4.20*</td>
</tr>
<tr>
<td>Irritability</td>
<td>14.0*</td>
<td>14.0*</td>
</tr>
<tr>
<td>Crying</td>
<td>0.00*</td>
<td>0.00*</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.80*</td>
<td>4.20*</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.40*</td>
<td>0.00*</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.00*</td>
<td>0.00*</td>
</tr>
<tr>
<td>Seizures</td>
<td>0.00*</td>
<td>0.00*</td>
</tr>
<tr>
<td>Dry skin</td>
<td>0.00*</td>
<td>0.00*</td>
</tr>
<tr>
<td>Paleness</td>
<td>0.00*</td>
<td>1.40*</td>
</tr>
<tr>
<td>Kawasaki Syndrome</td>
<td>0.00*</td>
<td>0.00*</td>
</tr>
<tr>
<td>Muscular pain</td>
<td>5.60*</td>
<td>5.60*</td>
</tr>
<tr>
<td>General malaise</td>
<td>5.60*</td>
<td>9.70*</td>
</tr>
</tbody>
</table>

*This table includes in the research, only 2 reported no sign or symptom within the seven days after vaccination. On the contrary, the remaining 70 persons reported some adverse reaction, including local pain [84.72% (61)], general malaise [63.11% (26)] and fever [22.22% (16)] within the first seven days after Bexsero®. The “latency” and “duration” variables could not be analyzed due to lack of record by patients. Table 2 shows the grouped outcomes.

**Figure 2. Profile of pain reported in the injection site according to number of doses, at 24 hours after vaccination, according to the AVS scale: mild (1-3), moderate (4-6) or intense (7-10).**
A recent systematic review of the safety of the 4CMenB vaccine vs. Trumenba® (a recently marketed vaccine against meningococcus B) and vaccines routinely administered in children and adolescents, reached the conclusion that the most frequently reported severe adverse reactions were febrile seizures. These results cannot be compared with this study that has been conducted in adults in special situations; besides, only one severe case was identified. It is worth noting that the same review found a 74% prevalence of pain at the injection site, and a 24% prevalence of fever; both results are higher than those found in our research, although matching the Product Specifications of the vaccine for this group. On the other hand, the quantitative evaluation of local pain through the AVS represents an innovation regarding previous studies on the safety of the 4CMenB vaccine. So far, studies such as Santolaya and Gisson used qualitative scales where pain was rated according to its intensity: mild, moderate or severe. However, using a quantitative scale allows more accurate comparisons of local pain intensity, and this scale is the most frequently used in research associated with pain measurement. No significant differences have been found in terms of pain intensity between the first and the second doses. Unlike what other authors have done, i.e. administering Bexsero® and placebo, or Bexsero® and other vaccines, in this case both doses were administered in the same conditions, and therefore these results cannot be compared.

Finally, the main limitation in our study is sample size. In this sense, the implementation of inclusion criteria and vaccination conditions, as well as the target population chosen to conduct this research, made it difficult to obtain a large sample within a reasonable period of time; in the future, it could be considered to conduct multicentre studies. Summing up, vaccination against meningococcus B with Bexsero® in adults in special situations shows a good safety profile; however, there is limited information available, given the low number of patients studied. The frequency of fever in this population is higher than expected for the same age group according to the Product Specifications. Local pain is the adverse reaction most frequently reported for both vaccine doses; however, pain intensity is low.

Funding
No funding.

Conflict of interests
No conflict of interests.

Contribution to the scientific literature
The great majority of studies so far regarding the four-component vaccine against meningococcus B (4CMenB) have been conducted in paediatric population; only a minority of studies have been conducted in adolescents specifically healthy. This study is innovative not only in terms of its subjects, i.e. patients in special situations, but also for the use of the AVS pain scale unlike other studies for vaccine safety, where qualitative scales were used. It is important to highlight that the results shown by this study seem to differ with the information contained in the product specifications for the vaccine, mostly regarding fever >38°C, because this reaction is not described in clinical trials for the >11-year-old children and adults group. For this reason, it could be justified to extend this research, and to review the product specifications of the 4CMenB vaccine.

Table 2. Frequency of adverse reactions described in the PS for Bexsero® and reported by participants within the first seven days after vaccination ("not requested")

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th>Headache</th>
<th>16 (22.22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI disorders</td>
<td>Nausea and vomiting</td>
<td>9 (12.50)</td>
</tr>
<tr>
<td>Musculoskeletal and conjunctive tissue disorders</td>
<td>Myalgia and arthralgia</td>
<td>17 (23.61)</td>
</tr>
<tr>
<td>General disorders and alterations at the site of administration</td>
<td>Pain at the injection site</td>
<td>61 (84.72)</td>
</tr>
<tr>
<td></td>
<td>Fever or feverishness</td>
<td>14 (19.44)</td>
</tr>
<tr>
<td></td>
<td>General malaise</td>
<td>26 (36.11)</td>
</tr>
</tbody>
</table>

Bibliography


