Overview

A new meningococcal B vaccine for adolescents and adults: characteristics and methods of use

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Keywords

Meningococcal B vaccine • Directions of use • Adolescent

Summary

The invasive disease from Neisseria meningitidis is one of the leading causes of death for meningitis and sepsis at all ages. The highest incidence of cases occurs at paediatric and adolescent age, but no age of life is considered protected from this infection and disease.
Prevention against the five main serogroups is possible using the combined conjugated polysaccharide vaccine against the ACWY (anti-MenACWY) serogroups and the meningococcal B (anti-MenB) protein vaccines.
Trumenba® vaccine, approved by the EMA (European Medicine Agency) for use in individuals aged ≥ 10 years, protects against serogroup B invasive disease.
This bivalent, recombinant vaccine is able, when given with a 0-6 month schedule, to induce a protective response in adolescents and young adults, comparable with a 3-doses schedule.
For this reason, the Trumenba® vaccine should be used routinely with the 2-dose schedule (0-6 months). The 3-doses use could be considered in particular situations, like an occurring epidemic or particular individual risk factors such as asplenia or complement deficit, but is not needed for underlying conditions like diabetes or heart diseases.

Introduction

The invasive disease from *Neisseria meningitidis* is one of the leading causes of death for meningitis and sepsis at all ages [1]. The highest incidence of cases occurs at paediatric and adolescent age, but no age of life is considered protected from infection and disease. There are five *Neisseria meningitidis* serogroups most frequently involved in invasive infections: A, B, C, W, Y [2, 3]. There is now the possibility of prevention against the five serogroups using the combined conjugated polysaccharide vaccine against the ACWY (anti MenACWY) serogroups and the meningococcal B (anti-MenB) protein vaccines.
The use of anti-meningococcal C and tetravalent anti ACWY vaccines is well established; data regarding safety, protective efficacy and administration protocols to be used are well known.
Prophylaxis against meningococcus B can be performed with two vaccines, the Bexsero® vaccine, marketed in Italy by GlaxoSmithKline and indicated for use both in childhood and adolescence and in adulthood, and the Trumenba® vaccine, marketed in Italy by Pfizer and registered for use in adolescents and adults. Both are protein vaccines. The proteins inserted in the vaccines are produced with recombinant DNA technologies. The Bexsero® vaccine is used with a 2-dose protocol in children > 2 years and adolescents; the Trumenba® vaccine, recently introduced in use in Italy, has a 2- or 3-dose posology [4, 5]. This has raised some issues in healthcare workers regarding the calendar to be used with this vaccine.
Moreover, since the University of Florence is conducting a Health Technology Assessment (HTA) study to support health policy makers in the use of Trumenba® within vaccine policies funded by the *Servizio Sanitario Nazionale* (National Health Service), it is crucial, to establish the conditions where the use of the two-dose schedule is indicated and, on the other hand, when three doses are advised. The aim of this work is therefore to provide the most recent scientific evidence that can support the use of one schedule or the other, and facilitate the HTA evaluation of the product.

Trumenba® vaccine in adolescents: immunogenicity studies and bactericidal activity.

The bivalent, recombinant Trumenba® vaccine contains two variants of factor H-binding protein (fHBP) and has been approved by the EMA (European Medicine Agency) for use in individuals aged ≥ 10 years [5]. Like in the past for meningococcal polysaccharide vaccines, also for meningococcal B protein vaccines, it was not possible to carry out clinical efficacy studies due to the low incidence of invasive meningococcal disease. Instead, several immunogenicity studies have been performed: antibody production and bactericidal activity have been considered as a correlate of protection.

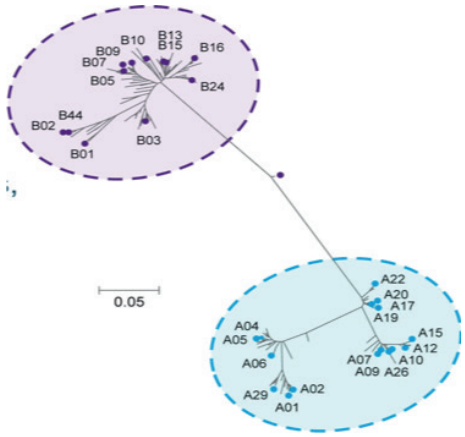
The fHbp protein is present on virtually all meningococci; however, for antibodies induced by the vaccine to guarantee bactericidal activity, the amount of fHbp present on the surface of the meningococcus needs to be sufficiently high as to be recognised by the antibodies. In this regard, the studies that analysed the amount of fHbp present on the meningococcal surface have been able to demonstrate, on more than 2,150 meningococcus strains, that over 90% of the isolates present a sufficient amount of fHbp to trigger the antigen-antibody reaction, and therefore the bactericidal activity of vaccine-induced antibodies [5, 6].

The peculiarity of the studies of bactericidal activity of the Trumenba® vaccine is that they were performed by testing the vaccine-induced antibody production against heterologous strains (i. e. strains that exhibit antigens other than those contained in the vaccine) of meningococci, expressing different sub-variants of fHbp, and a different amount of protein on the surface of the meningococcus. Another peculiarity is that the vaccine antigens of Trumenba® (A05 and B01) are derived from both existing subfamilies of fHbp (A and B) with the aim of including the set of circulating forms of meningococcus B (subfamily A comprises about 30% of circulating forms, whilst subfamily B comprises about 70%).

In detail, fHbp proteins are different from meningococcus to meningococcus: there are numerous forms that can be grouped in the two indicated subfamilies (in detail, subfamily A and B according to the Pfizer classification, or variants 1, 2, 3 according to the Novartis classification (Oxford classification), with Pfizer's subfamily A corresponding to the Oxford variants two and three, and Pfizer's subfamily B corresponding to the Oxford variant 1 [7]. Within these subfamilies, there are many (over 200) fHbp sub-variants. For this reason, it is very important to be sure that the antibodies produced by the vaccine are effective against most of these sub-variants (i. e. directed against both subfamilies) and therefore against different meningococcus strains. Today we know that not all the sub-variants are equally frequent and that in 80% of meningococcus strains, the same 10 sub-variants are present [8].

Regarding the bactericidal activity against different sub-variants, studies have been conducted towards the main sub-variants A22, A56, B24 and B44, detected by current epidemiological investigation (actual invasive MenB disease strains from reference laboratories in Europe and the United States) and belonging to both meningococcus subfamilies A and B. These aspects characterise the development of the vaccine. The studies were then further extended to other 10 sub-variants also circulating in Europe and the USA, for a total of 14 sub-variants expressed by current epidemiology [9]. Despite the antibody titre needed to induce protection (correlate of protection) being a hSBA 1:4 titre, in the Trumenba® development studies a higher dilution titre was used as a protection correlate (1:8 for A56, B24 and B44 and 1:16 for A22) to strengthen the certainty of achieving a sufficient antibody titre, using a higher threshold value. A 4-fold increase in the seroconversion index was also evaluated. These studies were conducted with different protocols, including two or three doses [5].

Fig. 1. Phylogenetic tree of meningococcal fHbp proteins (Donald et al., mod. [8]).



Trumenba® vaccine in adolescents: 2 or 3 doses?

The Vesikari study, conducted in Finland on adolescents and young adults, assessed the percentage of subjects who achieved or exceeded the antibody titre of bactericidal activity (hSBA) of 1:8 (i. e. with double dilution compared to the protection correlate 1:4). With the 2-dose protocol (0-6 months), the subjects who achieved this titre were respectively > 90% against the A22 variant, > 98% against the A56 variant, > 69% against the B24 variant and > 70% against the B44 variant [10].

The data therefore confirmed the ability of antibodies induced by the vaccine to induce a sufficiently protective response against meningococci expressing different variants of fHbp (i. e. heterologous to the vaccine). The data of the study allowed to conclude that the Trumenba® vaccine is able, when given with a 0-6 month calendar, to induce a protective response in adolescents and young adults comparable with a 3-dose schedule. The authors also conclude that increasing the time between the two doses improves the induced antibody response so much that protocol 0-6 month is preferable to protocol 0-4 or 0-2 or 0-1 month.

The results of the study were therefore that both the 2- and 3-dose calendars induce a robust immune response [10].

Precisely for this reason, the Trumenba® vaccine should be used routinely with the 2-dose schedule (0-6 months). The 3-dose use could be considered in particular situations, when it is necessary, for example in travellers heading to endemic areas, to be protected in a short time because of an outbreak occurrence; in that case, a schedule 0-1 month (before departure) can be used, followed by a third dose at month 6.

For example, this was indicated in the recommendations of the Advisory Committee on Immunization Practices

(ACIP) updated as of May 2017, which show that, in routine conditions, two doses are recommended in subjects not exposed to risk. It is important to remember that "patient at increased risk" does not mean a patient with an underlying disease (e. g. diabetes, heart disease, etc.). The first 2015 ACIP recommendations indicate precisely the conditions of increased risk and specifically: "*Persons with persistent complement component deficiencies, persons with anatomic or functional asplenia, microbiologists routinely exposed to isolates of Neisseria meningitides, persons identified as at increased risk because of a serogroup B meningococcal disease outbreak.* " The recommendations mentioned above also indicate that if the interval between the two doses is equal to or greater than 6 months, the third dose in those at risk is no longer necessary, demonstrating a 3-dose rationale linked solely to the need to accelerate the schedule [11, 12].

Adding further doses to vaccination calendars often causes a reduction in adherence to the prescribed number of administrations in patients and families, and this is especially true in adolescents, who are in any case difficult to reach. US data obtained on a typical adolescent vaccination, the anti HPV, have shown that vaccination coverage decreases with doses following the first: 60% for the first dose, 50. 3% for second and 39. 7% for the third dose [13]. A similar decreasing trend is also present in Italy.

The data obtained in the Vesikari [10] study were evaluated and analysed in further publications with the conclusion that a two-dose schedule (0-6 months) is perfectly usable in vaccination practice [14, 15].

Given the very rapid evolution of the clinical conditions characteristic of the disease (which may evolve towards a very serious or even fatal situation in less than 24 hours), it appears appropriate to provide a periodic booster dose for all subjects at risk for age or other conditions (work, travel) in order to take advantage of the immunological memory induced by vaccination. This procedure is appropriate also for vaccination against meningococcus B, just as for vaccinations against meningococcal vaccines C or ACWY [5, 15]. The timing recommended for carrying out this booster vaccine should be established in the future by monitoring the antibody kinetics in populations of vaccinated subjects followed in the years after the basic immunisation course.

Conclusions

Trumenba® vaccine is able, when given with a 0-6 month schedule, to induce a protective response in adolescents and young adults, comparable with a 3-doses schedule. For this reason, the Trumenba® vaccine should be used routinely with the 2-dose schedule (0-6 months). The 3-doses use could be considered in particular situations. These are clearly addressed in the recommendations of the Advisory Committee on Immunization Practices (ACIP) updated as of May 2017: three doses are recommended in subjects at increased risk, not meaning patients with an underlying disease (e. g. diabetes, heart disease, etc.) but, as the first 2015 ACIP recommendations precisely indicate: "Persons with persistent complement component deficiencies, persons with anatomic or functional asplenia, microbiologists routinely exposed to isolates of Neisseria meningitides, persons identified as at increased risk because of a serogroup B meningococcal disease outbreak. "

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Conflict of interest statement

The Authors previously participated in advisory boards, expert meetings, or were speakers or organizers of congresses/conferences on different vaccines sponsored by Pfizer, GlaxoSmithKline, Sanofi Pasteur MSD, MSD, Sanofi Pasteur, Seqirus, and occasionally received grants for scientific studies from the same manufacturers.

Authors' contributions

CA and PB have made equal contribution to the conception, design, analysis and interpretation of data, drafted the article; they approved the final version submitted to the Journal of Preventive Medicine and Hygiene.

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