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ORIGINAL ARTICLE

Antibody persistence 5 years after a 13-valent pneumococcal conjugate vaccine in asplenic patients with β-thalassemia: assessing the need for booster

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Abstract

Streptococcus pnemoniae is a major cause of morbidity and mortality among splenectomised patients with β-thalassemia major. We have previously shown that a 13-valent pneumococcal conjugate vaccine (PCV13) induces robust early immune responses in such patients, while history of repeated immunisations with the 23-valent polysaccharide pneumococcal vaccine (PPSV23) results in attenuation of the response to PCV13. However, the duration of vaccine-induced protection in splenectomised thalassemic patients and the associated need for booster immunisation remains unclear. In the current study, we enumerate antibody persistence 5 years post-PCV13 and investigate any correlation with early immune response and immunisation history. Pneumococcal serotype (PS)-specific antibodies against 5 vaccine antigens were measured 5 years post-PCV13 in 34 asplenic adults with β-thalassemia. PS-specific antibodies against 5 vaccine serotypes had declined significantly at 5 years post-PCV13 (year 5).Year 5 antibody titres remained above baseline for PS9V, 19A and19F, returned to baseline for PS23F, and dropped below baseline for PS3 ($p < 0.001$).Year 5 antibodies were positively correlated with day 28 antibody titres, while no correlation was found with early memory B cell response. Previous PPSV23 history was correlated with impaired antibody persistence against serotype 19A. Antibody levels dropped significantly but remained at protective levels 5 years post-PCV13.We propose that asplenic patients with β-thalassemia may benefit from measurement of antipneumococcal antibodies after 5 years post-PCV13 as they may eventually be in need for booster pneumococcal vaccination. Clinical Trials Registration ID: www.clinicaltrials.gov NCT01846923.

Keywords β-thalassemia major · Pneumococcal vaccine · Antibody persistence · Immunological memory

Introduction

Streptococcus pnemoniae is a major cause of life-threatening invasive infections and mortality among asplenic individuals, such as the splenectomised patients with β-thalassemia major [1, 2]. Therefore, their protection through vaccination has always been an important priority.

The guidelines for pneumococcal immunisation of persons with asplenia and other immunocompromising conditions have changed significantly over the last two decades, due to accumulating evidence regarding PPSV23-driven immune hyporesponsiveness, a state in which vaccine recipients are unable to mount higher or at least equal immune response to booster than to primary vaccination [3]. Therefore, sole repeated use of the 23-valent polysaccharide vaccine (PPSV23) had been replaced by a combined schedule of a 7-valent pneumococcal conjugate vaccine (PCV7) and PPSV23. More recently, a 13-valent pneumococcal conjugate vaccine (PCV13), containing 6 additional serotypes, replaced PCV7 and a PCV13/PPSV23 schedule is currently recommended for asplenic patients [4].

We have previously shown that PCV13 induces robust early memory B cell (MBC) and antibody responses in asplenic young adults with β-thalassemia major [5]; however, the

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longevity of vaccine-induced immunity and associated need for revaccination in asplenic patients remains largely unknown [6]. Moreover, we have shown that history of repeated PPSV23 vaccinations has a negative effect on PCV13-induced early MBC and antibody responses [5], but the effect of previous PPSV23s on the persistence of PCV13-induced humoral response has not yet been studied.

In this follow-on study, we enumerate the circulating pneumococcal serotype (PS)-specific antibodies 5 years after immunisation with PCV13 in the same cohort of asplenic adults with β-thalassemia major in order to longitudinally investigate the antibody persistence against vaccine antigens. We also examine the correlation of antibody persistence with the early kinetics of MBCs and antibodies and investigate whether patients with history of multiple PPSV23s are at increased risk for a rapid decline of immunity, due to PPSV23-driven hyporesponsiveness.

Methods

Thirty-four splenectomised adults (19 males) with transfusion-dependent β-thalassemia aged 24–53 years were re-enrolled to the study. All patients have received one dose of PCV13, which contains 2 μg each of 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F and 23F, and 4 μg of 6B conjugated to a mutant diphtheria toxin (CRM197), 5 years earlier and MBCs and IgG antibodies had been enumerated at baseline (day 0, D0) and 28 days (day 28, D28) post-immunisation. All patients had also received one dose of PCV7 7 years prior to PCV13 and overall 1–4 doses of PPSV23 in the past (1–3 before PCV7 and 1–2 between PCV7 and PCV13). All immunisations have been administered intramuscularly in the left deltoid muscle. In the context of the present study, a single blood sample before transfusion was obtained from each patient at 5 years postvaccination with PCV13(year 5, Y5). The World Health Organization (WHO) enzyme-linked immunosorbent assay protocol was used for the detection of immunoglobullin G (IgG) antibodies (Abs) in serum samples against pneumococcal serotypes (PS) 3, 9V, 19A, 19F and 23F.

Statistical analysis

Continuous variables are presented with mean and standard deviation (SD). Variables were first tested for normality using the Kolmogorov-Smirnov criterion. Spearman correlation was calculated to relate IgG antibody levels with number of PPSV23s, years since last PPSV23, IgG MBCs, IgM and IgG antibody levels from baseline to day 28. IgG antibody levels were log-transformed to obtain normality for analysis, but untransformed numbers with mean values are presented as descriptive data. To longitudinally assess changes in IgG antibody levels, mixed linear regression models with time were fitted that account for multiple measurements per individual obtained at different time points. All reported p values are two-tailed. Statistical significance was set at 0.05 and analyses were conducted using STATA statistical software (version 11.0).

Results

PS-specific antibodies against the five vaccine serotypes studied had declined significantly at 5 years post-PCV13 in comparison to day 28 post-PCV13: Geometric mean titres (GMTs) 0.93 vs. 4.02 μg/ml, $p < 0.001$; 2.76 vs. 7.76 μg/ml, $p < 0.001$; 12.15 vs. 15.01 μg.ml, $p = 0.043$, 8.53 vs. 18.42, $p < 0.001$; 8.75 vs. 17.47, $p < 0.001$ for serotypes 3, 9V, 19A, 19F and 23F respectively (Fig. 1a). Antibody GMTs at year 5 remained above baseline levels (day 0) for PS 9V, 19A and 19F, returned to baseline levels for PS 23F, but dropped below baseline for serotype 3 ($p < 0.001$) (Fig. 1a). PS-specific antibodies against the PPSV23-only serotype 22F was also measured at year 5 for comparison. Antibody GMT against serotype 22F was 7.43 μg/ml, above the threshold of protection.

IgG antibody geometric mean titres at year 5 were positively correlated with antibody GMTs at day 28: $r = 0.35$, $p =$ ns; $r = 0.54$, $p < 0.01$; $r = 0.79$, $p < 0.001$; $r = 0.53$, $p < 0.05$; $r = 0.88$, $p < 0.001$ for serotypes 3, 9V, 19A, 19F and 23F respectively. In contrast, no correlation was seen between year 5 IgG antibody GMTs and IgM or IgG MBC numbers at baseline or day 28.

The investigation of the impact of previous PPSV23s on the persistence of humoral response to PCV13 in a dose-dependent (Fig. 1b) and time-dependent manner (Fig. 1c) revealed no significant correlations for most serotypes tested, except 19A, for which antibody persistence at year 5 was negatively correlated with the number of previous PPSV23 immunisations ($p < 0.05$) (Fig. 1b).

Discussion

This is the first study to our knowledge to investigate the persistence of PCV13-induced PS-specific IgG antibodies 5 years post-immunisation as well as the impact of previous immunisation history in a cohort at high risk for IPD, such as the patients with β-thalassemia major. Long-term protection after immunisation is thought to rely both on protective serum antibody levels and immunological memory in the form of antigen-specific memory B cells (MBCs). We have previously shown that one dose of PCV13 induces immunological memory with significant increase of IgG MBCs at 28 days post-immunisation in

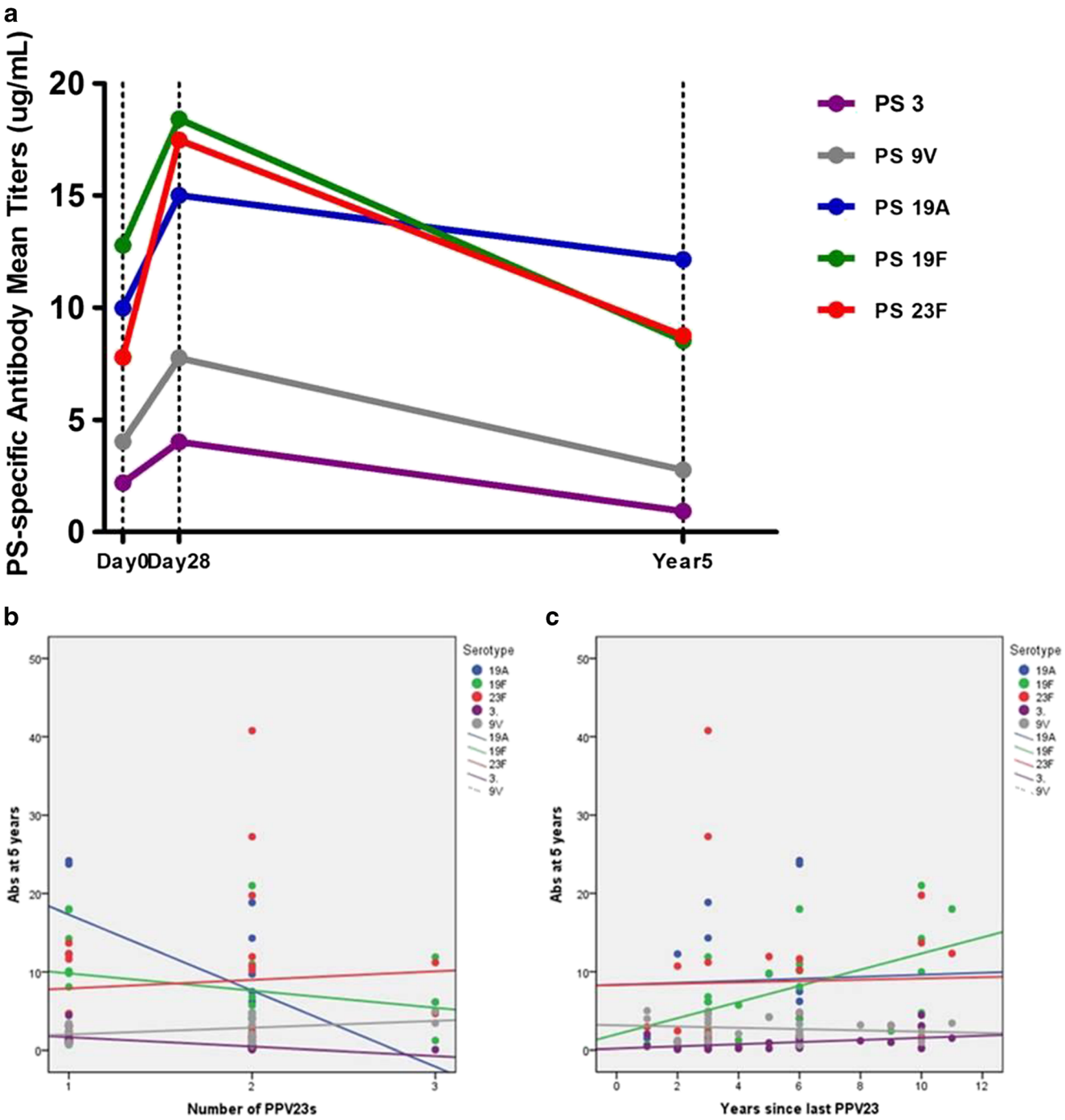

Fig. 1 Mean immunoglobulin G (IgG) antibody (Abs) levels through follow-up period after vaccination with one dose of 13-valent pneumococcal conjugate vaccine against pneumococcal serotypes 9V, 19F, 23F, 19A and 3 in 39 adults with β-thalassemia major and asplenia (**a**); correlation of IgG antibody levels at 5 years post-immunisation with one dose of 13-valent pneumococcal conjugate vaccine against pneumococcal serotypes 9V, 19F, 23F, 19A and 3 in 39 adults with β-thalassemia major and asplenia with number of 23-valent pneumococcal polysaccharide vaccine (PPSV23) immunisations in the past (**b**); (Spearman correlation coefficient) and with time elapsed since last PPSV23 immunisation (**c**) (Spearman correlation coefficient). Abs, antibodies; IgG, immunoglobulin G; PPSV23, 23-valent pneumococcal polysaccharide vaccine; PS, polysaccharide

this cohort of asplenic patients with β-thalassemia [5]. However, it has been shown that immunological memory alone may not suffice upon acute invasive infection from encapsulated bacteria in the absence of protective antibody levels [7]. Consequently, long-lasting persistence of PS-specific antibodies at protective levels seems to be a principal mechanism of direct protection against *Streptococcus pneumoniae* and is therefore indispensible

for asplenic individuals, who are at life-long risk for fulminant sepsis post-splenectomy [8]. Splenectomy alone is known to lead to increased risk for bacterial infection and accelerate the decline of antibodies and memory B cells post-immunisation [4]. The significant decline of antibody levels at year 5 found for some of the serotypes assessed in this study suggest that asplenic patients with β-thalassemia major would benefit from assessment of their immunity status against Pneumococcus after 5 years post-immunisation with PCV13, in order to monitor antibody decline and assess the need for booster vaccination with PCV13 when antibody titres drop below the threshold of protection. The timing of such an intervention would depend on the rate of antibody decline.

In the present study, PS-specific antibodies had declined significantly from day 28 at 5 years post-immunisation with one dose of PCV13 but remained at protective levels of > 1 μg/ml for all serotypes tested except for serotype 3 (0.93 μg/ml at year 5). More specifically, PS-specific antibodies at year 5 post-immunisation with PCV13 remained above baseline levels for serotypes 9V, 19F and 19A; they returned to baseline for PS 23F and even dropped below baseline for PS 3. These findings are in accordance with previous reports for suboptimal immunogenicity and efficacy of serotype 3 as a component of PCV13 [9] and the diversity of antibody kinetics due to antigen-specific characteristics that influence the magnitude and durability of the humoral response to a particular pneumococcal serotype [10].

Moreover, we examined the correlation of antibody persistence with early memory B cell and antibody immune response. We found that antibody levels at 5 years were significantly correlated with antibody levels at day 28 after PCV13 immunisation, demonstrating that the magnitude of early antibody response was a strong predictor for the persistence of humoral immunity in our cohort. The magnitude of the early antibody response in combination with antibody half-life is thought to be an important factor for antibody persistence and has been proven a robust correlate of long-term antibody persistence in several studies [11, 12]. In contrast, there was no correlation found between early kinetics of IgG or IgM MBCs and the persistence of antibody levels in our study. Although there has been some evidence that MBCs could also contribute to antibody persistence through a continuous turnover to antibody-secreting cells overtime [13] and there are reports of MBCs correlating with antibody levels at various intervals post-immunisation [11], other studies found no correlation between cellular memory and humoral immunity [14]. It seems that the exact mechanisms that dictate long-term persistence of humoral immunity after immunisation remain unclear [13] and therefore, further studies are needed in order to investigate the role of MBCs and other cell types in the persistence of antibodies.

At last, we have previously shown that past PPSV23 immunisations attenuate the early antibody response to PCV13 in a dose- and time-dependent manner by depletion of PS-specific MBCs [5]. However, in the present study, we found little association of PPSV23 history and the 5-year persistence of PS-specific antibodies. Interestingly, previous history of multiple PPSV23s was negatively correlated with year 5 antibody levels only for PS 19A, a PCV13-only serotype. This finding suggests that the lack of immunological priming and induction of PS-specific immunological memory by PCV7 for this serotype could make the immunological memory against it more susceptible to PPSV23-driven hyporesponsiveness than for the PCV7/PCV13 common serotypes. Moreover, antibody levels against a PPSV23-only serotype 22F were also above the threshold of protection at year 5, suggesting that additional doses of PPSV23 would not offer additional benefit in our cohort. However, further studies focusing on the longitudinal monitoring of PPSV23-induced antibodies are needed to further evaluate PPSV23 duration of protection in asplenic individuals.

In conclusion, antibody levels against the vaccine serotypes tested remained at protective levels 5 years post-immunisation with one dose of PCV13 in this cohort of asplenic adults with β-thalassemia major. Previous history of PPSV23 immunisations did not affect antibody persistence. However, due to the significant decline of humoral immunity over the 5 years for some of the serotypes tested, we propose that such individuals would be eligible for longitudinal monitoring of their immunity status after 5 years post-immunisation and would eventually benefit from booster pneumococcal vaccination when antibody levels fall under the threshold of protection.

Author contribution All authors have contributed to this work and approved the submission.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Ram S, Lewis LA, Rice PA (2010) Infections of people with complement deficiencies and patients who have undergone splenectomy. Clin Microbiol Rev 23:740–780
2. Ladis V, Chouliaras G, Berdoukas V, Chatziliami A, Fragodimitri C, Karabatsos F, Youssef J, Kattamis A, Karagiorga-Lagana M (2011) Survival in a large cohort of Greek patients with transfusion-dependent beta thalassaemia and mortality ratios compared to the general population. Eur J Haematol 86:332–338
3. CDC (2012) Use of 13-valent pneumococcal conjugate vaccine and 23- valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 61:816–819
4. Wasserstrom H, Bussel J, Lim LC-L, Cunningham-Rundles C (2008) Memory B cells and pneumococcal antibody after splenectomy. J Immunol 181:3684–3689
5. Papadatou I, Piperi C, Alexandraki K, Kattamis A, Theodoridou M, Spoulou V (2014) Antigen-specific B-cell response to 13-valent pneumococcal conjugate vaccine in asplenic individuals with β-thalassemia previously immunized with 23- valent pneumococcal polysaccharide vaccine. Clin Infect Dis 59:862–865
6. Papadatou I, Orthopoulos G, Theodoridou M, Spoulou V (2015) Long-lasting hyporesponsivenss induced by the 23-valent pneumococcal polysaccharide vaccine (PPSV23) in asplenic patients with β-thalassemia major. Vaccine 33(32):3779–3783
7. Auckland C, Gray S, Borrow R, Andrews N, Goldblatt D, Ramsay M, Miller E (2006) Clinical and immunologic risk factors for meningococcal C conjugate vaccine failure in the United Kingdom. J Infect Dis 194:1745–1752
8. Bisharat N, Omari H, Lavi I, Raz R (2001) Risk of infection and death among post-splenectomy patients. J Inf Secur 43:182–186
9. Poolman J, Kriz P, Feron C, Di-Paolo E, Henckaerts I et al (2009) Pneumococcal serotype 3 otitis media, limited effect of polysaccharide conjugate immunisation and strain characteristics. Vaccine 27: 3213–3222
10. Madhi SA, Adrian P, Kuwanda L, Jassat W, Jones S, Little T, Soininen A, Cutland C, Klugman KP (2007) Long-term immunogenicity and efficacy of a 9-valent conjugate pneumococcal vaccine in human immunodeficient virus infected and non-infected children in the absence of a booster dose of vaccine. Vaccine 25:2451–2457
11. Blanchard Rohner G, Snape MD, Kelly DF, John T, Morant A, Yu LM, Borkowski A, Ceddia F, Borrow R, Siegrist CA, Pollard AJ (2008) The magnitude of the antibody and memory B cell responses during priming with a protein-polysaccharide conjugate vaccine in human infants is associated with the persistence of antibody and the intensity of booster response. J Immunol 180:2165–2173
12. Liakou CD, Askiti V, Mitsioni A, Stefanidis CJ, Theodoridou MC, Spoulou VI (2014) Safety and immunogenicity of booster immunization with 7-valent pneumococcal conjugate vaccine in children with idiopathic nephrotic syndrome. Vaccine 32(12):1394–1397
13. Amanna IJ, Slifka MK (2011) Contributions of humoral and cellular immunity to vaccine-induced protection in humans. Virology 411:206–215
14. Trück J, Mitchell R, Jawad S, Clutterbuck EA, Snape MD, Kelly DF, Voysey M, Pollard AJ (2017) Divergent memory B-cell responses in a mixed infant pneumococcal conjugate vaccine schedule. Pediatr Infect Dis J 36(5):e130–e135