

Opsonophagocytic activity against group b meningococci: An additional laboratory correlate of protection against meningococcal disease?

Audun Aase

Norwegian Institute of Public Health, P.O.Box 4404 Nydalen, NO-0403 Oslo, Norway

email: audun.aase@fhi.no

Opsonophagocytic activity and serum bactericidal activity against group B meningococci were compared in sera from three vaccine groups given two different outer membrane vesicles vaccines separately or in combination. Opsonophagocytic activity defined more responders and revealed more cross-reactivity against heterologous strains than observed with serum bactericidal activity, and it showed the highest correlation with IgG-binding to live meningococci. Determination of opsonophagocytic activity may therefore be a valuable laboratory supplement to serum bactericidal activity for monitoring protection against group B meningococcal disease.

Keywords: Opsonophagocytic activity, correlate of protection, group B meningococci.

Introduction

Serum bactericidal activity (SBA) has been accepted as the “gold standard” laboratory correlate of protection for meningococcal disease. This concept was first based upon the excellent works by Goldschneider et al. (1) among army recruits, and has since been supported in more recent studies as reviewed by Borrow et al. (2). However, as also pointed out in the Goldschneider paper, several recruits who became carriers with the epidemic strain did not develop meningococcal disease although they had no detectable SBA. More recent studies in USA and UK indicate that the prevalence of healthy people with SBA titre <4 (with human complement) is increasing, while the incidence of meningococcal disease of the same population has decreased, although the carrier rate is still high (3). This indicates that other protective mechanisms may play a role like e.g. opsonophagocytosis, particular for group B disease (4). In this study we have compared the SBA, opsonophagocytic activity (OPA) and IgG-binding to live meningococci in sera from a clinical vaccine trial. Two group B OMV vaccines (MenZB™ and MenBvac) were administered each or in combination to three groups of healthy adults (5). The results indicate that OPA may identify more responders and also recognize more cross-reactivity against heterologous strains than SBA.

Material and methods

A clinical trial investigating the immunogenicity and safety of a combination of two serogroup B meningococcal outer membrane vesicle vaccines was performed (5). Groups of app. 30 persons were immunized with three doses of either MenBvac (25 mg/dose) (strain 44/76; B:15:P1.7,16), MenZB™ (25 mg/dose) (strain NZ98/254; B:4:P1.7-2) or a combination of MenBvac and MenZB™ ((12.5 mg + 12.5 mg)/dose). The

doses were given at six weeks intervals, and blood samples collected before and six weeks after each dose.

SBA was measured by the “tilt method” as described previously using human serum as complement source (2, 5). OPA was measured as respiratory burst as described (6), using live meningococci as target, human serum as complement source and human polymorphonuclear leukocytes (PMNs) as effector cells. The highest reciprocal serum-dilution giving respiratory burst in $\geq 50\%$ of the PMNs is recorded as OPA titer.

An indirect immunofluorescent method was used to measure the levels of IgG antibodies binding to live meningococci by a flow cytometry method as described (6).

The geometric mean titers (GMTs) and geometric mean concentrations (GMCs) and the associate 95% confidence interval (CI) were calculated for the SBA, OPA and IgG-binding, respectively. The proportion of responders, defined as at least a fourfold increase in response from pre-vaccination to 6 weeks post 3rd dose, and the 95% CI was determined. Linear regression analyses were performed to look for relationship between the assays, and the Pearson’s correlation coefficient calculated.

Results and discussion

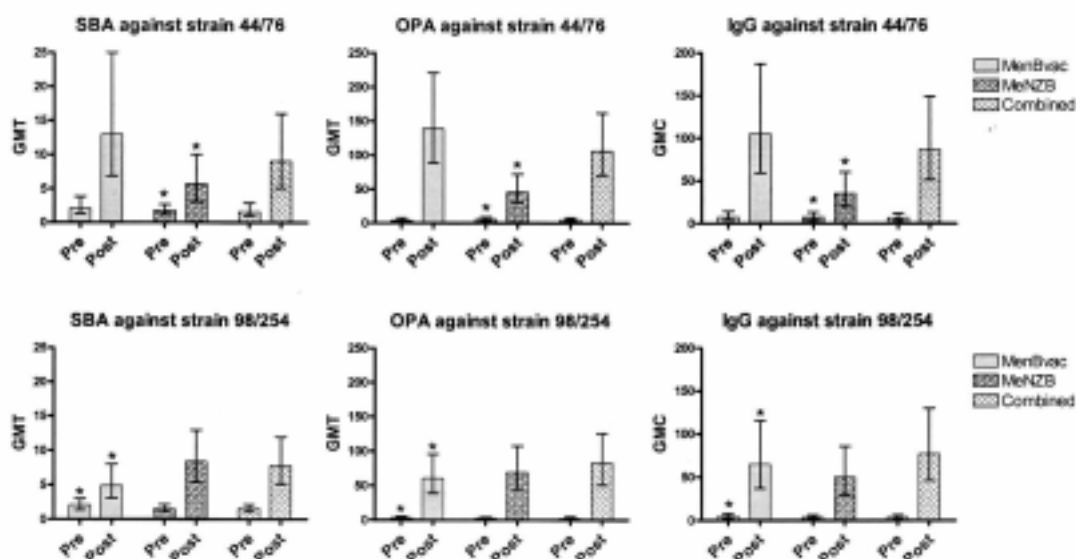
In this study we tested out two different OMV group B meningococcal vaccines administered separately or combined, and compared the SBA and OPA responses. All the vaccines induced significant responses as measured by SBA and OPA. The proportion of pre-vaccinated sera with titers ≥ 4 (defined as positive) was higher in the OPA (range: 30% - 53%) assay than in the SBA assay (range: 13% - 29%), depending on the vaccine group and target strain (Table 1).

Table 1. Proportion of subjects (%) with serum titers ≥ 4 pre-vaccination and six weeks after the 3rd dose within the different vaccine groups against the two target strains.

| Vaccine | NZ98/254 | | | | 44/76 | | | |
|----------|----------|----------|---------|----------|---------|----------|---------|----------|
| | SBA pre | SBA post | OPA pre | OPA post | SBA pre | SBA post | OPA pre | OPA post |
| MenBvac | 29 | 65 | 36 | 96 | 25 | 78 | 44 | 100 |
| MeNZB™ | 15 | 81 | 33 | 100 | 22 | 58 | 53 | 93 |
| Combined | 17 | 87 | 30 | 97 | 13 | 77 | 53 | 100 |

Table 2. Pearson's correlation coefficients of the different assays against the two target strains and vaccine groups.

| Vaccine | MenBvac (N=24) | | MeNZB (N=27) | | Combined (N=30) | |
|---------------|----------------|-------|--------------|-------|-----------------|-------|
| Target strain | NZ98/254 | 44/76 | NZ98/254 | 44/76 | NZ98/254 | 44/76 |
| SBA vs OPA | 0.55 | 0.70 | 0.75 | 0.63 | 0.82 | 0.69 |
| SBA vs IgG | 0.71 | 0.81 | 0.83 | 0.70 | 0.89 | 0.84 |
| OPA vs IgG | 0.91 | 0.84 | 0.89 | 0.88 | 0.93 | 0.86 |

**Figure 1.** Geometric mean SBA and OPA titer, and IgG concentration against live bacteria (AU/mL) with 95% CI. (* indicate activity against heterologous strain.) (Note different scaling of Y-axis).

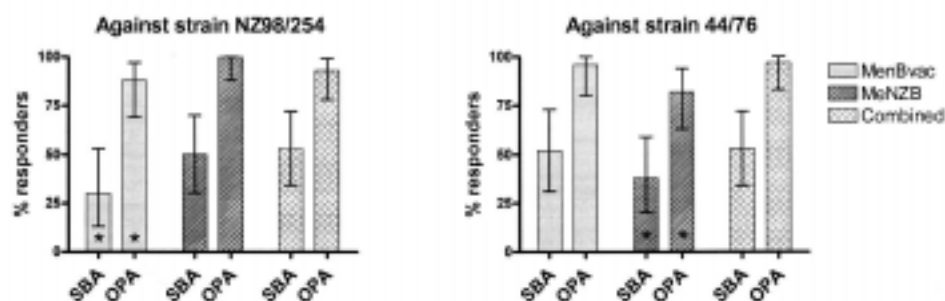


Figure 2. Proportion of responders (%) i.e. at least a fourfold increase and 95% CI, from pre-vaccination to post 3rd dose. (* indicate activity against heterologous strain.)

These subjects, with positive OPA and negative SBA, may possibly be protected against serogroup B disease. After the 3rd dose, 93% - 100% of the participants achieved a titer ≥ 4 in OPA, whereas in the SBA 58% - 87% obtained a titer ≥ 4 (Table 1).

The pre-vaccinated sera had slightly higher OPA titers than SBA titers, particular when tested against strain 44/76 (Figure 1). Six weeks after the third dose the geometric mean OPA titre had increased 9 to 36-fold depending on the vaccine group and target strain. The SBA revealed an increase of 3 to 6.5-fold and the IgG-binding an increase of 5 to 22-fold.

When we looked at the proportion of responders defined as ≥ 4 -fold increase from prevaccination to after the 3rd dose, 100% of the participants given the MeNZBTM vaccine were responders in the OPA assay, against the homologous strain (NZ98/254), whereas 50% were responders in the SBA assay (Figure 2). Of the MenBvac group, 96% were responders in the OPA against the homologous strain (44/76); the corresponding number for the SBA was 52%.

The combined vaccine induced a ≥ 4 -fold OPA increase in 93% and 97% of the vaccinees against strain NZ98/254 and 44/76, respectively, whereas in the SBA the corresponding number of responders were 53% against both strains. Interestingly, against the heterologous strain, the MeNZBTM induced a ≥ 4 -fold OPA response in 82% (95% CI: 63-94%) of the vaccinees, whereas 38% (95% CI: 20-59%) obtained a similar increase in SBA. The MenBvac induced a ≥ 4 -fold OPA response against the heterologous (NZ98/254) strain of 88% (95% CI: 69-97%) of the participants, while there were 30% (95% CI: 13-53%) responders in the SBA assay (Figure 2).

This high cross-reactivity demonstrated with the OPA but not with the SBA, may signify higher cross-protection against group B meningococcal disease than indicated by SBA. However, we do not know if this is a general occurrence or if it is only restricted to the two group B strains examined in this study. The IgG-binding to live meningococci was very similar to the OPA, also demonstrating high cross-reactivity (Figure 1).

Linear regression analysis between assays and corresponding Pearson's correlation coefficients demonstrate a very strong correlation between OPA and IgG-binding to live bacteria (Table 2). There was higher correlation between SBA and IgG than between SBA and OPA, indicating interesting differences between these two functional assays. IgG antibodies binding to live meningococci are thought to be the primary inducers of both SBA and OPA in these studies. It is possible that some IgG specificities may activate complement through C3, but not produce functional terminal complement complex activation and bacteriolysis; thus favoring OPA rather than SBA.

Reference

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