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Development of a Monocyte Activation Test to Assess the Reactogenicity of a Candidate Gonococcal Outer Membrane Vesicle Vaccine

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Background

Monocyte activation tests (MATs) constitute an in vitro approach to evaluating the reactogenicity of pharmaceutical products including vaccines. By measuring interleukin-6 (IL-6) secretion from monocytes, an inflammatory cytokine involved in the fever response, MATs can be used as an alternative to the rabbit pyrogen test (RPT) and align with the 3Rs principle of replacing animal-based methods in research.

Aim/Methods

We aimed to develop a MAT to evaluate the reactogenicity of an outer membrane vesicles (OMV)-based gonococcal vaccine. OMV-based vaccines are potentially reactogenic due to the presence of a range of surface antigens, particularly lipo-oligosaccharide (LOS). To reduce reactogenicity, we genetically removed an

acyl chain from the lipid A component of our OMV vaccine LOS, replacing hexacylated with pentacylated lipid A. Peripheral blood mononuclear cells (PBMCs) were prepared from human volunteers at 106 viable cells/mL. PBMCs were stimulated at 37°C with OMVs administered in a 10-fold serial dilution series. IL-6 in supernatants was then measured using an enzyme linked immunosorbent assay (ELISA). The licensed meningococcal vaccine Bexsero, containing meningococcal OMVs; gonococcal OMVs derived from wild type gonococcus with hexacylated lipid A; and purified endotoxin were used as comparators.

Results

We were able to detect a dose-dependent rise in IL-6 production associated with our gonococcal OMV candidate vaccine. The amount of gonococcal OMVs required for IL-6 induction varied between PBMC donors but was comparable with the amount of Bexsero (by OMV protein equivalents) required for a given PBMC batch. Much higher concentrations of candidate vaccine gonococcal OMVs (with pentacylated lipid A) were needed to induce a rise in IL-6 production compared with OMVs derived from wild-type gonococcus.

Conclusions

We have developed a MAT for the assessment of reactogenicity of gonococcal OMV-based vaccines that discriminates the reduced reactogenicity of OMV with pentacylated compared with hexacylated LOS. The IL-6 response is similar to that measured for Bexsero and using endotoxin equivalent values, in-line with other licensed vaccines. Since IL-6 production varies depending on PMBC donor, use of a comparator batch of OMVs to act as a standard is key.