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Specific antibody response against pneumococcal polysaccharide and conjugated vaccine in Crohn's disease patients treated with immunosuppressive drugs alone or in combination with biological therapy or untreated

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ABSTRACT

Background: Patients with Crohn's disease (CD) have a higher risk of infectious diseases including pneumococcal infections, and the risk increases with immunotherapy. The primary endpoint of this study was to investigate the specific antibody response to two pneumococcal vaccines in CD patients with and without immunosuppressive treatment four weeks post vaccination.
Methods: In a randomized trial of the 23-valent pneumococcal polysaccharide vaccine (PPV23) and the 13-valent pneumococcal conjugated vaccine (PCV13), a group of CD patients treated with immunosuppressive drugs (IS) alone or in combination with TNF-α antagonists were compared to a group of CD patients not treated with any of these drugs (untreated). Specific pneumococcal antibody concentrations were measured against 12 serotypes common to the two vaccines before and 4 week after vaccination.
Results: PCV13 induced a significantly higher antibody response for one serotype (23F) in IS treated patients and for two serotypes (9V and 23F) in untreated patients compared to CD patients vaccinated with PPV23. Untreated PPV23 recipients had higher responses for serotypes 9V and 18C compared to IS + TNF-α treated PPV23 recipients. Comparison between treatment groups showed that immunosuppressive treatment impaired the antibody response to both vaccines and that TNF-a treatment further conveyed additional impairment of the response.
Conclusion: PCV13 induces higher antibody response for some serotypes compared to PPV23. In addition, CD patients treated with immunosuppressive drugs alone or in combination with TNF-α antagonists had an impaired antibody response to both PPV23 and PCV13 compared to patients not receiving any of these treatments.
The study has been registered in the European Clinical Trials Database (EudraCT, record no 2012-002867-86) and ClinicalTrials.gov (record no. NCT01947010).

1. Background

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) of unknown etiology [1]. CD is caused by an inappropriate response of a defective mucosal immune system [2]. This lack of appropriate immune response predisposes CD patients for opportunistic infections [3]. The treatment strategy for CD is to prevent the inappropriate immune response; however, this treatment strategy can result in the adverse event that the individual becomes more susceptible to infections. Immunomodulators, such as azathioprine and mercaptopurine, or biological therapy with tumor necrosis factor alpha (TNF-α) antagonists increase the risk of infection in CD patients [4–8].

A frequent pathogen could be *Streptococcus pneumoniae* or pneumococcus, which may cause invasive pneumococcal disease

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(IPD) including pneumonia, septicemia, and meningitis. A retrospective study from the UK reported a significant increase in incidence of IPD in hospitalized patients with immune-mediated diseases, such as CD, compared to other hospitalized patients [9]. Similarly, a recent Danish study has shown that especially CD patients have a higher risk of IPD both prior to and after IBD diagnosis [10].

Currently, two types of pneumococcal vaccines are being used in Denmark: a 23-valent polysaccharide vaccine (PPV23) and a 13-valent conjugated vaccine (PCV13), where the polysaccharides are conjugated to an immunogenic carrier protein [11]. All of the PCV13 serotypes, except 6A are included in PPV23. PPV23 prevents IPD caused by the serotypes included in the vaccine in immunocompetent adults; however, the effectiveness decreases over time, and a protective effect against non-invasive pneumonia has not been demonstrated [12]. However, PPV23 has demonstrated efficacy against all-cause pneumonia in low-income countries [13]. PCV13 prevents IPD caused by the serotypes included in the vaccine, and due to the conjugated protein it also induces immunological memory and therefore potentially prevents non-bacteremic pneumococcal pneumonia [14]. PCV13 is more immunogenic than PPV23 in healthy adults [14,15]. A definitive and consistent advantage of PCV13 has, however, not been demonstrated [16].

Several studies have shown an inadequate response of PPV23 in CD patients, especially when treated with immunosuppressive drugs [17–19]. To our knowledge, no studies of PCV13 in IBD patients have been published.

Here we present the 4-week follow-up results of a randomized trial of specific antibody responses to PCV13 compared to PPV23 in CD patients. Furthermore, the specific antibody response was investigated in patients with and without immunosuppressive treatment.

2. Methods

2.1. Study design

We conducted a multicenter randomized phase-IV vaccine trial including adults diagnosed with CD. Eligible for inclusion were adults (above 18 years of age) diagnosed with CD, non-pregnant, with no previous pneumococcal vaccination, and with medical treatment for CD according to one of the following groups:

i. Immunosuppressive drugs containing azathioprine or mercaptopurine (IS).
ii. IS and TNF-α antagonists (IS + TNF-α).
iii. Not receiving any immunosuppressive drugs (untreated).

Patients must have received IS for at least three months and TNF-α treatment for at least six months before inclusion. Likewise, patients not receiving immunosuppressive drugs must be without IS for at least three months and without TNF-α treatment for at least six months before inclusion.

The CD activity was evaluated at inclusion using the Harvey–Bradshaw Index (HBI) [20].

After having obtained informed consents from study participants, the participants were randomized to receive either PPV23 or PCV13 using a randomized block design. Study participants were recruited at two Danish hospitals, each having its own randomized block. Randomization blocks were generated by using a random number generator.

2.2. Vaccination

Each patient was randomized to receive either PPV23 (Pneumovax, Merck, Whitehouse Station, NJ; containing serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F) or PCV13 (Prevenar13, Pfizer; containing serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, and 23F).

Blood samples were obtained pre-vaccination and 4 weeks post-vaccination.

2.3. Serotype specific antibody measurement

Antibody measurement of specific anti-pneumococcal IgG to serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, all included in both PPV23 and PCV13, was performed using an in-house Luminex-based assay described in detail elsewhere [21,22]. Pneumococcal polysaccharide serum calibrated to FDA 007SP reference serum was used as a reference [23]. Antibody concentrations were expressed as μg/ml. Specific antigens were purchased from LGC Standards (American Type Culture Collection, Virginia, USA) or SSI Diagnostica (Hillerød, Denmark).

Samples from each individual were analyzed simultaneously on the same plate with the same bead batch to minimize analytical variation. Laboratory personnel were blinded to the participants' vaccine status.

2.4. Safety

This study was not designed to evaluate the safety of the vaccines. However, as part of Danish and European legislation, the reporting of serious adverse events (SAE) is mandatory. Adverse events (AE) were registered at the time of vaccination and at the time of the 4-week post-vaccination blood sample.

2.5. Study endpoints

The primary endpoint was to evaluate and compare the serotype specific antibody responses for the two vaccines for 12 common serotypes regardless of medical treatment for CD. The secondary endpoint was to compare the serotype specific antibody responses stratified by medical treatment for CD.

Furthermore, we evaluated the post-vaccination serotype specific antibody concentrations crosswise between vaccines and medical treatment.

2.6. Statistical analysis

All demographic and medical treatment results are expressed as mean ± standard deviations (SD). Differences in continuous variables were tested using the Mann–Whitney test and differences in proportions were tested using χ^2 statistics or the Welch two-sample t-test.

Antibody concentrations are expressed as geometric mean concentrations (GMC). The response is defined as the net increase in the antibody GMC concentration from pre-vaccination to post-vaccination.

For the comparison of vaccine response regardless of treatment and within treatment groups we used a ratio calculated as the GMC difference pre-vaccination to post-vaccination of PPV23 divided by the GMC difference pre-vaccination to post-vaccination of PCV13 (GMC net PPV23/GMC net PCV13). Ninety-five percent confidence intervals (CI) for the ratio were calculated by back transformation of the 95% CI of a t-test between the net difference on a logarithmic scale between PPV23 and PCV13 [24]. Adjustment for multiple testing was done by the Bonferroni method, where the p-value was divided by 12.

Comparison between the treatment groups was done by t-test of the antibody response on a logarithmic scale, with and without Bonferroni correction for multiple testing. Only results from the Bonferroni adjusted analysis are reported here. Results are reported

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