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Review

The effect of immunosuppressive agents on immunogenicity of pneumococcal vaccination: A systematic review and meta-analysis

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ABSTRACT

Introduction: Patients with a weakened immune system due to immunosuppressive treatment are at increased risk of infection with *Streptococcus pneumoniae*. Although pneumococcal vaccination is highly recommended for those patients, the effectiveness of pneumococcal vaccination in this population remains largely unknown. Therefore, the objective of this PROSPERO-registered systematic review and meta-analysis was to evaluate the effect of the most commonly prescribed immunosuppressive agents such as azathioprine, methotrexate, anti-Tumor Necrosis Factor α (TNFα), or rituximab, on the initial serologic response to pneumococcal vaccination in patients with auto-immune disease.

Methods: We included 22 articles comprising 2077 patients, of whom 1623 were treated with immunosuppressive agents, and 454 were controls.

Results and discussion: The findings of our systematic review indicate that, in patients treated with immunosuppressive medication and compared to controls, the initial serologic response to pneumococcal conjugate vaccine (PCV) and pneumococcal polysaccharide vaccine (PPSV) are impaired. Moreover, this impaired response was more profound after PCV than after PPSV. We hypothesize that the immunosuppressive medication mainly compromises the cellular immunity, explaining the more severely reduced response rate to PCV (which induces a T-cell dependent immune response), compared to PPSV. Treatment with TNFα blocking agents was associated with a more favorable response, compared to patients treated with other immunosuppressive medication. Targeted research applying uniform correlates of protection is needed to bridge the knowledge gap in vaccination immunology in this patient group.

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Contents

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1. Introduction

Streptococcus pneumoniae is the most important cause of pneumonia, meningitis and bacterial sepsis worldwide [1]. In case of invasive disease, mortality rates vary from 5 to 35% [2]. Patient groups at increased risk for invasive pneumococcal disease (IPD) are those with an impaired immune response [1,3] (see Table 1).

To prevent IPD in these patients, international guidelines recommend pneumococcal vaccination with a sequential vaccination schedule of 7- or 13-valent pneumococcal conjugated vaccine (PCV), followed by the 23-valent pneumococcal polysaccharide vaccine (PPSV) two months later [4]. The rationale behind this vaccination schedule is that PCV is more immunogenic than PPSV, because of the conjugation to the diphtheria toxoid CRM197. Through this conjugation, a robust T cell-dependent immune response is evoked, through which T helper cells provide help to memory B cells in the generation of a humoral immune response [5,6]. PCV covers 13 (or 7) most prevalent of 96 known pneumococcal serotypes; PPSV provides both coverage of a broader spectrum than PCV, as well as a booster stimulus to serotypes present in both vaccines [7]. However, PPSV provokes a T cell-independent immune response; with minimal T cell-mediated B cell stimulation. Therefore, at least theoretically, long-lasting memory against PPSV serotypes not covered by PCV may be limited [5,6].

In immunocompetent individuals, pneumococcal vaccination reduces the IPD risk [8]. However, clinical efficacy data of the sequential vaccination schedule of PCV followed by PPSV in immunocompromised patients (ICPs) are scarce. Research on this topic is hampered by the fact that vaccine efficacy studies require complex study designs, large cohorts, and long follow-up periods. Instead, vaccine immunogenicity is often used as a proxy to evaluate efficacy. Although research suggests beneficial effects of PPSV in ICPs in terms of post-vaccination immunogenicity, the response in these patients is weaker than in healthy individuals [9]. Thus, precisely those who most need protection because of their increased infection risk, least benefit from vaccination [9].

Immunocompromising conditions consist of different subgroups, depending on underlying immunologic deficits. A major subgroup comprises patients treated with immunosuppressive agents, which are most frequently used to treat autoimmune diseases (AD), and to prevent rejection in solid-organ transplant recipients, or graft-versus-host disease in stem cell transplantation recipients.

In this systematic review, we evaluated the impact of different types of immunosuppressive agents on the initial serologic response to vaccination with PCV and/or PPSV [10]. To reach sufficient homogeneity of the studied group, we focused on the post-vaccination immune response in patients with AD treated with immunosuppressive agents, and did not include transplantation recipients.

In a meta-analysis, we analyzed how different immunosuppressive agents affected seroconversion rates and pre/post-vaccination antibody concentrations.

The aim of this systematic review and meta-analysis was to provide an inclusive insight in the immunogenicity of pneumococcal vaccination in patients with AD treated with immunosuppressive agents, and to provide guidance for health care providers advising on pneumococcal vaccinations in these patients.

2. Methods

We registered the protocol of this systematic review and meta-analysis with the PROSPERO systematic protocol registry (www.crd.york.ac.uk/prospero/; ID: CRD42017058364).

2.1. Search strategy

We conducted a literature search in PubMed and Embase (ovid) on February 5th 2018 (search terms and strategy are listed in Supplementary File 1). The search strategy was not limited to study design, year of publication, or language. We focused our search on studies evaluating the immune response to pneumococcal vaccination in adult patients treated with immunosuppressive agents because of AD.

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.07.039.

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