Influenza vaccination does not result in an increase in relapses in patients with ANCA-associated vasculitis

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Abstract

Background. Vaccination against influenza has been suggested to induce relapses of ANCA-associated vasculitis but evidence is lacking. In this study, we assessed whether vaccination against influenza increases the occurrence of relapses in patients with ANCA-associated vasculitis.

Methods. Two hundred and thirty consecutive patients with ANCA-associated vasculitis from our out-patient clinics of a tertiary referral center, with at least 1 year of follow-up, were included. Retrospectively, the relapse rate per 100 patients at risk in patients who had been vaccinated against influenza within the preceding year and in patients who had not been vaccinated within that time period were calculated.

Results. The relapse rate per 100 patients at risk was lower in patients who had been vaccinated against influenza (3.4) than in patients who had not been vaccinated (6.3), when analyzed for the entire year and for every quarter of the year. Also, the disease-free survival per separate year according to the vaccination status was lower in all 5 years in patients who had been vaccinated, being statistically significant in 2 years.

Conclusion. Vaccination against influenza does not increase the relapse rate in patients with ANCA-associated vasculitis.

Keywords: ANCA-associated vasculitis; influenza; vaccination; relapse; autoimmune disease

Introduction

Although the aetiology of autoimmune diseases is still unknown, it has been suggested that vaccinations may induce these diseases. Many case reports or small series described the development of autoimmune diseases, like antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), following vaccination against influenza ([1,2,5–9], review in [3,4]). Also, relapse of disease following vaccination against influenza has been reported in patients with autoimmune diseases, such as AAV [10]. These reported temporal associations can be explained by theoretical mechanisms such as molecular mimicry and bystander activation [11,12]. However, most reported associations between autoimmunity and vaccination were not confirmed in larger studies [3,13,14].

Despite international guidelines that advise to vaccinate patients with autoimmune diseases, like AAV, against influenza, many physicians are reluctant to do so. Indeed, influenza vaccination may be a two-edged sword in these patients. First, infections are a significant problem, leading to hospitalization in 26–46% and mortality in 3% of patients with AAV [15,16], though the contribution of influenza to these infections is unknown. Second, after influenza infection, increased disease activity has been reported [17,18].

No studies have been reported in patients with AAV exploring the relation between influenza vaccination and disease activity. Therefore, we examined retrospectively the association of influenza vaccination and the occurrence of relapses in a cohort of patients with AAV.

Subjects and methods

We included all consecutive AAV patients from our centre who had a follow-up of at least 1 year between 1999 and 2004. They were classified according to the Chapel Hill Consensus Conference definitions [19] as Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), Churg Strauss syndrome (CSS) or renal limited vasculitis (RLV). Data on demographics and disease characteristics were retrieved from their charts. During 2004, we interviewed these AAV patients about their influenza vaccination history in the period October 1999–December 2003, using a standardized questionnaire. In the case of uncertainties, we contacted the patient’s general practitioner to obtain additional data on the vaccination status. The influenza vaccine used in the Netherlands contains inactivated particles of influenza virus. The vaccine is administered from October to November each year.
Table 1. Patient and disease characteristics of all patients, of patients who were vaccinated at least once, and of patients who were never vaccinated.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n = 230)</th>
<th>Vaccinated at least once (n = 156)</th>
<th>Never vaccinated (n = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) age, y</td>
<td>52 (14–86)</td>
<td>52 (14–86)</td>
<td>45 (14–75)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>46</td>
<td>48</td>
<td>42</td>
</tr>
<tr>
<td>Diagnosis (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WG</td>
<td>75</td>
<td>76</td>
<td>72</td>
</tr>
<tr>
<td>MPA</td>
<td>11</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>CSS</td>
<td>8</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>RLV</td>
<td>7</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>ANCA specificity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR3</td>
<td>68</td>
<td>69</td>
<td>68</td>
</tr>
<tr>
<td>MPO</td>
<td>23</td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td>Atypical</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Negative</td>
<td>7</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Patients diagnosed before start of study (%)</td>
<td>68</td>
<td>70</td>
<td>58</td>
</tr>
<tr>
<td>Median (range) duration of disease before start of study</td>
<td>1.9 (0–29)</td>
<td>2.7 (0–29)</td>
<td>1.1 (0–23)</td>
</tr>
<tr>
<td>Relapses per patient before start of study (mean)</td>
<td>0.7</td>
<td>0.7</td>
<td>0.6</td>
</tr>
</tbody>
</table>

WG: Wegener’s granulomatosis; MPA: microscopic polyangiitis; CSS: Churg-Strauss syndrome; RLV: renal limited vasculitis; PR3: proteinase 3; MPO: myeloperoxidase.

All relapses that occurred between October 1999 and December 2004 were retrieved from the patients’ charts. Relapses were defined as new or increasing disease activity, requiring renewed or intensified immune suppressive therapy [20]. Relapses occurring within 1 year of the vaccination were attributed to that vaccination. During the first 6 months after diagnosis of the disease or a relapse, patients were considered to be not at risk for another relapse because of the use of high-dose immune suppressive medication in that period. We calculated relapse rates per 100 patients at risk per either the whole year or trimester of the year, per vaccination status. As vaccination status was determined for each year of observation, it was possible that a patient was analyzed as vaccinated one year, and not vaccinated the next year.

To check for possible bias by indication, we compared demographic and disease characteristics in patients who were vaccinated against influenza at least once and patients who were not vaccinated. Furthermore, we compared immunosuppressive medication used in the months October–November during 1999–2003, the months in which the decision is made whether the patient should or could be vaccinated.

Statistics

Values are presented as medians with ranges unless stated otherwise. Actuarial relapse-free survival was calculated per vaccination year for patients with and without vaccination using the Kaplan–Meier method. Differences between disease-free survival were tested using the log rank test. Numerical data between groups were compared using the Mann–Whitney U-test. A p-value <0.05 was considered statistically significant.

Results

In total, the vaccination status of 230 AAV patients with at least 1 year of follow-up was obtained. Demographic data and disease characteristics are shown in Table 1. The majority of the patients were diagnosed with WG and had been ANCA positive at diagnosis. During our observation period, 1999–2003, the annual vaccination rate varied from 59 to 62%. Eighty-five percent of the patients, who had been vaccinated during the first year, were also vaccinated in the following years.

During the 5-year study period, 166 relapses occurred, 78 in patients who had been vaccinated within 1 year prior to the relapse, and 88 in patients who had not been vaccinated against influenza. The relapse rate per 100 patients at risk over the period 1999–2004 was lower in patients who had been vaccinated within the previous year (3.4) than in patients who had not been vaccinated against influenza (6.3), both during the entire year and in every trimester (Figure 1). Disease-free survival per separate year for 1999–2003 according to vaccination status is shown in Figure 2. In all years, the disease-free survival was lower in patients not vaccinated, being statistically significant in 2001 and 2002 only.

We found few differences in demographics and disease characteristics between the patients who had been vaccinated once or more during the study period and the patients who had never been vaccinated (Table 1). The patients who were vaccinated were significantly older compared with those who were never vaccinated (median 52 and 45 years, respectively) (p = 0.0006). Furthermore, the duration of
Fig. 2. (A–E) Disease-free survival per year in patients who had been vaccinated and in patients who had not been vaccinated.

disease before start of the study was longer in the vaccinated patients ($p = 0.04$). The dosage of immunosuppressive medication used in the months October and November was slightly lower in the vaccinated group than in the group that was not vaccinated. Thirty-four patients were not vaccinated every year during the study period. In this group with a changing vaccination status, the relapse rate per 100 patients at risk was lower (6.2) in years after a vaccination than in the years in which these patients were not vaccinated (10.1).

Discussion

Whether vaccination against influenza increases disease activity in patients with autoimmune diseases is still controversial. Our retrospective study showed no increase in the occurrence of relapses in patients with AAV after vaccination against influenza. On the contrary, the relapse rate per 100 patients at risk was lower in patients who had been vaccinated within the previous year (3.4) than in patients who had not been vaccinated against influenza (6.3). This finding is consistent with controlled studies in patients with systemic lupus erythematosus (SLE) [14,21,22] and in patients with rheumatoid arthritis [22,23], in whom the occurrence of relapses after vaccination against influenza did not increase. Our finding contrasts case reports and case series, reporting the opposite in patients with vasculitis [10] and other autoimmune diseases [24]. So far, no controlled studies have been performed in AAV patients.

Relapses were attributed to vaccination if they occurred within 1 year after vaccination. This period was chosen to
be certain that every increase of disease activity possibly caused by the vaccination was attributed to the vaccination as disease activity is not always immediately recognized. In a previous case report, relapse of vasculitis occurred within 1 month after influenza vaccination [10]. In SLE patients, rises in levels of auto-antibodies after influenza vaccination normalized within 12 weeks [25]. Changing the period of vaccination-related relapse to 3 months following vaccination in our study, the relapse rate per 100 patients at risk was still lower in those who had been vaccinated (2.3 as compared to 7.2, respectively). Changing the period of vaccination-related relapse to 6 months in the same way, the relapse rate in the vaccinated group would have been 3.4 as compared to 6.2 in the not vaccinated group, which is similar to the relapse rates we found when the period of vaccination-related relapse was 1 year. Furthermore, patients were considered not to be at risk for having another relapse within the first 6 months after the start of treatment for new or relapsing disease activity. This criterion was chosen because we considered it unlikely that the disease relapsed when the patients used high doses of immunosuppressive medication in the first stage of the treatment. Indeed, in our cohort, no relapses occurred within 6 months of another episode of active disease.

Our study has one important limitation: it was performed retrospectively, allowing the possibility of bias by indication. However, by comparing the patients who had been vaccinated with those who were not, we were unable to demonstrate any difference in patient or disease characteristics except for a higher age in patients who were vaccinated. A possible explanation for this finding is the heightened awareness of the risk of influenza and the need for vaccination against it, of both patient and doctor in older patients [26]. Especially, we could not demonstrate a prior low tendency for relapse in the vaccination group. The total number of relapses prior to the start of the study was higher in the patients who were vaccinated, which may suggest even the contrary. However, as the duration of disease before the start of the study was also longer in those who were vaccinated, the mean rate of relapses prior to the study period was not different. Furthermore, we found immunosuppressive medication used between the groups almost identical, which is also not indicative of differences in tendency for relapse between the groups. To indisputably exclude this possible source of bias, a randomized prospective study should be performed.

Apart from the safety of vaccination against influenza, it would be interesting to know whether our results regarding vaccination against influenza can be extrapolated to other types of vaccination, for instance against hepatitis.

In conclusion, in our study we observed no increase of relapses of AAV after vaccination against influenza. Therefore, we consider vaccination against influenza safe in patients with AAV with respect to the occurrence of relapses. Prospective randomized studies are needed to confirm our findings, to evaluate the effect of influenza infections on the occurrence of relapses and to evaluate the protective effect of vaccination against influenza in patients with AAV.

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Conflict of interest. The results presented in this paper have not been published previously in whole or part, except in abstract format.

References


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