Risk factors for pneumocystis pneumonia in giant cell arteritis: a single-centre cohort study

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ABSTRACT

Objective. Pneumocystis jiroveci pneumonia (PCP) is a life-threatening opportunistic infection. Few PCP cases in giant cell arteritis (GCA) have been described, but it remains unknown, which patients need PCP prophylaxis.

Methods. Sixty-two patients with GCA from a prospective cohort were studied to identify treatment-related predictors of PCP infection.

Results. Four PCP infections occurred, all in patients treated with methotrexate in addition to prednisone. Moreover, PCP is associated with higher cumulative PDN doses and severe lymphocytopenia (<400/μl).

Conclusion. Our findings support PCP prophylaxis in GCA patients who are treated with methotrexate and PDN, and need high prednisone doses to achieve remission, or develop severe lymphocytopenia.

Introduction

Giant cell arteritis (GCA) is the most common primary vasculitis (1). Remission is induced by high dose prednisone (PDN) over weeks, followed by low dose PDN maintenance (2). Methotrexate (MTX) is used in some patients with modest steroid sparing effects (2, 3). Owing to immunosuppression, treatment related infections are common and represent an important cause of early mortality (4, 5).

Pneumocystis jiroveci is a fungus causing opportunistic pneumonia (PCP) in immunosuppressed individuals (6). Isolated cases of PCP have been reported in GCA (7, 8), and a retrospective study described seven patients with PCP pneumonia (9). Studies in other autoimmune inflammatory diseases proposed glucocorticoid therapy (10), lymphocytopenia (11), combination therapy with PDN plus additional immunosuppression (8), and pre-existing lung disease (10) as risk factors for PCP. However, the lack of control groups (i.e. same disease but no PCP) complicate interpretation in these studies and does not allow to draw firm conclusions.

Here we report four cases of PCP infection occurring in a prospective single-centre GCA cohort. Within-cohort comparison to patients without PCP infection allowed to test potential associations of PCP infection with treatment modality, intensity of PDN therapy and lymphocyte counts.

Methods

GCA cohort and retrospective data collection on PCP-positive BAL samples

Consecutive patients with newly-diagnosed GCA from our prospective, GCA cohort (Basel Riesenzell-Arteritis Kohorte; BARK) at the University Hospital of Basel, Switzerland, were included. The study was conducted in compliance with the Helsinki Declaration and informed consent was obtained from all participants. Those with less than two months of follow-up data were excluded. Information on PCP infection (pathology report, bronchoalveolar lavage (BAL), CT scan), demographic factors (gender, age), lymphocyte counts, prednisone tapering, combination therapy with MTX, and PCP prophylaxis with Trimethoprim/Sulfamethoxazole were recorded. PCP diagnosis relied on the microbiological detection using immunofluorescence on BAL samples in the setting of lower respiratory tract infection (coughing or dyspnea, signs of systemic inflammation, and/or infiltrates compatible with PCP on CT scan). The lowest lymphocyte count was determined for each individual for four defined treatment periods: (i) The first month, (ii) months 2–3, (iii) months 4–6 and (iv) months 7–12.

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Data analysis and statistics

For each study subject the cumulative prednisone dose curve was determined (Suppl. figure S1) and compared to the mean cumulative PDN dose of the cohort. Mean PDN doses in PCP cases were compared to the mean dose in the non-cases at the respective time-points PCP infection occurred. Group-comparison was performed using non-parametric t-test for two groups. Multiple groups were compared using non-parametric ANOVA (Kruskal-Wallis) followed by Dunn’s correction for multiple comparisons. Correlation analyses were performed using Spearman Rank.

Results

A total of 62 GCA-patients were studied; 39 (63%) on PDN monotherapy and 23 (37%) additionally treated with MTX. The median follow-up was 363 days (range 61–1429 days). Patients on MTX were more than twice as likely to be on PCP prophylaxis compared to those on PDN alone (30% (7/23) vs. 13% (5/39)). In four of the 62 patients (6%) PCP-affected (case no. 1); insulin-dependent type 2 diabetes (case no. 3). None of the affected subjects was on PCP prophylaxis. Intriguingly, all patients (100%) with PCP were additionally treated with methotrexate (MTX) subcutaneously at 15 mg (case no. 1–3) or 20 mg (case no. 4) and a mean time of MTX treatment duration of 7.25 weeks (range 5–8 weeks) (Suppl. figure S2). Of note, the two cases with PCP early (i.e. within 4 months of treatment) in the disease course (case no. 2 and 4) received MTX due to steroid-refractory disease, while for the two others (case no. 1 and no. 3) MTX was started – in addition to increasing PDN – due to relapse (Fig. 1). When for the latter two the time since the relapse – rather than time on PDN overall – was looked at, the mean time between PCP and ‘treatment intensification’ was 1.9 months in the four cases (range 1.2–2.5 months) (Table 1).

MTX treatment is often initiated in GCA patients with relapse or flares after steroid-dose reduction. Therefore, we next tested whether the observed association of MTX with PCP might have been influenced by higher cumulative PDN doses in this group. To this end, we generated individual (Suppl. Figure S1) and group-based (Fig. 1A; Suppl. figure S3) cumulative PDN dose curves. These represent the total PDN burden and reflect both, treatment duration and high mean doses. Cumulative PDN doses in MXT/PDN-treated patients were only slightly higher than in PDN-treated patients (Fig. 1A, not significant at 3, 6 and 12 months). In contrast, in 3 of the 4 PCP cases the individual cumulative PDN dose at the time of opportunistic infection was substantially higher than the average cumulative dose of the rest of the cohort (Fig. 1B–D). Due to the small number of cases this difference did not reach statistical significance (p=0.15). As a high cumulative dose is linked to high mean doses, we also compared the mean PDN dose at PCP infection to the mean PDN of non-cases. Similar to the analysis of cumulative PDN doses, we found in the same 3 of 4 cases a higher mean dose (p=0.37).

Lymphocytopenia, especially CD4 lymphocytopenia, is a major risk factor for PCP in HIV-infection (6). This association is less clear, however, in non-HIV-infected PCP cases (12). Three of our PCP cases (75%) had profound lymphocytopenia (<400/μl) at the time of PCP diagnosis (Table I and Suppl. figure S4), and lymphocyte counts were lower in cases compared to non-cases (p=0.07). Lymphocytopenia was also frequent in non-PCP GCA patients of whom lymphocyte counts were available (25/47 <900/µl), yet only 4/47 (9%) dropped below 400/μl during the first three months of treatment, when lymphocyte counts are generally lowest (Fig. 1f). Lymphocytopenia in the first six months after diagnosis was independent of MTX treatment (Fig. 1g), and showed no correlation with the cumulative PDN dose in the cohort (data not shown). After six months, the median lymphocyte count was slightly lower, but not significantly so, in the MTX group (Fig. 1g).

Discussion

We describe four cases of PCP infection that occurred in patients on immunosuppressive therapy for GCA. In contrast to previous studies, we compared immunosuppressive treatment and lymphocyte counts in PCP-affected patients. Table I. Patient characteristics of GCA-patients with PCP.

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>PDN at PCP diagnosis</th>
<th>Months since PDN escalation (months PDN)</th>
<th>MTX dose/week</th>
<th>On MTX</th>
<th>Lymphocyte count [per μl]</th>
<th>Clinical Presentation</th>
<th>Diagnosis</th>
<th>Days in Hospital</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case no.1 (f, 70y)</td>
<td>30 mg/d</td>
<td>1.2* (11.3)</td>
<td>15 mg</td>
<td>5 weeks</td>
<td>364</td>
<td>Fever, deterioration of general condition</td>
<td>BAL</td>
<td>17</td>
<td>Alive</td>
</tr>
<tr>
<td>Case no.2 (f, 65y)</td>
<td>50 mg/d</td>
<td>1.5 (2.4)</td>
<td>15 mg</td>
<td>8 weeks</td>
<td>235</td>
<td>Coughing, Fever, Fatigue</td>
<td>BAL, CT scan</td>
<td>7</td>
<td>Alive</td>
</tr>
<tr>
<td>Case no.3 (m, 80y)</td>
<td>20 mg/d</td>
<td>2.5* (8.1)</td>
<td>15 mg</td>
<td>8 weeks</td>
<td>338</td>
<td>Coughing, Fever, Respiratory Failure</td>
<td>BAL, CT scan</td>
<td>13</td>
<td>Died (ARDS)</td>
</tr>
<tr>
<td>Case no.4 (f, 58y)</td>
<td>20 mg/d</td>
<td>2.5 (3.7)</td>
<td>20 mg</td>
<td>8 weeks</td>
<td>1748 (CD4 1330)</td>
<td>Dyspnea, Fever</td>
<td>BAL, CT Scan</td>
<td>5</td>
<td>Alive</td>
</tr>
</tbody>
</table>

* patient experienced a relapse.

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patients to GCA patients without PCP. This allowed us to determine risk factors that may identify patients at high risk for PCP.

The most striking observation was that all PCP cases occurred in patients treated with MTX in addition to prednisone (4/23 patients with vs. 0/39 without MTX). Moreover, and in line with previously published cases (7-9), all patients with PCP were on a daily PDN dose ≥20 mg and had a PDN dose escalation in the 2–6 months prior to PCP. In a previous report, two out of seven PCP cases had a history of recent MTX treatment (9). PCP has also been described in patients with rheumatoid arthritis receiving MTX treatment (13). However, in prospective trials on MTX in GCA PCP infection was not reported, although information on PCP prophylaxis was missing (14). Since MTX is often prescribed to patients with relapses, the high incidence of PCP amongst

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**Fig. 1.** PCP is associated with high cumulative PDN doses. (A, upper panel) Individual cumulative PDN dose curves were generated for each subject (Suppl. figure S1) and used to calculate average (geometric mean) cumulative PDN doses [in mg] over time [in days on PDN treatment] in subjects treated with PDN monotherapy (blue) vs. MXT/PDN (red). The grey dotted line indicates the anticipated cumulative PDN curve if PDN can be tapered according to the EULAR guidelines (19). (A, lower panel) Cumulative PDN doses in patients not receiving PCP prophylaxis (PDN n=34; MXT plus PDN n=16) are shown. (B-E) Cumulative PDN dose in the PCP cases (black) compared to the cohort (PDN and MXT/PDN combined, n=62). Geometric mean (grey solid line) and 95%CI of mean (grey dashed line) are depicted. Arrows indicate the time of PCP infection. (F) Lymphocyte counts at baseline (before treatment) and the lowest available lymphocyte counts during specific follow-up periods (nadir) are depicted. Open circles indicate counts from patients treated with PDN monotherapy and black dots those with MXT/PDN. The grey shaded area indicates the normal range for lymphocyte counts in our clinical lab. (G) Summary figure of nadir lymphocyte counts. Median and IQR are indicated. Asterisks indicate significantly lower lymphocyte counts compared to baseline for patients treated with PDN alone (above curve) or MXT/PDN (below curve). Non-parametric ANOVA with Dunn’s correction for multiple comparisons. *p_{corr}<0.05.
patients receiving MTX plus prednisone might – at least in part – relate to increased or prolonged high steroid dose. In fact, our data – in line with published literature on HIV negative patients (10) – suggests that PCP occurs preferentially within the first three months after PDN therapy or its intensification. This suggests high cumulative PDN doses as a PCP risk factor, especially if given over a short interval of time (i.e. high-intensity treatment). Our analysis of the individual cumulative PDN doses strongly supports this hypothesis and although the information on cumulative PDN doses is not available in most of the previously published cases, at least one published patient received very high doses within a short interval (>6000mg within <6 weeks) (7). Since high mean prednisone doses and high cumulative doses are interlinked, we were underpowered to resolve the relative contribution of each of these parameters. Either way, clinicians caring for patients with GCA should thus try to limit the use of high dose PDN to the shortest period of time possible (3). Obviously, this may at times be challenging, especially as recent studies pointed at the importance to completely control vascular inflammation to prevent long-term morbidity (15).

Immune-clearance of pneumocystis depends on functional CD4 T cells (6). Since no lymphocyte immunophenotype was available in our study, we compared total lymphocyte counts during treatment of GCA. Unexpectedly, the frequency of lymphocytopenia in the first six months of treatment was comparable in MTX/PDN – vs. PDN – alone-treated patients. In contrast, severe lymphocytopenia (<400/μl) preceded PCP in 3 of 4 patients, and was found in <10% of GCA patients without PCP. Together with the observations that PCP in GCA is rare in individuals treated with PDN monotherapy, and that PCP usually occurs within 3 months following intensified PDN treatment (Table I, Fig. 1 and (7-9)), this suggests that the combination of MTX and high-intensity prednisone treatment (7) contributes to severe lymphocytopenia and hence susceptibility to PCP.

PCP can be efficiently prevented with Trimethoprim-Sulfamethoxazole (16). In contrast to the HIV-setting, hematological malignancies or transplantation, PCP prophylaxis is much less frequently prescribed in patients treated with immunosuppression for autoimmune diseases (16-18). EULAR guidelines provide no clear recommendation for the use of PCP prophylaxis in GCA (19), and indeed, only 13% of patients on PDN monotherapy and 30% on MTX/PDN treatment in our study received prophylaxis. In contrast, prescription rates in US academic centres reach up to 81% (18). Thus, the higher incidence of PCP in our cohort compared to previous estimates (9) may relate to differences in PCP prophylaxis prescription practice in Europe versus USA.

From a clinical perspective our observations – combined with the published literature in other autoimmune/inflammatory autoimmune diseases (6, 10, 17) – strongly argue for PCP prophylaxis in GCA patients that: at least i) are treated with a combination of MTX/PDN (PDN >20mg/d); ii) need high initial PDN doses over a prolonged period of time to achieve GCA remission; and iii) show profound (<400/μl) lymphocytopenia. The evaluation of larger cohorts will be required to establish definite PCP-prophylaxis guidelines for patients with GCA.

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References