Should Pneumocystis jiroveci prophylaxis be recommended with Rituximab treatment in ANCA-associated vasculitis?

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Abstract

Reports in haematology, transplantation medicine and rheumatology indicate that Rituximab, a B cell depleting therapy, increases the risk for Pneumocystis jiroveci pneumopathy. Patients with ANCA-associated vasculitis have an increased incidence of Pneumocystis jiroveci pneumopathy compared to other autoimmune diseases and Rituximab is often used to induce and maintain remission.

Herein we present a case of a patient with granulomatosis with polyangiitis treated with Rituximab for relapse that developed Pneumocystis jiroveci pneumopathy 3 months after and we review the relevant literature to assess Pneumocystis jiroveci pneumopathy incidence and risks factors under Rituximab. We also discuss whether pneumocystis jiroveci screening before Rituximab and Pneumocystis jiroveci pneumopathy prophylaxis under Rituximab are indicated.

Pneumocystis jiroveci colonization is found in 25% of patients with autoimmune diseases. However the association between colonization and Pneumocystis jiroveci pneumopathy development is not very strong. Pneumocystis jiroveci pneumopathy incidence in ANCA-associated vasculitis patients treated with Rituximab is found to be 1.2%. Therefore evidence and practice do not support the use of Pneumocystis jiroveci pneumopathy chemoprophylaxis in all ANCA-associated vasculitis patients receiving Rituximab. CD4 cell count cut-off does not work well in patients treated with Rituximab as it does not reflect T-cell impairment following B cell depletion.

To help stratify the risk of both colonization and Pneumocystis jiroveci pneumopathy development, assessment of the patient's net stat of immunodeficiency before administering Rituximab – including age, renal or lung involvement, previous infections due to T cell dysfunction, blood tests (lymphocytopenia, low CD4 cell count) and concomitant therapy – is warranted.

Keywords

Pneumocystis jiroveci pneumopathy, Rituximab, ANCA-associated vasculitis, Granulomatosis with polyangiitis, chemoprophylaxis

Introduction

The incidence of Pneumocystis jiroveci pneumonia (PCP) is increased in patients with Granulomatosis with polyangiitis (GPA) and ANCA-associated vasculitis (AAV) compared with other connective tissue diseases (CTD) [1]. PCP usually has an acute onset (fever, dry cough and respiratory failure) and can be life-threatening with a mortality rate exceeding 30% [2,3]. Treatment with methotrexate [4], high-dose prednisolone [4] and cyclophosphamide [5] in association with lymphopenia increases the risk for PCP in GPA patients. While prophylaxis with trimethoprim-sulphamethoxazole (TMP-SMX) is effective [5,6], there are few formal recommendations. The use of PCP prophylaxis is recommended with prolonged daily systemic corticosteroid therapy - ≥20 mg of prednisolone daily for ≥ 1 month [2,7], while EULAR encourages its use during Cyclophosphamide therapy in AAV [8].

Rituximab (RTX) is a B cell depleting drug, that is effective both for remission induction [9,10] and maintenance [11-14] in AAV patients. There are multiple reports of PCP developing in patients treated with RTX for haematological malignancies, solid organ transplantation and autoimmune diseases.

Herein, we present a GPA patient who developed PCP 3 months after RTX treatment for relapse and discuss the literature regarding PCP prophylaxis strategies in AAV patients receiving RTX.

Case report (laboratory values in table 1)

The patient, a man born in 1932, was diagnosed February 1999 with PR3-ANCA positive GPA with kidney, lung, sinus and skin involvement. Disease relapses occurred in July 2001 and April 2011. He was successfully treated with cyclophosphamide (CYC) intravenous pulse at diagnosis and at the first flare for a cumulative dose of 25g. He used methotrexate (MTX) from 1999 to 2001 and mycophenolate mofetil (MMF) from 2002 to 2011 as subsequent remission maintenance therapy with a daily oral dose prednisolone of 5 mg.

The patient had Herpes-zoster infection 8 months after he began with MMF and pneumonia in 2006, which both resolved. Serum CMV-IgM was positive at several occasions between 2004 and 2006 indicating possible CMV reactivation without any signs of infection. April 2011, while on MMF 1500 mg and prednisolone 5 mg daily, the patient relapsed with increased activity in both sinuses and lungs. He was treated with two 1-g infusions of RTX 2 weeks apart (rheumatoid arthritis protocol) in monotherapy in combination with methylprednisolone 125 mg (without any additional IV methylprednisolone infusions). MMF was discontinued and the patient was discharged with a daily oral dose of prednisolone of 40 mg to be gradually tapered.

July 2011, the patient became acutely febrile with night sweats while using prednisolone 15 mg daily without any other symptoms and signs. The patient received blind broad spectrum intravenous antibiotics without any clinical improvement. Absolute white cell count was 8.3×10^9/L with an absolute neutrophile count of 6.8×10^9/L. Erythrocyte sedimentation rate was 45mm after the first hour and CRP was 55 mg/L. Immunophenotyping of lymphocytes showed undetectable B cells, low T cells and CD4 (respectively 0.66×10^9/L and 0.16×10^9/L). Serum total immunoglobulins was 7.5g/L with mild decrease of IgG class (5.6 g/L). PR3-ANCA titters (measured in 2 different laboratories) had increased since RTX treatment from 42 to 147 UI/L. Serology and PCR were negative for CMV and EBV as well as serologies for HCV, HBV, HIV, toxoplasmosis and syphilis. Transthoracal ultrasonography was negative for endocarditis. Chest high resolution computed tomography showed patchy ground-glass opacities dominating in the right upper lobe and bronchoscopy with broncheoalveolar lavage identified Pneumocystis jiroveci both by immunofluorescence and by PCR. The patient recovered from PCP after being treated with a reduced dose of Trimethoprim-sulfamethoxazole (TMP-SMX) 320 mg-1600mg bid for 21 days due to decreased renal function.

January 2013, the patient was in remission for his GPA while treated with prednisolone 5 mg daily. The B cell count (0.02×10^9/L) was low and the CD4/CD8 ratio was still inverted. The patient still received secondary PCP chemoprophylaxis - TMP-SMX 160mg-800mg daily.

Discussion

Pneumocystis jiroveci (PJ) is a low virulence organism and may be the result of a de novo infection (person-to-person transmission) or reactivation from a latent state (primary infection occurs early in life) [15]. Accumulating evidence points towards colonization and de novo infection. PJ colonization has been detected in 16-29 % of patients with a variety of systemic autoimmune diseases [16,17] and Mori et al identified a cluster of de novo PCP infections in RA patients from a single outpatient clinic over a 2-year period [18]. Risk factors for PJ colonization include age over 60, chronic pulmonary disease, smoking, low absolute lymphocytes and CD4 cells count, low serum immunoglobulins levels, use of corticosteroids (both its recent administration and daily dose of prednisolone over 15 mg) and methotrexate [16,17]. Even though none of these risk factors appear specific [16], age was the strongest contributor [17]. In a study by Mekinian et al, none of the patients with a systemic autoimmune disease and PJ colonization disease developed PCP, possibly due to the rapid decrease of the corticosteroid dose [16]. On the other hand in another study, 3 out of 9 RA patients with PJ colonization developed PCP 1 month after PCR identification even though these patients used low corticosteroids and methotrexate doses [19].

In a murine model, B cells play an antibody-independent role in clearance of Pneumocystis carinii f. sp. muris through antigen presentation to CD4 T cells [20]. B cells seem to be required for the generation of CD4 effector cells capable of migrating to the lungs as well as for the expansion and generation of memory CD4 cells [20]. In order to identify the risk of PCP due to RTX, we reviewed the literature in patients with haematological malignancies, solid-organ transplantation and AAV.

In haematological malignancies, a meta-analysis of randomized controlled trials identified patients with acute lymphoblastic leukaemia and allogeneic bone marrow transplant at increased risk for PCP and in need for prophylaxis [6]. Recent clinical observations suggest this association with PCP is related to RTX based treatment regimens [3]. The incidence of PCP is increased in patients receiving biweekly RTX, cyclophosphamide, adriamycin, vincrisitine and prednisolone (R-CHOP-14) therapy compared to standard R-CHOP every 21 days [21], from 2% with standard R-CHOP [22] to 6-11% with R-CHOP-14 [21]. PCP develops usually after four cycles of R-CHOP [21-23] with a point prevalence of PCP increasing with the number of cycles [22]. The median time to PCP onset is respectively 102 days from the first R- CHOP and 19 days from the last R-CHOP [22]. Patients with absolute lymphocyte count < 1.0×10^9/L [21,24], CD4 cell count < 0.2×10^9/L [23] before chemotherapy have a higher risk for PCP, but this association with low CD4 cell counts is not found in other

5

studies [25,26]. PCP chemoprophylaxis recommendations with the use of RTX in haematology are scarce and vary from routine PCP chemoprophylaxis in all patients receiving RTX regimens [23] to only patients receiving dose-dense therapy like R-CHOP-14 [21,25,26] and to not recommending routine chemoprophylaxis given the unclear risk-benefit ratio [22].

In transplantation medicine, renal transplant recipients have an increased risk for PCP in the early post-transplant period justifying the use of prophylaxis in the first 6-12 months after transplantation [6, 27]. However 2 cases of late onset PCP have also been described in where B cells counts at the time of PCP diagnosis were still low - respectively 0.01 and 0.05 x10^9/L –nearly 3 years after the administration of a single dose of RTX (500 mg) for humoral rejection [28].

PCP complicating AAV patients following RTX treatment is not uncommon. At least 6 AAV patients (1.2%) treated with RTX developed PCP among 516 patients from different cohorts [9-14,29-32] and proved fatal in 2 patients. PCP occurred 2, 3 and 32 months after the last RTX infusion in 3 patients including ours [13,29]. Half of the patients have chronic renal disease [13,14]. Half of the patients receive RTX in monotherapy [13,14] while the others receive RTX in combination with other immunosuppressive drugs [29,31].

A retrospective study from a single centre - Mayo Clinic Rochester between 1998 and 2011- identifies 30 patients that developed PCP after RTX treatment: 90% have haematological malignancies and 10% are only treated with RTX [3]. The patients are mostly older male -73% male with a median age of 70 years – and 27% have chronic renal disease [3]. PCP occurs after a median of 4 RTX cycles and a mean of 77 days after its last administration [3]. Patients have low lymphocytes (0.38x10^9/L), CD4 (0.25x10^9/L) and CD8 (0.77x10^9/L) counts at PCP onset with undetectable B cells count [3].

Some experts in AAV have recommended maintaining PCP chemoprophylaxis in patients treated with RTX for at least the duration of B cells depletion [33]. If the PCP incidence in AAV/GPA patients is close to 1%, this recommendation is not supported by the general principles of PCP chemoprophylaxis. Even though PCP chemoprophylaxis is effective and reduced the mortality rate from PCP, the risk for PCP must be over 3.5% to outweigh the side effects of chemoprophylaxis [6]. Others concerns are that neither primary nor secondary PCP chemoprophylaxis is perfect [3] and that bacterial resistance to TMP-SMX can occur [6].

PJ screening from induced sputum before RTX could help identify patients in need of eradication [19] and long-term prophylaxis [16]. However as the association between PJ colonization and PCP development is not very strong, it is still unclear if screening will decrease PCP incidence [16,19].

PCP chemoprophylaxis should not be administered solely when immunosuppressive therapy is intensified or when patients had low cell counts. In GPA patients, PCP chemoprophylaxis is usually administered during escalation of therapy with CYC and prednisolone but there is no solid evidence how long PCP chemoprophylaxis should continue [7]. PCP can even occur after chemoprophylaxis is stopped after CYC discontinuation in patients only taking low daily oral dose of prednisolone [7]. CD4 cell count serves as a useful marker in HIV patients but no CD4 levels cut-off works well in non-HIV immune compromised patients [34]. Long-term corticosteroids use can lower CD4 cell count [34] and the CD4 cell count does not reflect the impairment of T-cell mediated immunity following prolonged B cell depletion by RTX.

In summary, a thorough assessment of the patient's net state of immunodeficiency before administering RTX can help stratify the risk for both colonization and PCP development. Risk factors to be considered are age, renal or lung involvement, previous infections due to T cell-mediated immunity dysfunction, blood tests (lymphocytopenia, low CD4 cell count and inverted ratio) and concomitant therapy.

In the present case, the patient was an older male with GPA with lung and kidney disease that relapsed and was treated with an increased daily oral prednisolone dose and RTX. He had had previous Varicella-zoster infection as well episodes with CMV reactivation, low CD4 cell count and an inverted CD4/CD8 ratio. The patient was thus at increased risk for PJ colonization and PCP. Routine PCP chemoprophylaxis prescribed at RTX initiation and continued at least until B cells recovered might have prevented PCP. In such patients, PCP chemoprophylaxis could possibly be indicated indefinitely.

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Table

Laboratory values at diagnosis, during MMF maintenance, before RTX initiation, at PCP diagnosis and at last visit.

Date/ID	08.1999 CYCIV	02.2003 MMF	05.2010 MMF	04.2011 Relapse before RTX	07.2011 PCP diagnosis	01.2013 Last visit
WCC x10^9/L	2.5	7.0	8.2	5.4	8.3	6.5
Lymphocytes x10^9/L	NR	NR	0.6	1.3	NR	1.4
B cells x10^9/L	NR	NR	NR	0.04	<0.01	0.02
CD4 cells x10^9/L	NR	NR	NR	0.26	0.16	0.36
CD4/CD8 ratio	NR	NR	NR	0.43	NR	0.45
IgG g/L	3.5	5.7	8.3	10.6	5.6	8.3
PR3-ANCA UI/L	NR	11	41•	42•	147*	154†

CD: cluster of differentiation; CYCIV: intravenous cyclophosphamide; ID: immunosuppressive drug; MMF: mycophenolate mofetil; NR: not reported; PCP: Pneumocystis pneumonia; PR3-ANCA: proteinase 3 anti-neutrophil cytoplasmic antibody; RTX: rituximab; WBC: white cell count

* PR3-ANCA was measured in a different hospital.

• PR3-ANCA was measured in our hospital with conventional Elisa (Phadia GmbH): Normal ≤ 10

†PR3-ANCA was measured in our hospital with high-sensitivity Elisa (Phadia GmbH): Normal ≤ 2