Pneumocystis jiroveci pneumonia prophylaxis is a challenge in granulomatosis with polyangiitis patients treated with rituximab.

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Commentary

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Abstract

All strategies to prevent Pneumocystis jiroveci pneumonia (PCP) during rituximab treatment have their rationale in patients with granulomatosis with polyangiitis (GPA) and to some extent in patients with other autoimmune diseases (AID). Risk factors of PCP and severe infections are very similar in GPA patients. The decision of PCP prophylaxis should not be limited at RTX initiation and during RTX treatment, but should be reassessed continuously in all GPA patients.

Since PCP increases the mortality risk in GPA (and AID) patients, the treating physician should always consider PCP as a possible diagnosis in patients treated with RTX - receiving or not PCP prophylaxis.
Pneumocystis jiroveci (PJ) colonisation is increased in patients with autoimmune diseases (AID) (29 %) compared with healthy control (3 %) [1]. However PJ pneumonia (PCP) is uncommon and often fatal in patients with AID [2]. Patients with granulomatosis with polyangiitis (GPA) have an increased risk of PCP compared to other AID [2]. Lymphocytopenia due to the use of immunosuppressive drugs and daily systemic corticosteroid therapy partly explains the increased risk of PCP [3].

There are few formal recommendations on the use of PCP prophylaxis in GPA patients. The European League Against Rheumatism (EULAR) encourages PCP prophylaxis during cyclophosphamide (CYC) therapy in ANCA-associated vasculitis [4] and many experts recommend prophylaxis when patients are treated with prolonged daily oral dose of prednisolone ≥20mg [5]. Nevertheless the use of PCP prophylaxis has also its caveats: side-effects [7], patient’s compliance or physician’s omission [5], antibioresistance [7] and the appropriate timing of its discontinuation [5].

Rituximab (RTX) is a B cell depleting agent used to induce and maintain remission in GPA. At the Mayo Clinic in Rochester USA, patients treated with RTX developed more frequently PCP than HIV positive patients in the last decade [8]. However, very few GPA patients developed PCP while receiving RTX. Since B cells are required to eliminate Pneumocystis from the lungs in a mouse model via the generation of CD4 effector and memory cells [9], many experts have advocated the use of PCP prophylaxis during the course of RTX treatment until B cells recover.

Herein I will discuss possible strategies of PCP prophylaxis in GPA patients treated with RTX.
GPA patients treated with RTX do not need PCP prophylaxis since the risk of PCP during the course of RTX treatment is too low. Only 1.2% of the GPA patients treated with RTX developed PCP [6], far from the 3.5% risk that usually warrants PCP prophylaxis in adults [7]. If the risk is about 1%, the number needed to harm with regard to severe adverse events is much lower than the number needed to treat to prevent PCP when using prophylaxis. RTX seems to have a lower risk of PCP when compared with CYC since at least 3% of GPA patients developed PCP in one observational study [3]. However PCP increases the risk of death in GPA patients.

On the other hand, the risk of PCP-associated death in GPA patients treated with RTX should decrease when receiving prophylaxis. This risk was decreased by 83% in patients with mostly haematological malignancies and with transplantation who received prophylaxis [7]. However, the risk of PCP in patients treated with RTX still exists even if they receive prophylaxis [8]. As a consequence, prophylaxis could delay PCP diagnosis if one assumes complete protection with PCP prophylaxis. When experts advocate using PCP prophylaxis in GPA patients during the course of RTX treatment and until B cell recovers, their message focusing on RTX and B cell depletion may silence other important risk factors of PCP.

Other risk factors of PCP are important when recommending prophylaxis in GPA patients treated with RTX. PCP prophylaxis could be administered to GPA patients during the first 6 to 12 months after RTX initiation, similar to renal transplantation [7]. The risk of PCP seems increased during the active phase of GPA when patients are more immunosuppressed [3]. RTX was also shown to decrease the CD4 cell count during the first 6 months after its administration in RA patients [10].

PCP prophylaxis could be administered in GPA patients treated with RTX with low CD4 cell count (<0.20 x 10⁹/L). This threshold of CD4 cell count works well for HIV positive patients.
and has already been proposed in GPA patients receiving prolonged corticosteroids and especially CYC [5]. However this threshold does not work well in non-HIV patients such as organ transplant patients [5] and AID patients [11] at the time of PCP diagnosis. In a case control study of AID patients suspect for respiratory infection, CD4 cell count was not different between AID patients with PCP and AID patients with other infections (respectively means 0.43 vs 0.42x10⁹/L) [11]. In GPA patients treated with RTX, it is also possible that the CD4 cell count does not reflect the impairment of T-cell mediated immunity during prolonged B cell depletion [6].

B cell depletion, CD4 cell count and disease activity and indirectly CYC and higher daily oral prednisolone dose at RTX initiation should be all taken into account when PCP prophylaxis is started and how long it is maintained. But other possible risk factors of PCP in GPA including age, previous infections related with T-cell dysfunction, lung and kidney involvements, low serum immunoglobulins levels and use of other immunosuppressive drugs should also be considered (Table 1) [6]. Therefore the decision of PCP prophylaxis should be personalised after patients’ stratification according to PJ colonisation and PCP risk factors; in that case, RTX is only an additional risk factor of PCP in GPA patients.

In my opinion, all the different strategies of PCP prophylaxis defined above have their rationale in GPA patients (and to some extend in AID patients) receiving RTX. Risk factors of PCP and severe infections are very similar in GPA patients treated or not with RTX [12]. The decision of PCP prophylaxis should not be limited at RTX initiation and during RTX treatment, but should be reassessed continuously in all GPA patients. Since PCP increases the mortality risk in GPA (or AID) patients, the treating physician should always consider PCP as a possible diagnosis in case of fever of unknown origin, dry cough, acute dyspnoea and respiratory failure in patients treated with RTX - receiving or not PCP.
prophylaxis.
References


Table 1

Possible risk factors of Pneumocystis jiroveci pneumonia (PCP) in granulomatosis with polyangiitis (GPA):

- GPA itself [2]
- Early phase of the disease [3]
- Active phase of the disease [3]
- Age over 60 years [1]
- Lung involvement [3]
- Kidney involvement [3]
- Prior PCP infection [8]
- Infections associated with impairment of T-cell mediated immunity
  - Daily oral prednisolone dose > 15-20 mg over one month or more [5]
  - Cyclophosphamide either intravenously or orally [4]
  - Methotrexate
  - Rituximab [8]
- B cell depletion [8]
- Low CD4 cell count
  - Under $0.2 \times 10^9$ /L? [5]
  - Under $0.3 \times 10^9$ /L? [11]
- Low serum immunoglobulins:
  - IgG <10 g/L? [11]
  - Lower threshold?