Progress in the Research of *Pneumocystis* Pneumonia in Non-Human Immunodeficiency Virus-Infected Non-Hodgkin's B-Cell Lymphoma Treated With R-CHOP

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Increasing numbers of non-human immunodeficiency virus-infected individuals with non-Hodgkin's B cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone have been diagnosed with *Pneumocystis* pneumonia. *Pneumocystis* pneumonia is a serious infection with a high mortality rate and rapid progression. In these patients, the incidence of *Pneumocystis* pneumonia varied from 1.4 % to 13 %, according to a comprehensive literature review. The major clinical symptoms were dry cough, fever, tightness in the chest, progressive dyspnea and hypoxemia. The standard method of diagnosis is *Pneumocystis* detection in broncho alveolar lavage fluid and high-resolution computed tomography can be detected in diffuse interstitial infiltration of both lungs. Trimethoprim/sulfamethoxazole is the main treatment for *Pneumocystis* pneumonia and most studies have shown that preventive use of trimethoprim/sulfamethoxazole can help reduce the incidence of *Pneumocystis* pneumonia. In order to improve the accuracy of diagnosis and the prompt initiation of therapy for treatment and prevention to improve outcomes in these patients, a deeper knowledge of the relationship between rituximab use and the incidence of *Pneumocystis* pneumonia and the characteristics of *Pneumocystis* pneumonia in non-human immunodeficiency virus-infected patients with lymphoma is required.

Key words: *Pneumocystis* pneumonia, non-human immunodeficiency virus-infected, non-Hodgkin's B cell lymphoma, rituximab

Pneumocystis Pneumonia (PCP) is a life-threatening illness caused by *Pneumocystis jirovecii* (*P. jirovecii*) that affects immunocompromised individuals. A monoclonal antibody called rituximab can bind to the B lymphocyte's Clusters of Differentiation (CD) 20 antigen and eliminate B lymphocytes from the bloodstream. Non-Hodgkin's B cell Lymphoma (NHL) is now first line treated with Rituximab plus Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (R-CHOP)[1]. PCP is commonly reported in non-Human Immunodeficiency Virus (HIV) positive lymphoma patients receiving R-CHOP, and it is thought that rituximab is responsible for its incidence in these individuals[2,3]. According to Bienvenu research, PCP's 14 d mortality rate was only 1.4 % in HIV positive individuals, while it could reach 20.6 % in non-HIV-positive people[4]. Additionally, it has been documented that non-HIV patients with PCP require mechanical ventilation earlier and have an increased prevalence of respiratory distress[5]. A deeper understanding of the PCP related features in non-HIV infected patients with NHL treated with R-CHOP is essential for commencing treatment earlier and more precisely and for enhancing predictive value due to the elevated risk of PCP progression and higher mortality in non-HIV infected patients. This article systematically reviewed the incidence, clinical presentation, prevention, treatment and diagnosis of PCP in this population to provide better targeted treatment strategies for PCP. Although T lymphocyte immunodeficiency is typically associated with *P.*

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jiroveci infection, the integrity of B lymphocyte function is also crucial to the immune response against this infection. The studies by Lund confirmed that B lymphocytes are essential for $CD4^+$ T lymphocyte activation[6,7]. Elsegeiny established a mouse model that proved that a single application of rituximab could cause *P. jiroveci* infection in mice and weaken the type II immune response in the lungs, inactivating the role of $CD4^+$ T cells in the protective immune response[8]. These basic studies confirmed that B lymphocyte immunity plays an important role in host defense against *Pneumocystis* and that using rituximab depletes B lymphocytes, forming the theoretical basis for the role of rituximab in increasing the risk of PCP. Increasing reports in the literature indicate that using rituximab increases the risk of PCP. Martin-Garrido retrospectively analyzed 30 cases of PCP infection following rituximab administration in patients at the Mayo Clinic, including 3 patients administered rituximab alone and 27 patients administered rituximab combined with chemotherapy or glucocorticoids[9]. This study found that rituximab alone could cause PCP, although the incidence of PCP was higher when rituximab was combined with other therapies. The exact incidence of PCP after treatment with rituximab-containing chemotherapy in non-HIV infected individuals with NHL is unknown. However, retrospective cohort studies shows that, analyzed data from the last 15 y show a 1.4 %-13 % range[2,3,10-17]. The incidence of PCP increases with higher doses and more intensive chemotherapy regimens. For example, in the Kolstad study, the incidence of PCP was 13 % in the R-CHOPE-14 group, 6 % in the R-CHOP-14 group and 1.4 % in the R-CHOP-21 group. In the study by Hardak *et al.*,[14] the incidence of PCP was 6.6 % in the R-CHOP-14 group and 2.6 % in the R-CHOP-21 group. Part of the study also revealed that PCP mostly appeared during the 4^{th} course of chemotherapy[15,17]. Compared to chemotherapy administered alone, would the inclusion of rituximab increase the probability of PCP? Rituximab chemotherapy served as the experimental group in a retrospective analysis by Wei, while chemotherapy without rituximab served as the control group. The results showed that compared to the control group (n=4, 604, 2.95 % *vs.* 1.32 %, $p<0.001$), the prevalence of PCP was substantially higher in the rituximab group (n=7554) [3]. The prevalence of PCP in lymphoma patients treated with or without rituximab was compared in 11 observational studies by Jiang, who found that drug use was significantly linked to an increased risk of PCP (2.97 % *vs.* 0.52 %; hazard ratio was 3.65; 95 % Confidence Interval (CI): 1.65-8.07; $p=0.001$)[2]. The common signs and symptoms of PCP in non-HIV infected patients with NHL include dry cough, fever, chest tightness, progressive dyspnea and hypoxemia at rest or during exercise. Some patients rapidly progress to respiratory failure, with a high mortality rate of approximately 20 %-30 %[9,18]. Serological examinations revealed increased levels of Beta (β)-D-glucan. Radiographic features typically include diffuse interstitial infiltrations of both lungs, lobular infiltrations, or single or multiple nodules. It is crucial to perform a microbiological investigation screening for *Pneumocystis* to verify the diagnosis of PCP. Since *P. jiroveci* lives and multiplies on the surface of main type I alveolar cells, the highest bacterial load is found in Broncho Alveolar Lavage (BAL) fluid. The European Conference on Infections in Leukemia (ECIL) guidelines, therefore, recommend BAL fluid as the preferred specimen for microbiological detection[19]. *P. jiroveci* cannot be cultured *in vitro*, so it must be stained. Its trophozoites and cysts can be observed by direct fluorescent antibody staining with fluorescein-labeled monoclonal antibodies, the most commonly used technique, but its diagnostic detection rate may be lower[20]. Polymerase Chain Reaction (PCR) methods have higher sensitivity, and the specificity of PCP diagnosis using qualitative PCR (qPCR) analysis has been reported to be between 83 %-100 %[21]. The combination of fluorescence immunostaining and PCR can improve the positive rate of diagnosis. Testing for β-D-glucan in serum is also helpful for diagnosis, but since β-D-glucan is a component of all fungal cell walls, positive results require further differentiation from other fungal infections, while negative results can exclude PCP infection in high-risk patients. Identifying Rituximab induced Interstitial Lung Disease (RILD) is also important for PCP diagnosis. The clinical symptoms and imaging findings of the two are similar. Therefore an important part of identification is the acquisition of PCP pathogenic microbiology, which depends more on BAL fluid detection. However, bronchoscopy is somewhat invasive and not suitable for all patients. It is worthwhile to conduct additional research into developing a scoring system to differentiate PCP from RILD using simple and secure indicators. Park used the duration of symptoms, the presence or absence of Systemic Inflammatory Response

Syndrome (SIRS) and the severity of disease on Computed Tomography (CT) scan as three score indexes; symptoms duration ≤5 d was 1, the presence of SIRS was 1, and the presence of severe disease on CT scan (lesion range >75 %) was 4. For the diagnosis of PCP, a score ≥4 had a specificity of 92 %, and a score of 6 had a specificity of 100 %[17]. Patients with high scores require an immediate bronchoscopic examination and prompt treatment active against *Pneumocystis*, while patients with low scores may not need invasive examinations. Unfortunately, this scoring system has not been scientifically verified, although it does provide some guidance. The Infectious Diseases Society of America (IDSA) and ECIL standards both propose using Sulfamethoxazole/Trimethoprim (SMZ/TMP) first at a dose of 75-100 mg/kg/d (SMZ) and 15-20 mg/kg/d (TMP) for 21 d to treat PCP in non-HIV-infected patients with hematological diseases[22,23]. When PCP is strongly suspected, immediate initiation of therapy should occur concurrently with inspection of the pathogenic microorganisms because delayed treatment increases the need for mechanical ventilation and the mortality rate. The first treatment has not affected the presence of pathogenic microorganisms since *Pneumocystis* can still be detected in bronchial secretions multiple days after the treatment. After 1 w of treatment, the patient should show clinical improvement. If no improvement has been noted at that point, it is considered a treatment failure and second-line treatment should be initiated. The preferred second-line treatment is primaquine combined with clindamycin (primaquine 30 mg/day, clindamycin 600 mg/d 3 times daily). Limited data exist regarding the effectiveness of glucocorticoid assisted treatment of PCP in patients with non-HIV infection. A retrospective study of 30 patients with severe PCP who were not infected with HIV showed that, compared with 14 patients who received a dose equivalent to ≤30 mg/d of prednisone or who were undergoing gradual reductions in glucocorticoid doses, 16 patients who received doses equivalent to ≥60 mg/d of prednisone had significantly shorter durations of mechanical ventilation, Intensive Care Unit (ICU) stays and supplemental oxygen requirements[24]. Although the currently limited data cannot support the routine adjuvant administration of glucocorticoids in non-HIV infected patients with PCP, since these patients tend to present with severe pulmonary inflammation, there is a theoretical basis for the inclusion of glucocorticoid therapy[25]. Some experts suggest using glucocorticoid therapy in non-HIV infected patients with arterial blood gas analyses showing a blood oxygen partial pressure ≤70 mmHg or an alveolar artery oxygen gradient ≥35 mmHg, which signify blood oxygen saturation levels indicative of hypoxemia. Prednisone 40 mg twice daily for 5 d, then prednisone 40 mg once daily for 5 d, and finally prednisone 20 mg once daily for 11 d is one of the recommended glucocorticoid dosage titration[26,27]. In clinical practice, many physicians use empiric therapy against *P. jiroveci* and glucocorticoids to treat patients with lymphoma and diffuse interstitial infiltration of the lungs. While this treatment strategy may have clinical value, it is imprecise. TMP/SMZ therapy is ineffective in nearly 30 % of PCP cases, necessitating second-line salvage therapy. Suppose clinicians fail to distinguish between RILD and PCP. In that case, it is challenging to determine whether PCP rescue therapy is indicated in a given patient, whether to continue chemotherapy with rituximab, or to begin secondary prophylaxis with TMP/SMZ in lymphoma patients requiring further chemotherapy. An accurate diagnosis is, therefore, very important. Hospitalization and ICU occupancy rates are also higher among patients with PCP who are not infected with HIV[28]. Non-HIV-infected patients treated for PCP tend to have worse outcomes than HIV-infected patients; the PCP mortality rate of the latter is 10 %-20 %, while that of the former is 35 %-50 %[28-32]. Patients with cancer and PCP have the highest mortality rate[29]. There has been evidence that the clinical course of PCP in lymphoma patients receiving rituximab can result in a significant mortality rate of up to 33.3 %[33]. Martin-Garrido stated that acute hypoxemic respiratory failure occurred in 88 % of PCP patients who received rituximab treatment, 53 % needed ICU hospitalization and 30 % of people died due to the infection[9]. Do these patients need PCP prophylaxis? For non-HIV-infected patients with NHL treated with rituximab-containing chemotherapy, the need for PCP prevention remains controversial due to the lack of large-scale prospective randomized controlled studies to evaluate the benefits and risks of prevention. However, given the increased morbidity and mortality of PCP, some retrospective studies have demonstrated the value of preventive therapy[2,3,11,14,34-36]. Some of these studies were cohort studies in which TMP/SMZ preventive therapy was compared to no prevention. While no PCP was found in the group that received preventive therapy, PCP did occur in the no prevention group[11,14,35]. One meta-analysis

also demonstrated a positive correlation between PCP risk and prevention in patients treated with rituximab[2]. The study by Wei also revealed a survival benefit for patients administered TMP/SMZ as PCP prevention, with significantly improved 1st y survival in those patients who received preventive therapy compared with patients who received no prevention (73 % *vs.* 38 %)[3]. Many researchers recommend routine prophylaxis against PCP in patients receiving chemotherapy with rituximab[2,3,11-14,16,34-38]. Due to the possibility of TMP/SMZ-related negative drug reactions, some experts are against preventative measures. Nevertheless, unlike the deadly consequences of *Pneumocystis* infection, most negative outcomes correlated with TMP/SMZ are preventable[36]. The IDSA guidelines recommend PCP prevention if the risk of PCP is above 3.5 %[23]. According to this recommendation, PCP preventive therapy should be routinely administered during therapy with R-CHOP-14 and more intensive regimens. ECIL has also used R-CHOP-14 as an indication for preventive therapy. For patients with a history of treatment for PCP, secondary prevention should be administered during subsequent chemotherapy doses. TMP/SMZ is nowadays the drug of preference for PCP prevention. The recommended dosage is a single dose daily (80/400 mg) or a double dose daily (160/800 mg) three times a week. However, there is no definitive recommendation for the duration of prophylactic therapy[39]. As rituximab is widely used in patients with NHL to increase the intensity of chemotherapy, clinicians must pay more attention to the occurrence of PCP through active monitoring for pathogenic bacteria, the timely use of TMP/SMZ and with rational administration of glucocorticoids when necessary. Due to the potential benefits and the low toxicity of preventive therapy, prevention is recommended. More prospective studies of PCP in these patients are necessary to increase the accuracy of the diagnosis, treatment and prevention of this infection and to extend the survival time of these patients further.

Author contributions:

Fengping Zhou conducted a literature search and was primarily responsible for drafting and editing the manuscript. Shenhe Jin conducted the literature evaluation and data collection and Jin Zhang was in charge of manuscript supervision and revision for significant intellectual value. All author provides final permission for the final draft to be submitted and contribute equally to the study's design and conception.

Conflict of interests:

The authors declared no conflict of interests.

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