Pneumonia in Rheumatoid Arthritis Patients

Mohammed Jamal Alofaisan [1], Walaa Ali H Alkhalifah [2], Mohammed Ahmed Yahya Alyamani [3], Ali Hussain A ALDawod [4], Burir Mansour Al Jassas [5], Rana Mohammed M Nourah [6], Afaf Meshal Almjlad [7], Hassan Ali A Al-Mubarak [4], Sulaiman Alaa S Hanbazazah [6], Abdulhameed Ibrahim Alabdulhadi [1], Esra Mohammed Omar Alsayed [8], Bassam Adel Aljabri [9]

1- King Faisal university , 2- Alexandria university , 3- Imam Muhammad ibn Saud University , 4- Imam Abdulrahman bin Faisal university , 5- University of Dammam (Imam Abdurahman Bin Faisal University now), 6- King Abdulaziz University , 7- Northern Border University , 8- Jazan university, 9- Umm Al-qura universiy

ABSTRACT

Purpose: The purpose of this study was to compare the clinical characteristics of pneumocystis pneumonia (PCP) between patients with rheumatoid arthritis (RA) being treated with biologics and those being treated without biologics. **Methods:** From 220 patients with RA in our institution, we enrolled 12 patients who had developed pneumocystis pneumonia throughout the course of their management. They were divided into two groups according to the treatment they were receiving for rheumatoid arthritis: the biologics group (n = 6) and the nonbiologics group (n = 6). Clinical characteristics of pneumocystis pneumonia were compared between the two groups. **Results:** At pneumocystis pneumonia diagnosis, the biologics group showed significantly lower serum levels of β-D-glucan and C-reactive protein than the nonbiologics group, whereas the biologics group had significantly higher lymphocyte counts than the nonbiologics group. In the nonbiologics group, lower lymphocyte counts were associated with higher β-D-glucan levels; nonetheless, this was not witnessed in the biologics group.

Conclusion: The finding that rheumatoid arthritis patients being treated with biologics developed pneumocystis pneumonia with relatively normal lymphocyte counts and lower β-D-glucan levels suggests that the pathophysiology of pneumocystis pneumonia in those patients is different from that in patients being treated with other antirheumatic drugs.

Keywords: rheumatoid arthritis, inflammatory disorder, pneumonia.

INTRODUCTION

Pneumocystis pneumonia (PCP) is a rare but critical complication in immunosuppressed patients [1]. It was primarily revealed in human immunodeficiency virus (HIV) positive patients in the 1980s [2]. In the following years, PCP cases enlarged in patients with rheumatoid arthritis (RA) being treated with disease-modifying antirheumatic drugs (DMARDs), with high mortality rates recorded [3, 4]. More lately, PCP cases have likewise been reported throughout management with biologic agents targeted at precise molecules [5, 6]. Whereas immunosuppressive treatment is recognized as a risk factor for the progress of pneumocystis pneumonia, through lymphocyte count suppression [7], a former study described that pneumocystis pneumonia might develop throughout management with biologic agents in patients with rheumatoid arthritis, without apparent lymphocytopenia [8].

This recommends that distinct mechanisms can be intricate in the development of pneumocystis pneumonia throughout management with biologic agents. Nonetheless, little is known about the differences in the clinical characteristics of pneumocystis pneumonia throughout treatment with biologic agents in comparison with nonbiologic disease-modifying antirheumatic medications. The purpose of the present study was to clarify the differences in the clinical characteristics of pneumocystis pneumonia between patients being treated with biologic agents and patients being treated with nonbiologic disease-modifying antirheumatic medications.

MATERIALS AND METHODS

The study was a retrospective, observational clinical study conducted at our institution with approval by the institutional ethics committee. From a total of 220 consecutive patients with RA who visited our institution between August 2016 and November 2016, all patients who were diagnosed with pneumocystis pneumonia were enrolled in the analysis.

PCP was diagnosed as definite when patients met all the following criteria [9]:

- A- clinical manifestations and findings compatible with PCP on chest computed tomography (CT),
- B- microscopic detection of pneumocystis jirovecii or positive polymerase chain reaction test results

Received: 09/10/2017 DOI: 10.12816/0043078

Accepted: 19/10/2017

for pneumocystis jirovecii DNA in respiratory specimens, C- increased β-D-glucan serum levels. Pneumocystis pneumonia was diagnosed as probable when patients met criterion (a), with either criterion (b) or (c) in addition [9]. The manufacturer recommended that the upper normal limit for serum β-D-glucan was 11.3 pg/mL, but we defined 31.1 pg/mL as a cut-off value in this study to exclude pneumocystis jirovecii colonization, based on a previous study [10].

Demographic characteristics (age, gender, smoking status, and duration from onset of symptoms to PCP diagnosis), comorbidities, related medical conditions, and laboratory findings (white blood cell count, lymphocyte count, lactate dehydrogenase [LDH], C-reactive protein [CRP], immunoglobulin G [IgG], Krebs von den Lungen-6 [KL-6], and β-D-glucan) were retrospectively reviewed. The severity of pneumonia was evaluated with the oxygenation index determined from the arterial oxygen tension and the fraction of inspired oxygen (PaO2/FiO2 ratio).

The study was done according to the ethical board of King Faisal university.

Statistical analysis

Continuous variables were expressed as mean ± standard error. Mann–Whitney U test and Fisher's exact test were used to compare continuous and categorical variables, respectively. The relationships between variables were analyzed by Spearman correlation coefficient. SPSS version 22.0 was used for all statistical analyses, and $P < 0.05$ was considered as significant.

RESULTS

Figure 1 is an outline showing how patients were recruited for this study. Of the 220 patients with rheumatoid arthritis, 112 patients received biologics. Twenty-one patients were suspected to have PCP. Of these 21 patients, 9 patients were excluded from the analysis because they did not satisfy the diagnostic criteria stated above. Consequently, a total of 12 patients were enrolled in this study (definite PCP, n = 8, and probable PCP, n=4) and divided into two groups according to their treatment for rheumatoid arthritis (the biologics group, n = 6 (definite, n=3 and probable, n=3), and the nonbiologics group, n = 6 (definite, n=4 and probable, n=2)).

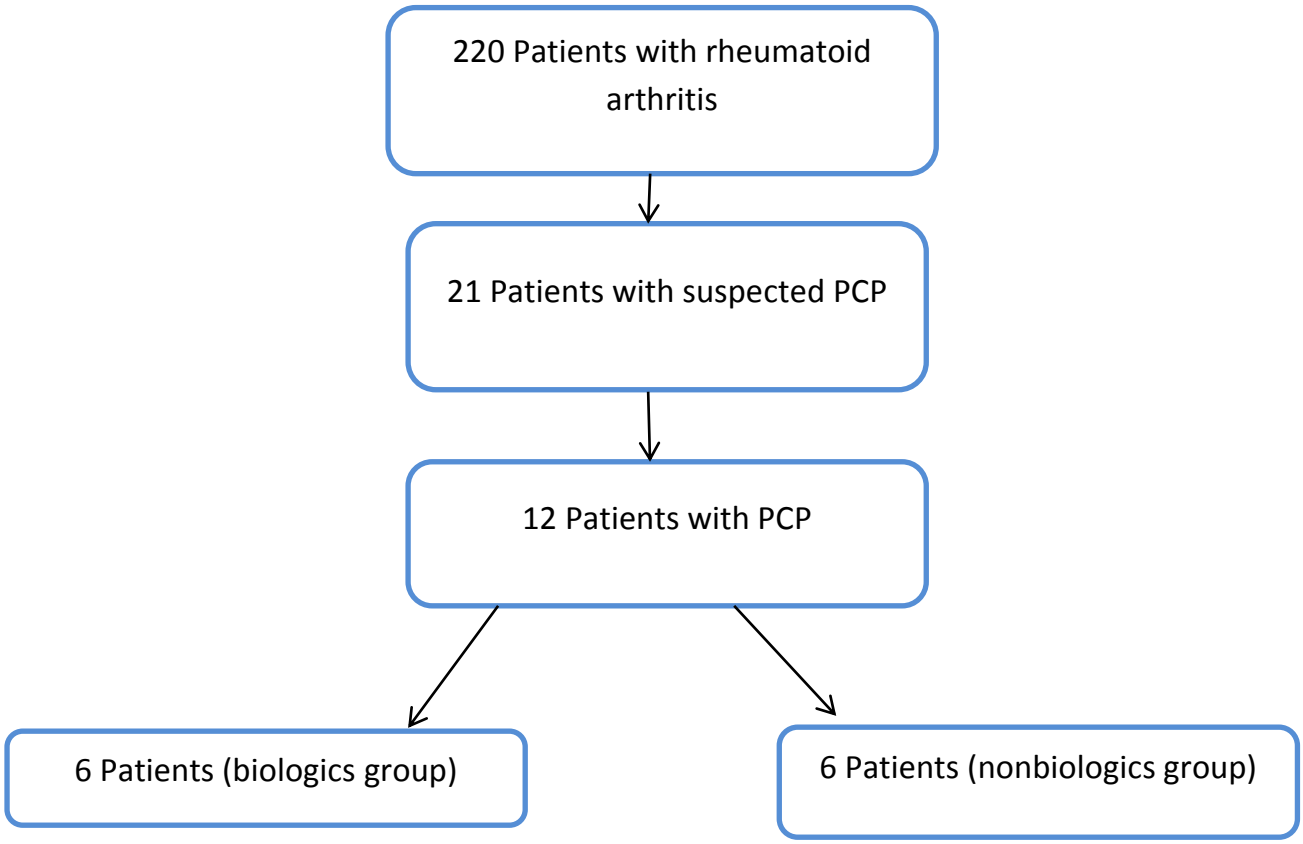

Figure 1: Flowchart of inclusion of patients. PCP, pneumocystis pneumonia.

Baseline demographic characteristics of the patients at the time of their diagnosis of PCP are shown in Table 1. The patients in the nonbiologics group were significantly older than those in the biologics group (71.1 versus 65.1 years, P = 0.039), but no significant differences were found in smoking history (33.3% versus 33.3%, P = 1.00), duration from onset of symptoms to PCP diagnosis (7.5 versus 10.9 days, P = 0.37),

comorbidities, and concomitant immunosuppressive treatments, between the biologics and nonbiologics groups.

Table 1: Comparison of demographic characteristics of RA-PCP at diagnosis

Characteristics	Biologics group N = 12	Nonbiologics group N = 12	Pvalue
Age, years, mean (SEM)	65.1 (2.1)	71.1 (1.6)	0.039
Female, n (%)	5/6 (83.3)	5/6 (83.3)	1
Smoking, n (%)	2/6 (33.3)	2/6 (33.3)	1
Disease duration, days, mean (SEM)	7.5 (1.0)	10.9 (4.1)	0.37
Comorbidity, n (%)			
Renal dysfunction	3/6 (50.0)	3/6 (50.0)	1
Lung disease	2/6 (33.3)	3/6 (50.0)	0.71
Heart failure	1/6 (16.7)	1/6 (16.7)	1
Liver dysfunction	2/6 (33.3)	3/6 (50.0)	0.71
Diabetes mellitus	2/6 (33.3)	2/6 (33.3)	0.68
Concomitant treatment, n (%)			
Glucocorticoid	4/6 (66.6)	5/6 (83.3)	0.41
Dose of glucocorticoid (mg/day), mean (SEM)	5.7 (1.1)	9.1 (2.7)	0.6
Methotrexate	5/6 (83.3)	6/6 (100)	1
Dose of methotrexate (mg/week), mean (SEM)	8.7 (0.7)	9.4 (0.8)	0.89

Whereas the biologics group had significantly lower serum levels of β-D-glucan (101 versus 225 pg/mL, P = 0.037) and CRP (5.12 versus 10.5 mg/dL, P= 0.039) than the nonbiologics group, the biologics group had significantly higher lymphocyte counts than the nonbiologics group (1431 versus 583 cells/μL, P = 0.029), implying that patients on biologics develop pneumocystis pneumonia with almost normal lymphocyte counts accompanied with low β-D-glucan levels. No significant differences were found in total white blood cell counts (5349 versus 7211 cells/μL, P= 0.47), the levels of IgG (1120 versus 901 cells/ μL, P = 0.24), LDH (296 versus 387 U/L, P = 0.11), KL-6 (629 versus 1010 U/mL, P = 0.22), and the PaO2/FiO2 ratio (291 versus 279, P = 0.49).

Table 2: Laboratory findings of RA-PCP at diagnosis

Laboratory findings	Biologics group N = 12	Nonbiologics group N = 12	Pvalue
PaO2/FiO2 ratio, mean (SEM)	291 (32)	279 (24)	0.49
White blood cells (/μL), mean (SEM)	5349 (728)	7211 (1159)	0.47
Lymphocytes (/μL), mean (SEM)	1431 (355)	583 (93)	0.029
Albumin, g/dL, mean (SEM)	3.3 (0.2)	2.7 (0.2)	0.06
CRP, mg/dL, mean (SEM)	5.1 (1.6)	10.5 (1.5)	0.041
IgG, mg/dL, mean (SEM)	1120 (119)	901 (131)	0.24
LDH, U/L, mean (SEM)	296 (23)	387 (37)	0.11
KL-6, U/mL, mean (SEM)	629 (98)	1010 (227)	0.22
β-D glucan, pg/mL, mean (SEM)	101 (28)	225 (49)	0.037
Death, n (%)	1/6 (16.7)	1/6 (16.7)	1

Additionally, we analysed the relationship between the PaO2/FiO2 ratio, which is used to evaluate the severity of pneumonitis, and laboratory findings. In all the patients (n = 12), serum levels of CRP and LDH negatively correlated with the PaO2/FiO2 ratio, while lymphocyte counts and serum albumin levels positively correlated with the PaO2/FiO2 ratio. Nevertheless, when we performed the same analysis separately in the biologics group and in the

nonbiologics group, only the CRP levels negatively correlated with the PaO2/FiO2 ratio in both groups. The significant correlation with the other variables, except for LDH in the nonbiologics group, was no longer detected in either group, suggesting that the CRP level was the most important index for assessing the severity of PCP.

DISCUSSION

In the present study, we discovered that, in patients with rheumatoid arthritis who are being managed with biologic agents, pneumocystis pneumonia developed with almost normal lymphocyte counts and lower β-D-glucan levels, while in those being managed with nonbiologic DMARDs, pneumocystis pneumonia was marked by high β-D-glucan levels with apparent lymphocytopenia. The findings suggest that the pathophysiology of pneumocystis pneumonia in patients being treated with biologic agents is different from that in patients being treated with nonbiologic DMARDs. Moreover, we found that only serum CRP levels, but not β-D-glucan levels, reflected the severity of pneumocystis pneumonia in patients with rheumatoid arthritis.

Supposing that β-D-glucan levels designate the growth of pneumocystis jirovecii and lymphocyte counts represent the degree of concession on the immune system, the differences in the burden of pneumocystis jirovecii and immunosuppression in our study recommend that the mechanism of pneumocystis pneumonia development with the utilization of biologic agents is noticeably dissimilar from that with the use of nonbiologic DMARDs. An earlier study described that alveolar macrophages are crucial in mediating the clearance of pneumocystis jirovecii from the lungs [11], through the production of a large amount of tumour necrosis factor-α (TNF-α) [12].

An experiment on murine models of pneumocystis pneumonia proved that the clearance of Pneumocystis jirovecii infection was reduced when TNF-α was neutralized by TNF-α inhibitors [13]. Consequently, pneumocystis pneumonia development throughout the use of biologic agents, which unswervingly inhibit cytokines such as TNF-α, might be initiated by impaired primary host immune reactions of alveolar macrophages, rather than by lymphocyte suppression. Contrariwise, the pathogenesis of pneumocystis pneumonia during the use of nonbiologic DMARDs can be ascribed to immunosuppression that manifests with lymphocytopenia. In fact, lymphocytes play a vital role in host defense against pneumocystis jirovecii, both in humans and in murine models, with an increased hazard of pneumocystis pneumonia development in patients with evidently reduced lymphocyte counts [14, 15].

Unswerving with these reports, the present study presented that there is a significant correlation between lower lymphocyte counts and the burden of pneumocystis jirovecii, indicated by serum β-D-glucan levels in patients receiving nonbiologic DMARDs.

Respiratory impairment is more strictly related with the extent of lung irritation than with the amount of pneumocystis jirovecii burden in HIV-infected patients, and the same finding was reported in non-HIV-infected patients [16]. Correspondingly, the present study presented that respiratory impairment, represented by the PaO2/FiO2 ratio, was related to the levels of serum CRP, but not to the levels of serum β-D-glucan in both the biologics and the nonbiologics groups. pneumocystis pneumonia severity can be a result of lung inflammation, disturbing gas exchange, and may be unaffected by the quantity of pneumocystis jirovecii.

LIMITATIONS

This is a retrospective, observational study with a small sample size, even though the initial sample of patients with rheumatoid arthritis, with or without pneumocystis pneumonia , was of a large number. Correspondingly, there is a little opportunity that some lost-to-follow-up patients may have developed pneumocystis pneumonia ; nevertheless, we believe they would be very few considering the low occurrence of pneumocystis pneumonia and would not change the outcomes of our study. We believe that the present study is vital for increasing the understanding of this rare, critical complication of pneumocystis pneumonia in patients with rheumatoid arthritis being treated with biologic agents. Further prospective studies in larger cohorts of patients are needed to confirm our results.

CONCLUSION

In patients with rheumatoid arthritis being treated with biologic agents, pneumocystis pneumonia develops with nearly normal lymphocyte counts and low β-D-glucan levels. Rheumatologists should recognize these newly identified characteristics of this is rare but critical complication during treatment with biologic agents to ensure early diagnosis and appropriate treatment.

REFERENCES

1. **Tasaka S and Tokuda H(2012):**Pneumocystis jirovecii pneumonia in non-HIV-infected patients in the era of novel immunosuppressive therapies,"

Journal of Infection and Chemotherapy, 18(6):793–806.

2. **Selik R, Starcher E and Curran J(1987):**Opportunistic diseases reported in AIDS patients: frequencies, associations, and trends. AIDS. 1(3):175–182.
3. **Mori S and Sugimoto M(2012):**Pneumocystis jirovecii infection: an emerging threat to patients with rheumatoid arthritis. Rheumatology, 51(12): 2120–2130.
4. **Kaneko Y, Suwa A, Ikeda Y *et al.* (2006):** Pneumocystis jiroveci pneumonia associated with low-dose methotrexate treatment for rheumatoid arthritis: report of two cases and review of the literature. Modern Rheumatology, 16 (1,): 36–38.
5. **Tanaka M, Sakai R, Koike R and Harigai M(2015):**Pneumocystis jirovecii pneumonia in Japanese patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors: a pooled analysis of 3 agents. Journal of Rheumatology, 42(9):1726–1728.
6. **Bruce E, Kearsley-Fleet L, Watson K *et al.*(2016):**Risk of Pneumocystis jirovecii pneumonia in patients with rheumatoid arthritis treated with inhibitors of tumour necrosis factor α: results from the british society for rheumatology Biologics Register for Rheumatoid Arthritis. Rheumatology, 55(7): 1336-1337.
7. **Walzer P, LaBine M, Redington T *et al.*(1984):**Lymphocyte changes during chronic administration of and withdrawal from corticosteroids: Relation to Pneumocystis carinii pneumonia.Journal of Immunology, 133(5):2502–2508.
8. **Komano Y, Harigai M and Koike R(2009):**Pneumocystis jiroveci pneumonia in patients with rheumatoid arthritis treated with infliximab: a retrospective review and case-control study of 21 patients. Arthritis Rheumatism, 61(3): 305–12.
9. **Kameda H, Tokuda H, Sakai F *et al.*(2011):**Clinical and radiological features of acute-onset diffuse interstitial lung diseases in patients with rheumatoid arthritis receiving treatment with biological agents: importance of pneumocystis pneumonia in japan revealed by a multicenter study.Internal Medicine, 50(4): 305–313.
10. **Tasaka S, Hasegawa N, Kobayashi S *et al.*(2007):**Serum indicators for the diagnosis of pneumocystis pneumonia.Chest, 131(4):1173–1180.
11. **Thomas C and Limper A(2007):**Current insights into the biology and pathogenesis of Pneumocystis pneumonia. Nature Reviews Microbiology,5(4): 298–308.
12. **Neese L, Standing J,Olson E *et al.*(1994):**Vitronectin, fibronectin, and gp120 antibody enhance macrophage release of TNF-α in response to Pneumocystis carinii.Journal of Immunology, 152(9):4549–4556.
13. **Wright T, Pryhuber G, Chess P and *et al.*(2004):**TNF Receptor Signaling Contributes to Chemokine Secretion, Inflammation, and Respiratory Deficits during Pneumocystis Pneumonia. Journal of Immunology, 172(4):2511–2521.
14. **Shellito j, Suzara v, Blumenfeld *W et al.*(1990):**A new model of Pneumocystis carinii infection in mice selectively depleted of helper T lymphocytes.Journal of Clinical Investigation, 85(5):1686–1693.
15. **Phair J,Muñoz A,Detels R *et al.*(1990):**The risk of Pneumocystis carinii pneumonia among men infected with human immunodeficiency virus type 1. Multicenter AIDS Cohort Study Group. New England Journal of Medicine, 322(3):161–165.
16. **Limper A, Offord K,Smith T *et al.*(1989):**Pneumocystis carinii pneumonia. Differences in lung parasite number and inflammation in patients with and without AID. American Review of Respiratory Disease, 140(5):1204–1209.