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Impact of medications for clinical recovery on *Pneumocystis pneumonia* (PCP) Subjects for exploitation of biomedical relevance

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Abstract
Pneumocystis jirovecii pneumonia (PCP) continues to be the most common serious opportunistic infection in HIV-infected patients despite the extensive use of prophylactic measures. PCP is the short form for Pneumocystis pneumonia. It is a lung infection that can be life threatening. It is one of the most common and most serious infections associated with AIDS and arthritis disease. HIV positive people with CD4+ counts below 250 are at risk of developing this type of pneumonia. Empirical therapy is inapropriate because pathogens other than *Pneumocystis jirovecii* are often responsible for pulmonary complications and anti-Pneumocystis therapy may be prolonged and potentially toxic directly and indirectly. Medications that are used to treat PCP drugs like Trimethoprim-sulfamethoxazole (TMP/SMX, Septra or Bactrim) by mouth or by IV (given through a vein) pentamadine by IV, Dapsone (Avlosulfon) and trimethoprim (Proloprim) by mouth, Clindamycin and primaquine by mouth atovaquine (Mepron) by mouth Prednisone may also be used in combination with the above medications in severe cases of PCP .
In present piece of study, the impact of different medicines against *pneumocystis pneumonia* (PCP) in clinical patients has been studies and compared under clinical observation and investigation in 102 subjects.

Keywords: *Pneumocystis pneumonia* (PCP), medication, Clinical investigation

Introduction
Pneumocystis jirovecii pneumonia (PCP) is a life-threatening infection in immunocompromised Subjects**.** Pneumocystis pneumonia is especially seen in people with cancer undergoing chemotherapy, HIV/AIDS, and the applicability of medications that suppress the developed immune system specially. Pneumonia is more leading infectious cause of death in developed countries. Among the vast diversity of respiratory pathogens, fungi accounted for only a small portion of community-acquired and nosocomial pneumonias [1]. However, fungal respiratory infections generate concern in expanding population of immunosuppressed patients. Symptoms of PCP concern fever, dry cough, tiredness and increasing shortness of breath. The cough in PCP is usually dry, especially in non-smokers. However, in smokers there may be sputum (phlegm) that comes with the cough [2]. The symptoms may appear mild at first and gradually get worse over several weeks. If PCP is detected early, it can usually be treated. However, if left untreated, PCP can be life threatening. Pneumocystis pneumonia (PCP) is an emerging infectious disease in immunocompromised hosts such as those with human immunodeficiency virus (HIV) infection, hematological malignancies, solid tumors, organ transplantations, and connective tissue diseases [3]. If you have these symptoms, you should see your doctor right away. Fungi may easily colonize body sites without producing disease or they may be a true pathogen, generating a broad variety of clinical syndromes. Fungal pneumonia is an infectious process in the lungs caused by one or more endemic or opportunistic fungi. Fungal infection occurs following the inhalation of spores, after the inhalation of conidia, or by the reactivation of a latent infection [4]. Hematogenous dissemination frequently occurs, especially in an immunocompromised host. There are different treatments that can be used for PCP. The choice of treatments depends in a person's general health, drug allergies and the seriousness of his or her symptoms [5].
Pneumocystis is thought to be a ubiquitous organism given the universal serologic response seen in humans [6-8].

Historically, it was thought that *Pneumocystis* infection was acquired during childhood and that PCP occurred via reactivation of latent infection when the host's immune system was compromised. It has recently been recognized that *de novo* exposure either from the environment or from individuals with PCP or colonized with *Pneumocystis* may result in transmission [9]. The mechanism of transmission of *Pneumocystis* has important clinical and public health implications. For example, if reactivation of latent infection is the primary cause of PCP, there is little reason to isolate patients with PCP when they are in the hospital as the risk of person-to-person transmission would be low [10,11]. Alternatively, if person-to-person transmission is a key component of the disease process, avoidance of exposure to infected persons, particularly by immunocompromised patients, would be important. Similarly, if particular environmental reservoirs of *Pneumocystis* are detected, at-risk patients should be counselled to avoid those exposures [12, 13].

People who are less sick can be treated at home on oral medications; those with very serious symptoms usually require hospitalization and treatment by intravenous medications. Usually the treatment for PCP needs to be taken for three weeks. It may take a whole week of treatment before a person with PCP starts to feel better. After that, the person should stay on medications to prevent PCP for life. Medications that are used to treat PCP include: Trimethoprim-sulfamethoxazole (TMP/SMX, Septra or Bactrim) by mouth or by IV (given through a vein) pentamadine by IV, Dapsone (Avlosulfon) and trimethoprim (Proloprim) by mouth, Clindamycin and primaquine by mouth atovaquine (Mepron) by mouth Prednisone may also be used in combination with the above medications in severe cases of PCP

In present piece of study impact of different medicines on *pneumocystis pneumonia* in clinical patients has been studies and compared for the purpose of population dominancy criteria.

Materials and Methods

The present study conducted on 102 patients suffered from Rheumatic arthritis (RA) and getting their proper treatment during April to September 2016. The experimental data and clinical finding has been observed and collected firstly from the department of Pathology, Shyam Shah Medical College Rewa (M.P.). The collected clinical data has significantly compared between those subjects who developed PCP and those patients who have not receive trimethoprim-sulfamethoxazole (TMP/SMX) prophylaxis.

The data were collected and evaluated under these following Clinical parameters to identify risk factors for development of PCP, age, duration of RA, disease activity score in 28 joints score and (ESR) Erythrocyte Sedimentation Rate (DAS28 ESR), coexisting pulmonary disease, diabetes mellitus (DM), ratio of patients who received glucocorticoid treatment, dose of glucocorticoid, dose of methotrexate (MTX), serum immunoglobulin G (IgG) and serum KL-6. Before starting biologic therapy, all patients underwent a bidirectional chest X-ray and/or chest computed tomography (CT) to identify coexisting pulmonary disease, including interstitial pneumonia, pleuritis, diffuse pan bronchiolitis, bronchiectasia, old tuberculosis and inflammatory nodules. We excluded the patients who were proven soon after the initiation of biologic agents to have complications due to either malignancy or HIV, which influence risk for PCP development frequently. TMP/SMX prophylaxis was begun when each physician considered a patient to be at relatively high risk for PCP based on following concern factors including age, dose of glucocorticoid, serum IgG level, coexisting pulmonary disease and complications of diabetes. We compared the characteristics of patients in PCP group were significantly compared with those in patients without PCP determined risk factors for PCP development. The sensitivity and specificity of the combination of risk factors were used to plan the primary prophylactic procedure, and that procedure was applied to patients with RA who initiated treatment with biologic agents starting in November 2015.

Results and Discussion

In present study to develop the prophylactic procedure, we evaluated to 102 patients with the rheumatoid arthritis (RA), who were being treated with biologic therapy (40 patients treated with IFX, 29 subjects treated with ETN, 17 were treated with adalimumab (ADA) and only 16 subjects treated with tocilizumab (TCZ). The studies patient population comprised 83 female subjects and 19 males only. It means (81.7%) subjects are female and (18.3%) subjects are male. The mean age of patients, when they received their first biologic agent was 58years having the age range between 14 to 86 years It is well-known that HIV patients with a CD4+ cell counts less than 200 cells/mm3 are likely to develop PCP, and the most common identifiable risk factor for developing PCP in patients with autoimmune disease or malignancy is glucocorticoid use [14-15]. Table 1.

Table 1: Comparison of baseline characteristics of two cohorts

Characteristics	Before treatment	After treatment	*P*-value
Patients No.	102	31	
Females No (%)	83 (82.3%)	19 (81.3%)	0.851
Age (years)	58.0 ± 14.3	58.9 ± 15.5	0.642
RA duration (months)	112 ± 125	92.9 ± 119	0.037
DAS28 score (ESR)	5.83 ± 1.24	5.45 ± 1.27	0.001
Coexisting pulmonary disease (%)	37.7	65.8	0.001
Diabetes mellitus (%)	12.7	9.80	0.268
Glucocorticoids (%)[b]	43.2	22.9	0.001
Methotrexate (%)[c]	43.2	87.9	0.002
Dose of methotrexate (mg/wk)	8.96 ± 2.46	9.51 ± 2.51	0.007
Serum level of IgG (mg/dl)	1590 ± 522	1600 ± 876	0.131
Serum level of KL-6 (U/ml)	271 ± 147	250 ± 194	0.086

The mean observation period was 16.6 months, started from initially 2 weeks to 60 months in last and 21 patients (20.1%) received TMP/SMX prophylaxis. A total no of 38 patients (37.7%) had coexisting pulmonary disease, 44 patients

(43.2%) received glucocorticoid therapy and the mean dose (±SD) of glucocorticoid (converted to the prednisolone (PSL) equivalent) was 4.46mg ± 3.64mg. We included not only active lung disease but also non active lung lesions, including inactive pulmonary fibrosis as coexisting pulmonary disease, which resulted in high ratio of patients with coexisting lung infection. 78.5% of patients were given MTX, treatment and the average dose of MTX were prescribed in patients treated with MTX was 8.96mg/wk.

The mean interval between the first infusion of the biologic agent and the onset of PCP was 7.17 months (range, 2 weeks to 20 months). The mean age of patients with PCP at the start of biologic therapy was 69.5 years when the range taken between 57 to 78 years, and the mean morbidity period of RA for PCP patients was 76.3 months (Table 2). Coexisting pulmonary disease was detected in seven (77.8%) of nine patients. Eight patients (88.9%) who developed PCP were receiving glucocorticoid therapy at a mean dose (±SD) of 8.83mg ± 14.9mg. Six (66.7%) of nine patients were given MTX, and average dose of MTX given to them was 9.83mg/wk.

Table 2: Baseline characteristics of the patients who developed *Pneumocystis pneumonia*.

Patient	Drugs	Age (y)	Sex	RA duration (month)	Treatment duration (months)c	Pulmonary Disease	DM	DAS28 score (ESR)	PSL (mg)	KL-6 (U/ml)
1.	IFX	71	F	72	10	-	-	6.24	2.5	ND
2.	IFX	78	F	79	1	+	-	6.99	1.0	178
3.	IFX	62	M	21	20	+	-	7.40	2.0	893
4.	IFX	78	F	40	1	+	-	8.04	8.0	398
5.	IFX	57	M	5	2	+	-	3.38	0	304
6.	ETN	73	M	2	3	+	-	7.20	50	366
7.	ETN	59	F	252	15	-	-	5.60	1.0	224
8.	ETN	75	M	132	5	+	-	6.75	5.0	624
9.	TCZ	73	M	84	8	+	-	7.00	10	445
Mean		69.5		76.3	7.2	7/9	0/9	6.51	8.83	429

Average in nine patients was 6.56mg/wk. Because TMP/SMX is known to inhibit development of PCP almost completely cured, we excluded from analysis the 21 patients treated with prophylaxis [16-18]. We first analysed the characteristics of these 21 patients who were thought to be at high risk for development of PCP and received prophylaxis [12]. Compared with the other 81 patients, the mean age in their group was significantly older (68.9 years vs. 55.3 years) the serum level of IgG was significantly lower (1,496 mg/dl vs. 1,619 mg/dl) the dose of MTX was significantly lower (6.09mg vs.7.28mg); and ratios of patients treated with glucocorticoids, PCP complicated with coexisting pulmonary disease and PCP complicated with DM were significantly higher 53.9% vs. 40.8%, 72.3% vs. 29.1% and 21.3% vs.10.5%, respectively.

The features of individuals in whom a clinical diagnosis of PCP was made were compared with those who had a confirmed diagnosis, we found that they were very similar. Furthermore, for nearly all those characteristics in which confirmed PCP group differed from non-PCP patients, the presumed PCP group differed as well. This concordance is not unexpected, since it is likely that the presence of typical PCP features contributed to clinical presumptive diagnosis of Pneumocystis infection [19-21]. Other reports and some post marketing surveillance studies have revealed that a low lymphocyte count is not a risk factor for PCP in patients with RA. Thus, we excluded no of lymphocytes as a risk factor from analysis. Post marketing surveillance of IFX revealed the development of PCP in RA patients treated with IFX was best predicted by an age of at least 65 years, dose of glucocorticoids (≥6 mg of PSL) and coexisting pulmonary disease [22-24]. However, that report was restricted to patients treated with IFX and did not include patients receiving other TNFα inhibitors or an IL-6 inhibitor. After analysing the patients treated with biologic therapy who developed PCP in this study, we found that four of nine patients had fewer than two of the above-mentioned risk factors.

The number of peripheral lymphocytes at 2 weeks after initiation of glucocorticoid treatment, not the number at the initiation of treatment, was a risk factor for PCP in patients with rheumatic diseases [25-28]. Next, we were observed the clinical and laboratory records of the 102 patients who did not receive TMP/SMX prophylaxis. If prophylaxis were given only to patients with three risk factors, we would have missed four of nine patients with PCP (sensitivity = 55.6%, specificity = 94.4%). On the basis of these results, we assumed that patients with two or three risk factors could benefit from prophylaxis with TMP/SMX (sensitivity = 77.8%, specificity = 76.1%). Assuming that TMP/SMX inhibits the development of PCP completely, the number needed to treat to prevent one case of PCP was 19.9 in the analysis of 102 patients.

Conclusions

The result and finding suggested that the primary investigation show that there are three major risk factors involved in the development of PCP in patients with RA receiving biologics. They reveal that patients with two or three risk factors could benefit from TMP/SMX prophylaxis against PCP. It means only some factors involved direct healing with TMP/SMK prophylaxis against PCP conditions. We also show the prophylactic effectiveness and safety of inclusion criteria. However, the number of patients was too low, because it is the rare disease so this prophylactic procedure needs to continue to be applied to further investigate its validity and safety.

Pneumocystis pneumonia (PCP) is a major cause of morbidity and mortality among immune compromised persons, and it remains a leading acquired immune deficiency syndrome (AIDS)-defining opportunistic infection in human immune deficiency virus (HIV)-infected individuals throughout the world.

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