Background: The era of biological therapy has revolutionized the management of autoimmune rheumatic diseases. There have been conflicting results about the incidence of infections related to these drugs. The purpose of this study was to compare the spectrum and severity of infection between patients on biological disease-modifying antirheumatic drugs (bDMARDs) versus conventional disease-modifying antirheumatic drugs (cDMARDs).

Materials and Methods: This hospital-based prospective observational study was conducted in a tertiary care hospital, and a total 200 patients were enrolled in this study. Patients on either bDMARDs or cDMARDs for at least six weeks presenting with evidence of infection were included. Patients with known immunodeficiency states, multiple comorbidities, and patients on prednisolone >7.5 mg were excluded. Data was expressed as percentage and mean ± SD. Kolmogorov-Smirnov analysis was performed for checking linearity of the data, and analysis of variance (ANOVA) followed by Tukey’s HSD test were used to test the significance of difference between more than two parameters in parametric data.

Results: Rheumatoid arthritis in 58 patients (29%) were the commonest ones presenting with infections, followed by systemic lupus erythematosus in 37 patients (18.5%). 135 patients (67.5%) were on cDMARDs and 65 patients (32.5%) on bDMARDs. Respiratory tract infection in 47 (34.8%) patients was found to be the commonest infection due to cDMARDs. Incidence of infection was higher with biologics, and types of infection in patients receiving infliximab and etanercept were significantly different from that of cDMARDs. Patients receiving etanercept had higher risk of infections and re-infections, but they were milder compared to cDMARDs. A significantly higher frequency of re-infection was found in patients who had not received vaccination. Conclusion: This study emphasizes that TNF-α inhibitors are significantly associated with higher risk of infections. Patients on etanercept have significantly higher but milder infections as compared to cDMARDs. Vaccination plays a pivotal role in prevention of re-infections.

Keywords: Autoimmune rheumatic diseases, Biologics, cDMARDs, Infections

Address for correspondence: Dr. Krishna Padarabinda Tripathy, Prof. Department of Internal Medicine, Kalinga Institute of Medical Sciences (KIMS), KIIT University, Bhubaneswar, Odisha, India. E-mail: drkptripathy@gmail.com

Received: 28-10-2021
Revised: 14-02-2022
Accepted: 18-02-2022
Published: 22-07-2022

Quick Response Code:
Website: www.jfmpc.com
DOI: 10.4103/jfmpc.jfmpc_2147_21

How to cite this article: Gupta P, Padhan P, Bhargava N, Behera PK, Tripathy KP, Panda SS. Spectrum of infections occurring in patients of autoimmune rheumatic diseases on treatment with biological versus conventional disease-modifying antirheumatic drugs: A comparative study. J Family Med Prim Care 2022;11:3575-83.
arthritides, systemic lupus erythematosus, Sjogren’s syndrome, etc., characterized by joint involvement along with a wide spectrum of systemic manifestations. The common line of treatment for such patients are non-steroidal anti-inflammatory drugs, conventional disease-modifying antirheumatic drugs. Glucocorticoids (GC) and cytotoxic agents (e.g., azathioprine, cyclophosphamide) are proven immunosuppressive agents.\(^1\)

ARDs itself are known to be associated with increased risk of serious infections, which contributes significantly to increased mortality. This increased risk of infection has been attributed to complex interactions of disease-associated immune dysregulation, accompanying comorbidities, and use of immunosuppressive medications.\(^2\) Biological disease-modifying antirheumatic drugs (bDMARDs) have transformed the management of inflammatory arthritis in terms of remarkable inflammation control and, consequently, reduction in mortality and morbidity. However, due to their mechanism of targeting key cytokines and cells of host immune response, concerns about infection risk have been raised and are perceived to cause increased risk of severe infection against conventional disease-modifying antirheumatic drugs (cDMARDs). Several studies have evaluated this issue, and some, but not all, have showed an increased risk of infection with bDMARDs compared to cDMARDs with different risk magnitudes.\(^3,4\)

India being a tropical country, there is a high prevalence of infectious diseases, and individuals are more prone to secondary infections. In this study, we assessed the spectrum and severity of infections in a group of patients with ARDs on bDMARDs and cDMARDs in order to apprise the patients of the risks involved in embarking on such a course of therapy as well as to maintain vigilance for these adverse events.

### Materials and Methods

The aim of our study was to assess the spectrum of infections occurring in patients of autoimmune rheumatic diseases on biological versus conventional disease-modifying antirheumatic drugs, and to assess the severity of infections in these groups.

This was a prospective observational study conducted from September 2018 to May 2020, and a total of 200 patients were enrolled for the study. Patients of ARDs on treatment with cDMARDs or bDMARDs, presenting with symptoms suggestive of infection (serious and non-serious) and getting admitted to the Department of Internal Medicine or Department of Rheumatology, at a tertiary care hospital and were enrolled and evaluated.

### Study protocol

All patients undergoing treatment with cDMARDs or bDMARDs, with or without steroids (low dose of \(\leq 7.5\) mg/day), and receiving treatment for at least six weeks prior to the initiation of the study were enrolled. Patients were stratified into different groups, that is, patients on cDMARDs, and patients on bDMARDs. Each bDMARD was analyzed separately. Patients were followed up at 3 months and 6 months after the infection to know the recurrence, morbidity, and mortality. History of anti-influenza and anti-pneumococcal vaccinations were recorded.

Study protocols were explained to the patients, and proper consent in their regional language was taken before registering them for the study. A detailed history regarding infections was taken from the patients, and general and systemic examinations were done for disease activity and infections; local examination was done to look for skin and superficial infections such as cellulitis, sexually transmitted diseases, fungal infections, etc., Routine investigations were done on every patient and specific investigations like urine culture, blood culture, sputum, and pus cultures, etc., were done according to their system or site involvement. This study was approved by the institutional ethics committee (Approval Number: IEC/133/2018).

### Definitions

Infections were defined according to demonstrated (clinically, or by imaging and/or microbiological analyses) or presumed etiology (bacterial, viral and/or fungal) and site (respiratory, urogenital, gastrointestinal, skin and soft tissue, bone and joints).

Serious infections (SIs) were defined as either when life-threatening, or requiring hospitalization and/or intravenous anti-infective treatment.

Non-serious infections were said when the patient only required a physician visit and/or no use of intravenous anti-infective medications.

Influenza-like-illness (ILI) episodes were identified based on the following clinical parameters: “acute respiratory tract infection and fever \(\geq 38^\circ\)C accompanied by systemic or respiratory symptoms.”\(^5\)

### Inclusion Criteria

All patients between 15 and 60 years of age, diagnosed with inflammatory arthritis, and undergoing treatment with the abovementioned drugs for six weeks or more, visiting OPD, or getting admitted with symptoms suggestive of infections or suspected case of infectious diseases were included in this study.

### Exclusion Criteria

Individuals with diabetes mellitus, chronic congestive heart failure, chronic liver disease, chronic kidney disease, HIV, and underlying malignancy, patients on high-dose steroids (>7.5 mg), post-transplant individuals on immunosuppressive drugs, pregnant and lactating mothers, old cases of tuberculosis, and patients who had a history of infection in the past three months were excluded from the study.

### Statistical analysis

Data was expressed as percentage and mean \(\pm\) SD. Kolmogorov–Smirnov analysis was performed for checking linearity of the
Gupta, et al.: Spectrum of infections occurring in patients of autoimmune rheumatic diseases on treatment with biological versus conventional disease modifying anti-rheumatic drugs—a comparative study

A total of 200 patients were enrolled and evaluated in this study. Out of the 200 patients, 152 were females (76%) and 48 were males (24%). 135 (67.5%) were on cDMARDs, and 65 (32.5%) were receiving bDMARDs out of which, 36 patients (18%) were on TNF-α inhibitors, 23 patients (11.5%) on B-cell depleting agent, that is, rituximab, and 6 patients (3%) were on IL-6 inhibitors. Rheumatoid arthritis patients (58, 29%) were the commonest ones presenting with infections, followed by systemic lupus erythematosus in 37 patients (18.5%). Disease-wise distribution of patients presenting with infection is shown in [Figure 1]. 134 patients (67%) had a treatment duration of 7 months to 5 years, and least number of patients developing infections (9 patients, 4.5%) had a treatment duration of more than 10 years. Descriptive statistics of the study population is shown in Table 1.

In the cDMARDs group, methotrexate in 82 patients (41%) and hydroxychloroquine in 69 (34.5%) were the commonest prescribed cDMARDs, mostly in the combination therapy. Amongst patients receiving bDMARDs, 22 patients (11%) on rituximab and 17 (8.5%) patients on etanercept had infections. Ongoing treatment of the study population is mentioned in Table 2.

Constitutional symptom (fever) was the commonest presenting symptom (159 patients, 79.5%) in the study population, followed by cough (67 patients). Spectrum of infections in patients with inflammatory arthritis on cDMARDs versus bDMARDs is shown in Table 3. Respiratory tract infections (47 patients, 34.8%) was found to be the commonest infection due to cDMARDs, followed by genitourinary tract infection (lower urinary tract infections, pyelonephritis, sexually transmitted diseases) seen in 38 patients (28.1%). Tuberculosis was seen in 6 patients (4.4%) on cDMARDs.

Skin and soft tissue infections (5 patients, 50%) was the commonest in patients on infliximab, followed by respiratory tract infections (3, 30%), and tuberculosis (2, 20%). Respiratory tract infection (6 patients) was commonest amongst patients receiving adalimumab. In patients receiving etanercept, gastrointestinal tract infection (9, 52.9%), that is, infectious diarrhea was the commonest. Tuberculosis was found in 3 patients out of 36 in TNF-α inhibitors, out of which 2 cases of tuberculosis was seen in patients receiving infliximab, and 1 case of tuberculosis was seen in a patient on etanercept.

Respiratory tract (8 patients) and genitourinary tract infections (7 patients) were the commonest in patients on rituximab. Incidence of gastrointestinal infections was reported more on patients receiving secukinumab, and respiratory tract infections was seen in patients on tocilizumab.

### Table 1: Descriptive statistics for study population

| Age (years) | Minimum | Maximum | Mean | SD |
|-------------|---------|---------|------|----|
| Duration of disease | 3 months | 20 years | 3.7151 | 3.57545 |
| Duration of treatment with steroids | 3 months | 20 years | 3.7859 | 4.04879 |
| BMI (kg/m²) | 14.51 | 33.51 | 22.6208 | 2.37627 |

### Table 2: Distribution of patients according to their ongoing treatment

| Class | Drugs | No. of subjects | Percentage |
|-------|-------|-----------------|------------|
| cDMARDs=135 patients (67.5%) | Methotrexate | 82 | 41 |
| | Sulphasalazine | 8 | 4 |
| | Hydroxychloroquine | 69 | 34.5 |
| | Leflunomide | 7 | 3.5 |
| | MMF | 22 | 11 |
| bDMARDs=65 patients (32.5%) | TNF-α inhibitors | | |
| | Infliximab | 10 | 5 |
| | Adalimumab | 6 | 3 |
| | Etanercept | 17 | 8.5 |
| | Golimumab | 3 | 1.5 |
| | B-cell depleting agent | | |
| | Rituximab | 23 | 11.5 |
| | IL-6 inhibitor | 2 | 1 |
| | IL-17 A inhibitor | 4 | 2 |

Figure 1: Type of inflammatory arthritis in patients presenting with infections
Table 4 shows the microbiological analysis of patients with inflammatory arthritis on cDMARDs. In the cDMARDs group [Figure 2], Klebsiella pneumoniae (12 patients) was found to be the commonest organism causing pneumonia. Escherichia coli (20 patients) was the commonest organism to cause genitourinary tract infection. Candida species (6 patients) were the commonest to cause gastrointestinal infections (oral candidiasis infectious diarrhea), and commonest to cause skin and superficial infections in patients on cDMARDs. Tuberculosis was found in 6 patients on cDMARDs.

Table 5 shows spectrum of infections and micro-organism growth on patients receiving bDMARDs. Diarrhea was commonly seen in patients receiving etanercept, in which isospora and cyclospora were seen in the stool sample of four patients. Tuberculosis was seen in one patient on etanercept. Genitourinary tract infection was the commonest in patients on rituximab, mostly caused by Acinetobacter baumannii. Skin and superficial infections were the next common ones caused by tinea and Serratia fonticola species.

In our study, E. coli was the commonest organism causing genitourinary tract infections. Klebsiella pneumoniae followed by Staphylococcus aureus and Acinetobacter baumannii were the commonest organisms causing respiratory tract infections. Gastrointestinal tract infection was commonly caused by Candida species. Significant findings in patients on bDMARDs had isospora- and Cyclospora-positive stools cultures and two patients also had CMV colitis and Clostridium difficile infection.

### Table 3: Spectrum of infections in patients with inflammatory arthritis on treatment with cDMARDs versus bDMARDs

| Drugs          | RTI   | GUT     | GIT     | TB (pulm. and extrapulm) | Skin and soft tissue | Sepsis | Grand Total | P     |
|----------------|-------|---------|---------|---------------------------|----------------------|--------|-------------|-------|
| cDMARDs        | 47    | 38      | 15      | 6                         | 27                   | 2      | 135         |       |
| Infliximab     | 3     | 0       | 0       | 2                         | 5                    | 0      | 10          | 0.028 |
| Adalimumab     | 3     | 1       | 1       | 0                         | 1                    | 0      | 6           | 0.882 |
| Etanercept     | 5     | 1       | 9       | 1                         | 1                    | 0      | 17          | 0.002 |
| Golimumab      | 2     | 0       | 0       | 0                         | 1                    | 0      | 3           | 0.694 |
| Rituximab      | 6     | 9       | 2       | 0                         | 6                    | 0      | 23          | 0.795 |
| S澈atinumab    | 1     | 0       | 2       | 1                         | 0                    | 0      | 4           | 0.062 |
| Tocilizumab    | 2     | 0       | 0       | 0                         | 0                    | 0      | 2           | 0.658 |
| Grand total    | 69    | 49      | 29      | 10                        | 41                   | 2      | 200         |       |

### Table 4: Spectrum of infections and microorganism growth in patients on cDMARDs

| Drugs                      | RTI | GUT       | GIT       | TB (pulm. and extrapulm) | Skin and soft tissue | Sepsis | Grand Total | P     |
|----------------------------|-----|-----------|-----------|--------------------------|----------------------|--------|-------------|-------|
| Acinetobacter baumannii    | 5   | 1         |           |                          |                      |        |             |       |
| Aspergillus fumigatus      |     |           |           |                          |                      |        |             |       |
| Burkholderia cepacia       | 2   |           |           |                          |                      |        |             |       |
| Candida albicans           | 1   | 2         |           |                          |                      | 5      | 8           | 0.002 |
| Candida parapsilosis       | 2   |           |           |                          |                      |        |             |       |
| Candida species            | 3   |           |           |                          |                      |        |             | 0.002 |
| Clostridium difficile      | 1   |           |           |                          |                      |        |             | 0.002 |
| Cyclospora cyst            | 2   |           |           |                          |                      |        |             | 0.002 |
| Cryptosporidium            | 2   |           |           |                          |                      |        |             | 0.002 |
| E. coli                   | 3   | 20        |           |                          |                      |        |             |       |
| E. faecalis                | 3   |           |           |                          |                      | 1      | 4           |       |
| Enterobacter               |     |           |           |                          |                      | 1      |             |       |
| Klebsiella pneumoniae      | 12  | 4         |           |                          | 1                    | 17     |             | 0.002 |
| Mycobacterium tuberculosis | 1   |           |           |                          | 6                    |        |             | 0.002 |
| No growth                 | 12  | 3         |           |                          | 5                    |        |             | 0.002 |
| Pseudomonas aeruginosa     | 1   | 2         |           |                          | 2                    |        |             | 0.002 |
| Salmonella typhi           | 1   |           |           |                          | 1                    |        |             | 0.002 |
| Serratia fonticola         | 1   |           |           |                          | 1                    |        |             | 0.002 |
| Serratia marcescens        | 2   |           |           |                          | 2                    |        |             | 0.002 |
| Staphylococcus aureus      | 6   |           |           |                          | 1                    | 2      | 9           |       |
| Staphylococcus haemolyticus| 1   | 5         |           |                          | 6                    |        |             | 0.002 |
| Streptococcus              |     |           |           |                          | 3                    |        |             | 0.002 |
| Tinea                      | 2   |           |           |                          | 3                    |        |             | 0.002 |
| Tinea corporis             | 2   |           |           |                          | 2                    |        |             | 0.002 |
Gupta, et al.: Spectrum of infections occurring in patients of autoimmune rheumatic diseases on treatment with biological versus conventional disease modifying anti-rheumatic drugs—a comparative study

Skin and superficial infections were caused commonly by candida species and tinea infection. Otomycosis was also seen in four patients, out of which three patients were on bDMARDs. Tuberculosis was seen in 10 patients (6 patients on cDMARDs, 3 patients on TNF-α inhibitors and 1 patient on secukinumab).

Out of 200 patients presenting with infections, 165 patients (82.5%) had severe infections requiring hospitalization and intravenous antibiotics. Patients on TNF-α inhibitors (infliximab, adalimumab, and golimumab, except etanercept) had the longest duration of hospital stay (8.5 days) as compared to other group of drugs. Etanercept was found to have significant association ($P = 0.007$) as compared to other drugs, as 58.82% of the patients on etanercept did not require hospitalization due to milder infections as compared to other bDMARDs and cDMARDs. 3 patients out of 200 died. All three were on cDMARDs. One patient died due to visceral disseminated infection, second patient due to emphysematous pyelonephritis, and the third patient due to...

| Table 5: Spectrum of infections and micro-organism growth in patients on bDMARDs |
|-----------------|---|---|---|---|---|
| Drugs | RS | GUT | GIT | TB (pulm. and extrapulm) | Skin and soft tissue | Grand total |
| Infliximab | 3 | 2 | 5 | 10 |
| Aspergillus fumigatus | | | | |
| E. Faecalis | 1 | | | 1 |
| Klebsiella pneumonia | 1 | | | 2 |
| Mycobacterium tuberculosis | 2 | | | 2 |
| Pseudomonas aeruginosa | | | 1 | 1 |
| Staphylococcus aureus | 1 | | | 1 |
| Staphylococcus haemolyticus | 2 | | | 2 |
| Rituximab | 6 | 9 | 2 | 23 |
| Actinobacter baumannii | 1 | 3 | | 4 |
| Candida albicans | 1 | 1 | | 2 |
| Candida species | 1 | 1 | | 2 |
| E. coli | 1 | | | 1 |
| Klebsiella pneumoniae | 1 | | | 2 |
| No growth | 2 | 1 | | 3 |
| Pseudomonas aerogenosa | 2 | | | 2 |
| Serratia fonticola | | | 1 | 1 |
| Staphylococcus aureus | 2 | | 1 | 3 |
| Streptococcus | 1 | | | 1 |
| Tinea | 2 | | | 2 |
| Adalimumab | 3 | 1 | 1 | 6 |
| Klebsiella pneumoniae | 1 | | | 1 |
| No growth | 1 | 1 | | 2 |
| Pseudomonas aerogenosa | 1 | | | 1 |
| Serratia marcescens | 1 | | | 1 |
| Staphylococcus aureus | | | 1 | 1 |
| Golimumab | 2 | 1 | | 3 |
| No growth | 1 | | | 1 |
| Staphylococcus aureus | 1 | | 1 | 2 |
| Etanercept | 5 | 1 | 9 | 17 |
| Actinobacter baumannii | 1 | | | 2 |
| Candida parapsilosis | 2 | | | 2 |
| Candida species | 2 | | | 2 |
| Cyclospora cyst | 1 | | | 1 |
| E. coli | 1 | | | 1 |
| Isospora and Cyclospora cyst | 3 | | 1 | 3 |
| Mycobacterium tuberculosis | | | 1 | 1 |
| No growth | 3 | 1 | | 4 |
| Staphylococcus aureus | 1 | | | 1 |
| Tocilizumab | 2 | | 1 | 2 |
| Staphylococcus aureus | 2 | | | 2 |
| Secukinumab | 1 | 2 | 1 | 4 |
| Candida parapsilosis | 1 | | | 1 |
| E. coli | 1 | | | 1 |
| Klebsiella pneumoniae | | | 1 | 1 |
| No growth | 1 | | | 1 |
ventilator-acquired pneumonia. Infectious diarrhea, pneumonia, skin and superficial infections, and urinary tract infection were seen more commonly in females whereas Pott's spine was seen more commonly in males.

At follow up after 3 months, no significant difference was noted between rate of re-infection in these groups. At 6 months follow-up, out of 135 patients on cDMARDs, 44 (32%) developed re-infection. Out of 36 patients on TNF-α inhibitors, 21 (58.33%) did not develop re-infection. Among patients receiving etanercept, 41.2% of patients developed recurrent infectious diarrhea at 6 months. Etanercept was found to have significant association ($P = 0.005$) with re-infection at 6 months as compared to other drugs.

Association of vaccination status with infection in 6 months was assessed using Fisher’s exact test. Significant association was detected between two parameters, indicating frequency of infections was higher in subjects who had not received vaccination.

**Discussion**

In our study, infections were most common in rheumatoid arthritis patients followed by SLE. A majority of patients (69%) had disease duration of two to nine years. This finding was consistent with the study by Ozen *et al.*, where they found increased risk of infection with higher disease duration. In our study, majority of patients (134, 67%) had developed infection within 7 months to 5 years of treatment duration, followed by 6 weeks to 6 months of treatment duration, which was consistent with their study in which the incidence rates of serious infections were higher in the first year of the treatment compared with those in the later duration.

In our study, the commonest infection found in patients receiving cDMARDs was respiratory tract infection (pneumonia), followed by genitourinary tract infections and gastrointestinal infections. The majority of patients on rituximab presented with pneumonia and urinary tract infections, and the patients on secukinumab and tocilizumab presented more commonly with infectious diarrhea, and pneumonia, respectively.

The most frequent infection in our study was respiratory tract infection (lower > upper) in patients treated with bDMARDs, which showed some similarity with the data from the clinical trials and registries conducted before. Thus, the risks should be carefully evaluated and the interventions for improving infection control should be followed such as vaccination, avoiding smoking, etc. Patients should be adequately vaccinated when possible and closely monitored for early signs of infection.

In this study, TNF-α inhibitors was associated with significantly ($P = 0.010$) increased risk of overall infections as compared to the other groups. There have been a few studies which contradict these findings, reporting no increased risk; however, our study reported an increased risk of infections with TNF inhibitors.
The common micro-organisms causing pneumonia in cDMARDs were *Klebsiella pneumoniae* and *Acinetobacter baumannii*, while *E. coli* was the commonest organism causing urinary tract infection in these patients. Even after minimization of the bias known to carry higher risk of infections, opportunistic infections such as pulmonary tuberculosis (6 patients), varicella zoster (4 patients), superficial and invasive candida infection (10 patients) were seen in patients receiving cDMARDs. 4 RA patients, 1 MCTD patient and 1 SpA patient had pulmonary tuberculosis. One patient on cDMARDs died due to varicella pneumonia. The hypothesis supporting the occurrence of opportunistic infection in patients on cDMARDs in spite of minimizing the bias is that the patients had prolonged duration of disease, were underweight, and had prolonged intake of low-dose prednisone. 50% of tuberculosis patients who were on cDMARDs had positive family history of tuberculosis. As India is a tropical country and tuberculosis is endemic in this region, it could be the contributory factor in the occurrence of pulmonary tuberculosis. According to the consensus recommendations of the American Thoracic Society and the Centers for Disease Control and Prevention, prednisone use of >15 mg daily for more than 1 month is a risk factor for *Mycobacterium tuberculosis*. However, a case control study by Jick et al. on more than 2.7 million patients reported that there was an associated two-fold risk of tuberculosis in patients who were on physiological dose of prednisone on prolonged use.

Despite proper screening for tuberculosis before initiation of bDMARDs, pulmonary tuberculosis was seen in three patients on TNF-α inhibitors, and one patient of ankylosing spondylitis receiving secukinumab had developed Port’s spine in our study. This finding is consistent with a meta-analysis of various randomized controlled trials showing higher risk of tuberculosis in patients receiving TNF antagonists. Unlike the equivocal association of tuberculosis with TNF antagonists, secukinumab is not found to have increased risk of tuberculosis according to various studies. Incidence of omycosis was also seen in patients on TNF-α inhibitors in our study.

There was incidence of isospora and cyclospora diarrhea in patients of MCTD on cDMARDs and TNF-α inhibitors (etanercept) in our study, presenting as recurrent infectious diarrhea, and all were negative for HIV infection. No other study has previously described the incidence of isosporiasis and cyclosporisis in ARD patients. Thisdeserves further study.

Skin and soft tissue infections were commonly seen in patients on TNF inhibitors (especially infliximab). Isolation of *Staphylococcus* species from 22% patients having serious infection confirmed its virulence. The skin and soft tissue infections due to TNF inhibitors were considered significant, as TNF-α is a crucial cytokine contributing to cutaneous endothelial activation and causing recruitment of inflammatory cells to the skin. It is also important in mobilizing langerhans cells from the epidermis to draining lymph nodes. Contrary to a study by Germano et al., no HBV and HCV re-activation were found in this study.

76% of patients had severe infections and 24% of patients had mild infections in our study. The severity of infections was more in patients on bDMARDs as 49 (75.4%) of the patients on bDMARDs required hospitalization, and the mean duration of hospital stay was more in patients on TNF-α inhibitors. This has also been found in few other studies. However, in our study, out of all the patients on etanercept, 58.8% did not require hospitalization and had milder infections which was statistically significant \(P = 0.007\) when compared to severity of infections with other group of drugs.

The spectrum of infections caused by etanercept was significantly different \(P = 0.002\) than cDMARDs. It had higher risk of infections and re-infections \(P = 0.005\) like other TNF inhibitors, but it was found to cause milder infections as compared to cDMARDs. Previous studies have concluded that serious infections were statistically higher in the MTX group compared with the etanercept-treated patients. In our study, etanercept was found to cause recurrent infectious diarrhea on follow up after 6 months, and there was growth of *Candida* species, and isospora and cyclospora cysts in their stool samples, which has not been reported before and deserves further study.

In a study by Schneeweiss et al., patients who were treated with TNF antagonists were more likely to have received minimum one influenza vaccination, which was found to be significantly protective towards the overall risk of infection in the multivariate analysis. A study by Germano et al. proposed that the protective effect of the vaccination is increased and remains statistically significant after the removal of confounding variables, such as compliance with long term medication, recruitment of patients with mild or moderate disease activity among the vaccinees. Their study also suggests the high statistical significance for skin, bone, or soft tissue infections, which may have specific protective action, and is also supported by recent studies demonstrating that anti-influenza response is induced by a plasmid influenza nucleoprotein DNA vaccine combined with HSV viral protein 22 gene, which may imply a high level of cross-induced anti-influenza protection by HSV antigen. In our study, the incidence of re-infection was significantly higher \(P = 0.02\) on follow up after 6 months in patients treated with cDMARDs who were not vaccinated.

**Strengths of the study:** This study explains briefly the spectrum of infections occurring in both conventional and biological disease-modifying antirheumatic drugs. The detailed analysis of the infections occurring in the above group of drugs contributes as one of the significant research projects, and helps in better decision-making regarding the management of patients with autoimmune rheumatic diseases.

**Limitations of the study:** Being a single center study, sample size was small. Better comparison could have been done regarding incidence of infections between TNF-α inhibitors, B cell depleting agents and IL-inhibitors (IL-6 inhibitor and IL-17 A inhibitor) with larger sample size. Multivariate analysis of risk of infection with individual disease type was not calculated in the
study, which could have shown the association of infection with individual autoimmune rheumatic diseases. Long-term follow-up is required in patients getting treated with bDMARDs.

**Conclusion**

The most frequent infection in our study was respiratory tract infection (lower > upper) in patients treated with cDMARDs and bDMARDs. This study emphasizes that TNF-α inhibitors are significantly associated with higher risk of infections as compared to B cell depleting agents, interleukin inhibitors, and cDMARDs in patients of autoimmune rheumatic diseases. Etanercept, like the other TNF-α inhibitors, has higher but relatively milder risk of infection as compared to other drugs. Vaccination plays a pivotal role in prevention of infections and re-infections.

**Key points**

- DMARDs are the class of drugs indicated for the treatment of autoimmune rheumatic diseases.[2] They are immunosuppressive and immunomodulatory, and classified as conventional and biological DMARDs.
- TNF-α inhibitors are associated with higher risk of infections in the patients of autoimmune rheumatic diseases.
- Since biological DMARDs have been proven as a boon to patients of autoimmune rheumatic diseases due to its high efficacy in decreasing the disease activity, vaccination can help reduce the risk of infections in such patients.
- Almost every patient receiving bDMARDs should be vaccinated before initiation of therapy to prevent occurrence of infections in immunosuppressed individuals.

**List of Abbreviations**

| Abbreviation | Full Form |
|--------------|-----------|
| ADA          | Adalimumab |
| AIRD         | Autoimmune rheumatic diseases |
| AOSD         | Adult-onset Still’s disease |
| AZA          | Azathioprine |
| bDMARDs      | Biological disease-modifying antirheumatic drugs |
| BMI          | Body mass index |
| cDMARDs      | Conventional disease-modifying antirheumatic drugs |
| CMV          | Cytomegalovirus |
| ETA          | Etanercept |
| ERA          | Enthesitis-related arthritis |
| GUT          | Genitourinary tract infection |
| GIT          | Gastrointestinal tract infection |
| HCQs         | Hydroxychloroquine |
| IBD          | Inflammatory bowel disease |
| IL           | Interleukins |
| IFN-γ        | Interferon-γ |
| INF          | Infliximab |
| JAK          | Janus kinase |
| MCTD         | Mixed connective tissue disorder |
| MMF          | Methyprednisolone |
| MTX          | Methotrexate |
| PsA          | Psoriatic arthritis |
| RA           | Rheumatoid arthritis |
| RTX          | Rituximab |
| RTI          | Respiratory tract infection |
| SLE          | Systemic lupus erythematosus |
| SpA          | Axial spondyloarthritis |
| SSc          | Systemic sclerosis |
| SSZ          | Sulfasalazine |
| TB           | Tuberculosis |
| TNF-α        | Tumor necrosis factor-α |
| URTI         | Upper respiratory tract infection |
| UTI          | Urinary tract infection |

**Acknowledgements**

The authors acknowledge the contributions of Dr Amle and Dr Mona Thakur for the statistical analysis of this study. We would also like to thank our patients who were the subjects of this study.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Van Vollenhoven RF, Geborek P, Forslind K, Albertsson K, Ernestam S, Petersson IF, et al. Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial. Lancet 2012;379:1712-20.
2. Tandon VR, Mahajan A, Khajuria V, Kapoor V. Biologics, and challenges ahead for the physician. JIACM 2006;7:334-43.
3. Walters HM, Pan N, Lehman TJ, Adams A, Huang WT, Stirar L et al. A prospective study comparing infection risk and disease activity in children with juvenile idiopathic arthritis treated with and without tumor necrosis factor-alpha inhibitors. Clin Rheumatol 2015;34:457-64.
4. Curtis JR, Yang S, Patkar NM, Chen L, Singh J, Cannon GW, et al. Risk of hospitalized bacterial infections associated with biologic treatment among US veterans with rheumatoid arthritis. Arthritis Care Res 2014;66:990-7.
5. Ozen G, Pedro S, England BR, Mehta B, Wolfe F, Michaud K. Risk of serious infection in patients with rheumatoid arthritis treated with biologic versus nonbiologic disease-
modifying antirheumatic drugs. ACR Open Rheumatol 2019;1:424-32.

6. Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowskï AP, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: Updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology 2011;50:312-31.

7. Richter A, Listing J, Schneider M, Klopsch T, Kapelle A, Kaufmann J, et al. Impact of treatment with biologic DMARDs on the risk of sepsis or mortality after serious infection in patients with rheumatoid arthritis. Ann Rheum Dis 2016;75:1667-73.

8. Quartuccio L, Zabotti A, Del Zotto S, Zanier L, De Vita S, Valent F. Risk of serious infection among patients receiving biologics for chronic inflammatory diseases: Usefulness of administrative data. J Adv Res 2019;15:87-93.

9. Aaltonen KJ, Joensuu JT, Virkki L, Sokka T, Aronen P, Relas H, et al. Rates of serious infections and malignancies among patients with rheumatoid arthritis receiving either tumor necrosis factor inhibitor or rituximab therapy. J Rheumatol 2015;42:372-8.

10. Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 2006;54:2368-76.

11. Schneeweiss S, Setoguchi S, Weinblatt ME, Katz JN, Avorn J, Sax PE, et al. Anti–tumor necrosis factor α therapy and the risk of serious bacterial infections in elderly patients with rheumatoid arthritis. Arthritis Rheum 2007;56:1754-64.

12. American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med 2000;161:S221-47.

13. Jick SS, Lieberman ES, Rahman MU, Choi HK. Glucocorticoid use, other associated factors, and the risk of tuberculosis. Arthritis Rheum 2006;55:19-26.

14. Zhang Z, Fan W, Yang G, Xu Z, Wang J, Cheng Q, et al. Risk of tuberculosis in patients treated with TNF-α antagonists: A systematic review and meta-analysis of randomised controlled trials. BMJ Open 2017;7:e012567.

15. Kammüller M, Tsai TF, Griffiths CE, Kapoor N, Kolattukudy PE, Breees D, et al. Inhibition of IL-17 A by secukinumab shows no evidence of increased Mycobacterium tuberculosis infections. Clin Transl Immunology 2017;6:e152.

16. Germano V, Cattaruzza MS, Osborn J, Tarantino A, Di Rosa R, Salemi S, et al. Infection risk in rheumatoid arthritis and spondyloarthropathy patients under treatment with DMARDs, corticosteroids and TNF-α antagonists. J Transl Med 2014;12:77.

17. Atzeni F, Sarzi-Puttini P, Botsios C, Carletto A, Cipriani P, Favalli EG, et al. Long-term anti-TNF therapy and the risk of serious infections in a cohort of patients with rheumatoid arthritis: Comparison of adalimumab, etanercept and infliximab in the GISEA registry. Autoimmun Rev 2012;12:225-9.

18. Harauoi B, Bykerk V. Etanercept in the treatment of rheumatoid arthritis. Ther Clin Risk Manag 2007;3:99-105.

19. Belostocki K, Leibowitz E, Tai K, Harrison M. Infections associated with etanercept treatment of Rheumatoid Arthritis: 2 years of experience in the “real world”. Arthritis Rheum 2001;44:S173.

20. Saha S, Yoshida S, Ohba K, Matsui K, Matsuda T, Takeshita F, et al. A fused gene of nucleoprotein (NP) and herpes simplex virus genes (VP22) induces highly protective immunity against different subtypes of influenza virus. Virology 2006;354:48-57.

21. Benjamin O, Bansal P, Goyal A, Lappin SL. Disease Modifying Anti-Rheumatic Drugs (DMARD) In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507863. [Updated 2021 Jul 6].