Infectious Complications in Patients Receiving Biologic Agents

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Abstract

Background: Biologic agents are the recommended options for patients with rheumatologic or inflammatory diseases, which did not respond to standard treatments. There have been several studies that demonstrated infectious diseases as one of the most common complications. This present study aimed to explore the incidence of infection related to biologic agents used, and to identify risk factors associated with infectious complications.

Methods: A retrospective chart review of the patients with biologic agent use, anti-tumor necrosis factors (anti-TNF; infliximab, etanercept), interleukin (IL)-6 receptor monoclonal antibody (tocilizumab), and anti-CD20 (rituximab) were included. The study was performed at Siriraj hospital from 2004 to 2014. All patients' demographic data, and characteristics of infection complication were reviewed and analyzed.

Results: A total of 186 patients were enrolled (female 60.8%). Mean age (SD) was 54 (14) years. Patients who were treated with biologic agents included rheumatoid arthritis (44.6%), psoriasis (25.8%), spondyloarthritis (22.6%), inflammatory bowel disease (1.6%), and others (4.8%). Overall infections were 75 events in 57 patients. The highest proportion of patients developing infections were treated with rituximab (28.9 %), followed by etanercept (27.0 %), infliximab (18.4%), and tocilizumab (16.7

%). There were 21 serious infection events, and most of them (19/21) occurred within the first year after drug initiation. TB was diagnosed in 2 infliximab users. The biologic agents infection incidence rate was 13.46/100 patient-year. Incidences of infection as per 100 patient-years in etanercept, infliximab, tocilizumab, and rituximab were 13.78, 12.26, 23.7, and 12.78, respectively. In multivariate analysis, only female gender increased the risk of infection (OR 2.4, 95%CI 1.1-5.6, p = 0.04), after being adjusted for age, conventional disease modifying anti-rheumatic drugs, immunosuppressive agents, glucocorticoid, type of biologic agents, and comorbidities.

Conclusion: Infection in biologic agent users should be monitored, especially in the first year after initiation. Even the infection screening guideline has been recommended from many guidelines, however local screening guideline should be established based on local data such as in this present study's results.

Background

Biologic agents are the substances that inhibit cell functions or cytokines which play an important role in inflammatory diseases. In Thailand, the available agents are anti-tumor necrosis α (anti-TNF) i.e. etanercept and infliximab, interleukin-6 (IL-6) receptor antagonist (tocilizumab), and CD20 monoclonal antibody (anti-CD20) i.e. rituximab.[1] These mentioned agents are used for treatment of rheumatologic diseases; i.e. rheumatoid arthritis, spondyloarthritis, psoriasis, and inflammatory bowel disease, in patients who are not responding well to first line therapy such as conventional disease-modifying antirheumatic drugs (csDMARDs), Non-steroidal anti-inflammatory drugs (NSAIDs), and glucoocrticoid.[2-6] According to the anti-inflammatory activity, these agents alter the immune functions and cause infectious complications. There were several studies that reported infections as an important complication following biologic agents use. The pathogenic organisms that caused these infections were reported and were mostly intracellular pathogens such as *Mycobacterium tuberculosis*, non-tuberculous mycobacteria, and *Nocardia* spp. Infections caused by fungus were also reported, *Histoplasma* spp., and *Pneumocystis jirovecii*. [7] In addition, some chronic infections, for example, hepatitis B virus or herpes zoster virus infection can be reactivated by using anti-TNF.[8] Most of infections occur in the first year after biologic agents use. Therefore, infection screening before prescription of biologic agent is suggested.[8-11] Previous studies demonstrated that the incidence and types of infection, as a complication of these agents used, were different and depended on the type of biologic agents.[12-17] For example, the report of bacterial infection in anti-TNF users was shown about 7-9/100 patient-years[11], incidence of serious infection after IL-6 use, varied from 2.29-9.98/100 patient-years[16], and incidence of severe infection in rituximab users was 5.0/100 patient-years[17]. However, there was no complete data for guiding either infection screening or risk factors associated with infectious complication screening, thus the recommended guideline was not well established.

In Thailand, few patients initially used these biologic agents because of its cost and specific indications. However, the number of patients using these agents was increasing and caused infection and serious complications. This current study was aimed to explore the incidence and epidemiology of infection after biologic agent use. The secondary objective was aimed to explore the risk factors associated with infection.

Methods

This study was a retrospective descriptive study. We searched the patient prescription data from the pharmacy department of Siriraj hospital for biologic agent use from 2004 to 2014. All medical records were reviewed for baseline characteristics, underlying diseases, biologic agent type, sites and pathogens of infectious complications, and concurrent DMARDs or glucoocorticoid used. Biologic agents included in this study were etanercept, rituximab, infliximab, and tocilizumab. The patients whom met the inclusion criteria without a condition in exclusion criteria, were enrolled. The inclusion criteria included adult patients (Age ≥ 15 years) who received biologic agents in Siriraj hospital from 2004 to 2014. The exclusion criteria included patients who were lost to follow up after biologic agent prescription and patients who had infection and/or other significant risk of infection; HIV, neutropenia, hematologic and solid malignancy. Infection was defined as the disorders or diseases which clinically suspicious or definitely caused by organism. Serious infection is the infection from any organism that required intravenous antibiotics or hospitalization. In this study infection in all systems and all severity was recorded after biologic agent administration until 3 months after biologic agent stop (five half-life).[19] From literature review, we calculated from the least infection incidence of the previous report that was performed in Thailand which is of 20.59/100 patient-years.[18] Sample size calculation was 283 which came from estimating the proportion of one group with type 2 error and 25% of incidence = 0.051 and Z-score = 1.96 at 95% confidence interval with equation. This study was approved by Siriraj Institutional Review Board.

Statistical analysis

The chi-square test or Fisher's exact test was used for the qualitative variables. An independent Student-t test was applied to compare the means of the variables with a normal distribution, and the Mann–Whitney U test was used for variables with a non-normal distribution. Multivariate analysis is performed by Logistic regression. A p value of less than 0.05, two-sided, was considered statistically significant. All statistical analyses were conducted with SPSS Statistics for Windows, version 18.0 (SPSS Inc., Chicago, Ill., USA).

Results

A total 186 patients were enrolled with a majority being female patients (113/186, 60.8%). The mean age (± SD) was 53.96 ± 13.94 years. Most indications for biologic agents were rheumatoid arthritis (44.6%). The number of patients that used the biologic agents etanercept, rituximab, infliximab, and tocilizumab were 141, 45, 38, and 6, respectively. The median disease duration before starting biologic agents was 5.67 (0.05, 57.00) years. Fifty-seven patients had infectious complications. All patients' characteristics compared between infection group and non-infection group are demonstrated in Table 1. Infections occurred 75 times in 57 patients. The highest proportion of patients developing infections were treated with rituximab (13/45 patients, 28.9 %), followed by etanercept (38/141 patients, 27.0 %), infliximab (7/38 patients, 18.4%), and tocilizumab (1/6 patients, 16.7 %).

Most of the patients were screened for occult infection before biologic agent prescription. Screening data is shown in Table 2. There were many tests for tuberculosis screening. Most of patients had a chest x-ray. The other test was a tuberculin skin test which was used by 28 patients, and 5 persons had positive results. Of the five, four patients were without a TB history and the other patient was from old TB and lung nodule. Three of them were prescribed isoniazid for latent TB treatment. The latest test for TB screening is interferon gamma release assay for TB and was used in the 5 patients. Two of them had positive results (normal chest X-ray) and were treated as latent TB with isoniazid for 9 months. Infeciton prevention strategies included viral hepatitis B (HBV) vaccination in 12 anti-HBs-negative patients (6.5%), influenza vaccination in 53 patients (28.5%), and anti-HBV prophylaxis was prescribed in 1 patient who had positive HBsAg before rituximab therapy and five patients with positive anti-HBc antibody while anti-HBs antibody was negative before infliximab/rituximab/etanercept therapy to prevent HBV flare. No report of HBV flare or reactivation was noted.

Sites of infection and causative pathogens are demonstrated in table 3 and 4, respectively. Upper respiratory tract infection was the most common infection, follow by bronchitis/pneumonia, skin infection, and UTI. Most organisms of infection were bacteria (64%) with clinical diagnosis (72.9%) more than culture proved. Intracellular pathogen was not increased as expected, only 1 case of *Salmonella* spp. infection in an infliximab user, and no PCP or histoplasmosis infection was found.

There were 21 episodes of severe infections in 17 patients (9.1%) but no serious infection in tocilizumab was reported (table 5). Three patients died, 1 from pneumonia and bowel perforation after 99 days of etanercept use, another patient died from bowel perforation with hospital-acquired

pneumonia after 55 days of infliximab use, and the last patient died from acute coronary syndrome while admitted due to pneumonia at 345 days after etanercept use.

All biologic agent infection incidence rate was 13.46/100 patient-years. Incidences of infection as per 100 patient-years in anti-TNF, etanercept, infliximab, tocilizumab, and rituximab were 13.53, 13.78, 12.26, 23.7, and 12.78, respectively.

We found older age, female sex, bronchiectasis, chronic kidney disease, less biologic agent duration, and more than one biologic agent used, were significantly different between the infection and non-infection groups. Multivariate analysis using logistic regression, in only the female sex showed an increased risk of infection (OR 2.4, 95%CI 1.1-5.6, p = 0.04), after being adjusted by age, concomitant DMARDs/immunosuppressive agents, steroid, type of biologic agents, and comorbidities.

Discussion

According to the purpose of this present study, we demonstrated a lower infection incidence than other studies (13.46 vs 18.35-28.27/100 patient-years).[20,21] The baseline characteristics of our patients were similar to several studies but slightly lower in the number of female patients when compared to another study (60.8% VS 70.8-78.1%).[20] The previous study showed that comorbidities i.e. chronic lung disease (1.6 VS 7-8%) and shorter duration of underlying disease before starting biologic agents (5.67 VS 8-9 years)[20]were associated with increasing the infection rate. However, this present study found lower numbers of comorbidities and this result might explain our infection incidence when compared to the mentioned studies.[20, 21]

Our study had an infection incidence from anti-TNF of 13.53/100 patient-years, from etanercept at 13.78/100 patient-years and from infliximab at 12.26/100 patient-years. However, the results from other studies, anti-TNF users from the German biologic registry (RABBIT) and the Japanese post-marketing study, demonstrated a higher infection incidence of 22.56/100 patient-years in etanercept[20] and 18.35-28.27/100 patient-years in infliximab.[20-21] The higher incidence of infection in the RABBIT study might be confounded by higher steroid use, 85.2-87.4%, while our present study found only 26.9% of steroid use. Sites of infection in our study were similar to other studies. The duration of follow up may not long enough and clinical diagnosis without microbiological proof may not be adequate enough to see this kind of infection. Two cases of TB in infliximab users were diagnosed (5.3%) in our study, which was higher than in Japan (0.3), and could be from higher prevalence of TB in Thailand.

Serious infections in the present study and previous studies were similar, mainly pneumonia and urinary tract infection. We found 3 patients with complicated bowel perforations which should have been related to disease severity (1 with ulcerative colitis, 1 with Crohn's disease, and 1 with rheumatoid arthritis). However, for infliximab, infection incidence in our study was quite similar to another study, 7.06/100 patient-years and 6.15/100 patient-years, respectively.[20] The type of biologic agents used may affect the incidence of infection complication.

The other study in Thailand at Ramathibodi hospital during 2001-2007, demonstrated infectious profiles of anti-tumor necrosis factor use. One hundred anti-TNF users' medical records were reviewed. The infection incidence rate of anti-TNF use was 13.9/100 patient-years (etanercept 12.2/100 patient-years and infliximab 20.1/100 patient-years).[18] This result was similar to our study but the infection incidence of infliximab use was higher while similar to another mentioned study.[20] This may be the result from more subjects in our study. They also reported an incidence of TB infection of 1% which is less than in our study (5.3%). Our study demonstrated, based on more patients included, with more comorbidities such as diabetes mellitus (8.1 VS 3%), and bronchiectasis or chronic lung disease (1.6 VS 1%), while other characteristics were quite similar. A number of patients received infection screening in the present study and were greater than the previous study in Thailand, i.e. chest x-ray of 95.7 VS 39%, and of HBsAg 86 VS 14%, respectively.

The significant factors that seemed to be associated with infection complication were older age (59 VS 53 years, p= 0.02), female sex (77.2% and 53.5%, p=0.003), and biologic agents ever used > 1 agent (38.6% and 22.3%, p= 0.03). It's reasonable that older age should significantly relate to infection because of more comorbidities and organ dysfunctions, including impairment of immune function itself. Females are known for a higher incidence of inflammatory and autoimmune disease, which was a major population receiving biologic agents and influenced the infection complication rate. Biologic agent use of more than one agent could relate with more disease severity and more steroid or other immunosuppressive drugs use, which increase infection risk. No significant infection incidences were found in the comorbidities, which were known as compromised immune function i.e. diabetes mellitus and cirrhosis, while chronic kidney disease (CKD), which was compromised immune function, found significant underlying disease in the infection group and may be the risk factors (7%, p=0.01). However, the small sample size might affect this finding. The dose of prednisolone and dose of biologic agents were not different between groups. The duration of biologic agents in the infection group seemed to be

shorter than in the non-infection group. This might be an effect from the biologic agent termination as well as because of infection. However, multivariate analysis was done and demonstrated only females had increased risk of infection (OR 2.4, 95%CI 1.1-5.6, p = 0.04). Further study should be performed to investigate other risk factors or correlations with the female sex.

This current study had strength because the study was performed in Thailand with a larger sample size and included more types of biologic agents and compared between anti-TNF, IL-6 antagonist, and anti-CD20. The limitations were completeness of data, according to the retrospective study. Further prospective study should be performed. This data will emphasize for doctors to screen the occult of infection before initiating biologic agents, especially in the first year, and close monitoring of infection complication for early recognition of infection and therapy should be established as a clinical practice guideline.

In summary, an increase of infections has been demonstrated in patients with biologic agent use. Most infections occur in the first year of biologic agent initiation, with a median duration of 278 days. Despite the infection screening of occult infection prior to initiation of these agents, close follow up and prevention, such as vaccination, should be considered for implementation. However, the local data of some endemic infection i.e. TB should be of concern and guide physicians' awareness. Further prospective study with larger sample sizes should be performed.

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289 **Table 1 Demographic data**
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Demographic data	Infection (N=57)	Non-infection (N=129)	Total (N=186)	p-value
Age(years), median (min,max)	59 (23,82)	53 (16,90)	55 (16,90)	0.02
Sex (female), %	44 (77.2)	69 (53.5)	113 (60.8)	0.003
Duration of disease before start of biologic agents (years), median (min,max)	7.2 (0.1,35.5)	5.1 (0.1,57)	5.7 (0.1,57)	0.22
Known comorbidities,%	48 (84.2)	92 (71.3)	140 (75.3)	0.06
-Hypertension	28(49.1)	50 (38.8)	78 (41.9)	0.51
-Dyslipidemia	15 (26.3)	33 (25.6)	48 (25.8)	0.67
-Diabetes mellitus	6 (10.5)	9 (6.9)	15 (8.1)	0.58
-Allergic rhinitis	8 (14.0)	6 (4.7)	14 (7.5)	0.05
-Fatty liver	4 (7.0)	8 (6.2)	12 (6.5)	0.99
-Asthma	6 (10.5)	3 (2.3)	9 (4.8)	0.06
-Obesity	3 (5.3)	1 (0.8)	4 (2.2)	0.12
-Cirrhosis	1 (1.8)	3 (2.3)	4 (2.2)	1.00
-Bronchiectasis	3 (5.3)	0 (0)	3 (1.6)	0.04
-Chronic kidney disease	4 (7.0)	0 (0)	4 (2.2)	0.01
-Concurrent DMARDs use, %	51 (96.4)	107 (82.3)	158 (84.9)	0.13
-Concurrent steroid use, %	20 (38.5)	30 (28.0)	50 (26.9)	0.18
-Prednisolone dose (mg/day), median (min, max)	5 (2.5,60)	5 (1.3,10)	5 (1.3,60)	0.10
Biologic agent ever used > 1 agent	22 (38.6)	30 (23.3)	52 (28.0)	0.03
Biologic agent dose, median (min, max) -Etanercept (mg/week)	50 (25,100)	50 (25,100)	50 (25,100)	0.31
-Infliximab (mg/kg/dose)	3.3 (2.8,6.9)	3.4 (1.5,9.3)	3.4 (1.5,9.3)	0.84
-Tocilizumab (mg/week)	80	75 (21.4,80)	77.5	0.67

	(1 case)		(21.4,80)	
-Rituximab (mg/week)	71.4 (27.4,83.3)	62.5 (17.9,87)	62.5 (17.9,87)	0.90
Biologic agent duration (days), median(min,max)	278 (25,2814)	515 (1,3333)	412.5 (1,3333)	0.001 0.01
-Etanercept	301 (25,2814)	529 (18,3333)	422 (18,3333)	
-Infliximab	266 (55,1155)	397 (48,1855)	309 (48,1855)	0.53
-Tocilizumab	317 (1 case)	371 (1,869)	344 (1,869)	1.00
-Rituximab	449 (69,1853)	885 (1,2430)	704 (1,2430)	0.28

Table 2 Infection screening before biologic agent prescription

Screening	Done		Not done, %
	Normal or negative, %	**Abnormal or positive, %**	
Chest x-ray	159 (85.5)	19 (10.2)	8 (4.3)
Sputum AFB	12 (6.5)	0(0)	174 (93.5)
Tuberculin skin test	23 (12.4)	5 (2.7)	158 (84.9)
IFN-ϒ for TB	3 (1.6)	2 (1.1)	181 (97.3)
HBsAg	157 (84.4)	3 (1.6)	26 (14)
Anti-HBs antibody	56 (30.1)	52 (28)	78 (41.9)
Anti-HBc antibody	64 (34.4)	50 (26.9)	72 (38.7)
Anti-HCV antibody	150 (80.6)	4 (2.2)	32 (17.2)
Anti-HIV antibody	86 (46.2)	0 (0)	100 (53.8)

295 **Table 3 Sites of infection**

Sites of infection	Etanercept	Infliximab	Tocilizumab	Rituximab	All
URI	17	-	1	4	22
Sinusitis	3	1	-	2	6
Bronchitis	1	-	-	4	5
Infected bronchiectasis	1	-	-	1	2
Pneumonia	3	3	-	2	8
Diarrhea	1	-	-	-	1
Appendicitis	1	-	-	-	1
Bowel perforation	1	2	-	-	3
UTI	3	-	-	2	5
Meningitis	1	-	-	-	1
Herpes zoster	4	1	-	3	8
Bacterial skin infection	3	-	-	1	4
Candida skin infection	2	-	-	-	2
Septic arthritis	-	2	-	-	2
Others	2	3	-	-	5
Total infection	43	13	1	18	75

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298 **Table 4 Pathogenic organisms**

Pathogenic organisms	Etanercept	Infliximab	Tocilizumab	Rituximab	All
Bacteria					
Unknown	23	3	-	9	35
K. pneumoniae	1	2	-	-	3
E. coli	1	1	-	1	3
P. aeruginosa	-	1	-	-	1
H. influenzae	-	-	-	1	1
A. baumnanii	-	1	-	-	1
Citrobacter spp.	-	-	-	1	1
Salmonella spp.	-	1	-	-	1
Nocardia spp.	-	1	-	-	1
Gram negative rod	1	-	-	-	1
Virus	9	-	1	2	12
Unspecified					
VZV	4	1	-	3	8
Fungus					
Candida spp.	3	-	-	-	3
Cryptococcus spp.	1	-	-	-	1
Aspergillus spp.	-	-	-	1	1
M. tuberculosis	-	2	-	-	2
Total	43	13	1	18	75
Incidence of infection (per 100 patient-years)	13.78	12.26	23.70	12.78	13.46

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304 **Table 5 Serious infection in number of events**

Infection	Etanercept	Infliximab	Rituximab	Overall
Respiratory tract				7
- Pneumonia	3	1	2	
- Fungal sinusitis	-	-	1	
Gastrointestinal tract				4
- Bowel perforation	1	2	-	
- Appendicitis	1			
UTI	3	-	2	5
Skin & soft tissue and Musculoskeleton				3
- Ecthyma	1	-	-	
- Septic arthritis	-	2	-	
Cryptococcal meningitis	1	-	-	1
Sepsis, unknown source	1	-	-	1
Total events	11	5	5	21
Incidence of serious infection (per 100 patient-years)	3.27	7.06	3.94	3.91

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306 **Figure 1 Indications for biologic agents**

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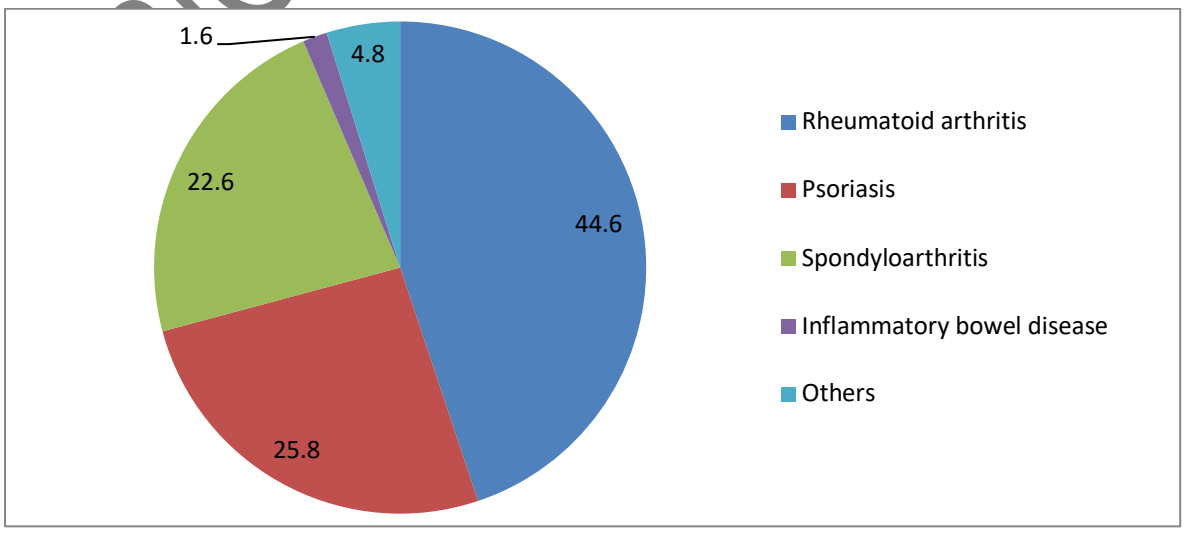

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