Awareness of Biological Treatments in Treated Rheumatoid Arthritis Patients

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Abstract: Background: The use of biologic agents in the treatment of rheumatoid arthritis (RA) patients sometimes lead to increase in the risk of infections and opportunistic infections such as tuberculosis (TB). Improving awareness might help in a more efficient and safer practice. Objectives: To evaluate patient awareness towards potential risks of drugs prescribed to rheumatoid arthritis (RA) patients. Methods: The present research study was conducted at King AbdulAziz University Hospital (KAUH), Jeddah Region (western province of Kingdom of Saudi Arabia). A total of 72 subjects were recruited for the study and were further categorized into 42 females and 30 males. The study included participants 20 years of age and above. A structured questionnaire along with a consent form was asked from each patient (phone interview) to obtain their demographic and clinical information. Patients were categorized by age, gender, level of education, occupation, biologics they use, other treatments, side effects of biologics and history of TB exposure. A simple descriptive statistical analysis is reported as proportions for qualitative variables to assess the awareness of biologic treatment in arthritis patients such as type of biologics they used and their side effects. Results: The finding showed that the majority of the arthritis patients 35(48.6%) were above 50 years of age, where female predominance 42(58.3%) was found. It was noted that 33(41.7%) were literates and have achieved college education, however, 25(34.7%) were noticed without any occupation. It was further documented that 41(56.9%) of patients were aware of the biologics they were using. In patients' frequency of usage of Adalimumab 66(91.7%) was high compared to Etanercept 6 (8.3%). Patients with other treatments like MTX treatment were also in high frequency 38(52.8%). However, less number 18(25%) of patients were aware of the side effects of the biologics and 41(56.9%) of them were aware that biologics are teratogenic in nature. High frequency of patients 24(33.3%) stopped using medications when they have UTI symptoms. Moreover, 45(62.5%) of patients were not familiar about vaccination prior to treatment and 35(48.6%) of patients were aware of side effects of anti-TB. Throughout the questionnaire, it was noticed that 7 (9.7%) were exposed to T.B. and 2(2.8%) and 3 (4.2%) of patients had previous history of T.B and family history of T.B respectively. Further, 12 (18.2%) of patients were positive for PPD skin test. One of the patients had a positive CXR. Conclusion: Based on the results it is clear that the awareness of biologics and their complications in the arthritis patients requires more effort, especially T.B. UTI, skin diseases and other side effects of biologics being used, which may cause potential adverse effects in patients. [Yasser Mohammed Bawazir, Sami Bahlas, Ibtisam Jali, Atlal Abusanad, Hibatallah Issam Mashat and Marwa Ziyad Rambo. Awareness of Biological Treatments in Treated Rheumatoid Arthritis Patients. N Y Sci J 2018;11(4):45-51]. ISSN 1554-0200 (print); ISSN 2375-723X (online). http://www.sciencepub.net/newyork. 6. doi:10.7537/marsnys110418.06.

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1.0 Introduction

Rheumatoid Arthritis (RA) is one of the chronic inflammatory autoimmune diseases which has articular and extra articular manifestations. Articular damage occurs when pro-inflammatory cytokines attack the body's own cells of cartilage, elastic tissue that covers the ends of bones in a joint, as well as the bones themselves resulting in unchecked inflammation causing joint deformity which cannot be reversed. Moreover, RA can cause extra articular manifestations which affectsthe "entire body" systems, such as anaemia, fatigue and low-grade fever, with other extra-articular manifestations and complications, includes ardiovascular problems like pericarditis, myocarditisor respiratory systems, vasculitis, and pulmonary fibrosis are sometimes present and are generally associated with more severe clinical disease(1)(2).

Various drugs are used to treat RA; however, some drugs like Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) are prescribed primarily to ease the symptoms of RA, followed by conventional disease modifying antirheumatic drugs (cDMARD) and/ or Biologics, to slow down the progression of the disease and to prevent any structural damage. When compared to the traditional medications for the treatment of RA, rheumatologists find Biologics a subset of DMARDs (bDMARDs) safe to treat RA and more effective than the conventional DMARDs. It is believed that when RA patients are given bDMARDs, it will affect certain targets of the inflammatory process with minimum impact on the immune system. Similarly the bDMARDs helps to reduce, modify or limit the progression of RA(2).

In the Biologics to treat RA the largest group is the Tumor Necrosis Factor Inhibitors such as etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab. bDMARDs with alternative mechanisms of action include anakinra (interleukin [IL]-1 receptor antagonist), tocilizumab (IL-6 receptor antagonist), abatacept (cytotoxic T lymphocyte antigen [CTLA]-4 immunoglobulin), and rituximab (anti-CD20 B cell antagonist)(3).

According to the European League Against Rheumatism (EULAR) recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying anti-rheumatic drugs (2013 update), treatment should be aimed at reaching a target of remission or low disease activity in every patient in as short a time as possible.(3)

We have initiated the investigation on biologics Adalimumab and Etanercept to evaluate the risk of drugs prescribed to Rheumatoid Arthritis (RA) patients and to assess awareness of the patients taking these Before performing the research a review was conducted on the drugs. They are few scanty reports available on these drugs and awareness of its side effects. Hence, we prefer to conduct a trial in our Saudi Arabia population at King Abdut-Aziz University Hospital (KAUH), Jeddah Region (western province of Kingdom of Saudi Arabia).

2. Methodology

The present research is a case-control study conducted on 72 RA subjects recruited at King Abdul-Aziz University Hospital (KAUH), Jeddah Region (western province of Kingdom of Saudi Arabia) and was further categorized into 67 females and 5 males. The age range was from 20 to 50 years of age. Duration of the study was from2013 to 2017 (5 years).Patients getting treated with non-steroidal, antiinflammatory drugs and having a previous history of anti-TNF α treatment were studied. Ethical approval was taken to conduct the study. Further patients were categorized by age, gender, level of education, occupation. A structured questionnaire along with consent form was asked to each patient (phone interview) to obtain their demographic and clinical information. The questions asked were (Please find in the appendix I)

Further, biochemical analysis was retrieved from patient's files and that included urinary analysis, PPD skin test, CXR and LFT tests by obtaining urine, blood and serum samples.

A simple descriptive statistical analysis is reported as proportions for qualitative variables to know the awareness of biologics treatment in arthritis patinas such as frequencies and percentages of type of biologics and their side effects.

3. Results

A prospective study was conducted using a sample size of n=72 patients. All patients included in this study were diagnosed with RA. The data collected was entered into MS. Excel then exported to SPSS software (20.0 version) for statistical analysis. The statistical analysis was carried out on percentage basis to find out the demographical information of the respondents. Similarly, descriptive statistical measures were carried out for each variable. Chi-square analysis was used to evaluate the link between categorical variables. Logistic regression model was used to assess the association between dependent and one or more independent variables, to look at the fit of the model and significance between each relationship. P<0.05 was considered statistically significant.

Demographics variables	N (%)
Female	42 (58.3)
<20	2 (2.8)
20-30	4 (5.6)
21-40	12 (16.7)
41-50	19 (26.4)
>50	35 (48.6)
Saudi	60 (83.3)
Non-Saudi	12 (16.7)
Adalimumab	66 (91.7)
Etanercept	6 (8.3)
PPD skin Test	64 (90.1)
CXR	60 (83.3)
LFT	70 (98.6)
Total	72 (100.0)

Table (1) presents the frequency of demographic of the patients. Majority of the patients were females (58.3%), above 50 years of age (48.6%) and Saudi nationality (83.3%). The most used biologic was Adalimumab by 91.7%, while Etanercept used only by 8.3%. Majority 90.1% of the patients had done purified protein derivative skin test, 83.3% of the patients had taken chest x-ray and 98.6% of the patients had tested for liver function tests.

Table (2) and Fig. (1) Comparison between gender and other variables. 97.6% of the female patients and 83.3% of the male patients were aware of biologics that they have used. The association between gender and name of biologics was found to be statistically significant (p=0.031). When considered gender and side effects of biologics, it is observed that

25% of the patients had side effects frombiologics, 36.7% were male patients and it is statistically significant (p=0.043). Furthermore, 56.9% of the patients knew that biologics were teratogenic, from those patients 73.8% were female and 33.3% were male. Gender and knowledge towards teratogenicity had shown a statistical significance (p=0.001).

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Table 2: Association between gender of other variables							
	Gender Female (n=42) N (%)	Male (n=30)	Total	Chi-Square	p value		
Name of Biologics							
Adalimumab	41 (97.6)	25 (83.3)	66 (91.7)	4.675	0.031*		
Etanercept	1 (2.4)	5 (16.7)	6 (8.3)				
Side effects of biologics	7 (16.7)	11 (36.7)	18 (25.0)	3.733	0.043*		
Know that biologics are teratogenic?	31 (73.8)	10 (33.3)	41 (56.9)	11.694	0.001**		

**p<0.01, *p<0.05



Figure 1: Association between gender of other variables

Table 3 and Fig. (2) compares the knowledge towards biologics and other variables. It was observed that 25% of patients knew what biologics were and 41.5% of them were aware of their side effects. Furthermore 56.9% of patients who knew what

biologics were and out of them 70.7% knew that they were teratogenic. It was shown that only 37.5% of patients knew about the importance of vaccination prior to starting biologics.

Table 3: Relationshi	p between	side e	effects of	f biologics	and what	biologics	are

	Do you know w	hat Biologics are?			
	Yes (n=41) n (%)	No (n=31)	Total	Chi-Square	p value
Side effects of biologics	17 (41.5)	1 (3.2)	18 (25.0)	13.766	0.000**
Know that biologics are teratogenic?	29 (70.7)	12 (38.7)	41 (56.9)	7.383	0.007**
Vaccination before starting the treatment	22 (53.7)	5 (16.1)	27 (37.5)	10.608	0.001**
*** 0.01					

**p<0.01



Figure 2: Relationship between side effects of biologics and what biologics are

Table 4 compares the knowledge about anti-TB medications and their side effects. It was noted that 10 (50%) patients used anti-TB medications and 8 (80%)

of them were aware of their side effects, which wasn't statistically significant (p=0.064).

Table 4: Relationship between the knowledge about anti-TBmedications and their side effects

	Did you use anti-TBmedications				
	Yes (n=10)	No (n=56)	Total Squa		p value
	n (%)			Square	
Side effects of anti-TB medications	8 (80.0)	25 (44.6)	33 (50.0)	4.243	0.039*
*p<0.05					

The table 5 presents the logistic regression in which the study variables are entered into independent and dependent variable. In logistics regression use of anti-TB medications is considered as an independent variable and the knowledge side effects of anti-TB medications is considered as the dependent variable. If the significance level of the Wald statistic is small (less than 0.05) then the parameter is useful to the model. The knowledge towards the anti-TB medications is significant (beta=1.601, p>0.001)

which is greater than 0.05. The meaning of a logistic regression coefficient is not as straightforward as that of a linear regression coefficient. While B is convenient for testing the usefulness of predictors, Exp (B) is easier to interpret. Exp (B) represents the ratio-change in the odds of the event of interest for a one-unit change in the predictor. Hence there is no association in mean the knowledge of the use anti-TB medications between side effects of anti-TB medications.

	Data	се	Wald	n valua	OP	OP CI	
	Beta 5.	S.E. walu	p value	UK	Lower	Upper	
Constant	-0.215	0.269	0.640	0.424	0.806	0.965	25.483
Use anti-TB medications	1.601	0.835	3.678	0.055	4.960		

Table 5: The knowledge between side effects of anti-TB medications and their use

Dependent variable: Side effects of anti-TB medications

4. Discussion:

Various drugs are used to treat RA, traditional as well as biologic DMARDs. Biologic DMARDs are safe to treat RA patients which is because of its easy availability at clinics and when injected they may provide quick effectiveness to the patients who are resistant to the traditional DMARDs. (3).

In this present study, the use of Adalimumab and Etanercept biologic drugs were used on RA patients and evaluated their knowledge toward the treatment. When a demographic analysis was performed, older age group females more than 50 years showed higher frequency of RA, though the reason is unknown, it is said that the activation status of peripheral blood lymphocytes could be responsible which might be due to the low anti-inflammatory levels in them. Besides the fact that RA is a chronic disease, several hormonal and immunological changes may contribute to higher prevalence in older females. (4).

It is known that Methotrexate (MTX) is the most disease modifying anti-rheumatic drug used for rheumatoid arthritis (RA), has been available for clinical use since 1951 (5). The side effects of MTX are usually mild however, patient's sensitive to MTX drugs were reported of developing oral ulcers, alopecia, cytopenias, liver transaminase elevations etc. Hence, patients administered with MTX should be monitored for the above clinical and biochemical signs (6). Similarly, LFTs may be abnormal in up to 50% of patients with RA and this has been shown to correlate with disease activity. The 'rheumatoid liver' has long been a topic of interest and previous studies noted histological changes in the liver of RA patients who were not on treatment with DMARDs such as fatty change, cellular necrosis, chronic passive congestion and gross atrophy (7).

Albumin levels can also be measured when chronic liver disease or damage to the liver from medications is suspected. There is evidence that suggests abnormal results of the liver function tests seen with methotrexate therapy in RA may not be as frequent as previously suggested, with very few patients discontinuing methotrexate treatment because liver function test result abnormalities over 10 to 15 years of use(8).

In our study, it is observed that females were less prone to side effects than males and had more awareness on biologics that they possess teratogenic nature. When considered gender and side effects of biologics, it is observed that 25% of the patients had side effects from Tumor Necrosis Factor (TNF)antagonists.

In our survey in literature we found that the first targeted biologic for RA is a Tumor Necrosis Factor (TNF)-antagonist, which can be taken alone or with methotrexate. It helps to reduce signs and symptoms of RA by preventing joint damage and improving motility in patients with moderate to severe RA. Though it works on our immune system to fight against infections, many studies have reported serious illness which are viral, fungal or bacterial origin and occurrence of tuberculosis (TB) in RA patients Several studies have reported serious side effects on taking such as hepatitis B, multiple sclerosis, heart failure, eye inflammation, psoriasis, allergic reactions etc. (3). (9).

The uses of biologics have sometimes lead to the risk and progression of opportunistic infections mainly like tuberculosis (TB) (10), urinary tract infection (UTI) (11) and skin diseases (12). Other risk factors or side effects can also be associated with biologics like improper storage of medicine, disease affecting daily activities, unawareness of TB history in patients. Hence, bringing awareness on these critical obstacles might help in advancement in the treatment strategy.

In our study, it was noted that 10 (50%) patients used anti-TB medications and 8 (80%) of them were aware of their side effects.

Patients treated with therapeutic TNF antagonists are initially screened for TB using purified protein derivative (PPD) based tuberculin skin testing. Although this test enables one to identify the TB status before drug treatment for RA, it may not be effective in patients who are already on immunosuppressive drugs (13). In PPD positive patients it is necessary to get the treatment for latent TB before starting the biologics as treatment of RA. The main purpose is to achieve the eradication of bacillus spread in patient and it may also interfere with the drugs used to treat the RA and successful treatment outcome of RA. Our study results are in accordance with study performed by(14), suggests that patients taking anti-TB are significantly prone to other disease, hence it is suggestible to limit the adverse effects of antituberculosis drugs, which must be modified in such a way that it should not cause any adverse events while patients are getting treated for RA.

Although anti-TNF has improved the treatment of rheumatoid arthritis and other immune -mediated diseases, a concern regarding their potential to increase the risk of malignancy is still debateable. Evidences to either support or refute such assertion are conflicting. For an instance, a systematic review and meta-analysis of harmful effects in randomized controlled trials of anti-TNF antibody therapy in rheumatoid arthritis patients concluded that there is a dose-dependent increased risk of malignancies in association with anti-TNF(15). Nonetheless, other overviews of systematic reviews and meta-analyses of malignancy risk of anti-TNF concluded that there are no sufficient evidences to support that TNF blockers is associated with increased malignancy risk (16,17).

It is important to note that establishing causality between anti-TNF and malignancies is challenging. Several variables may confound such observation including risk from underlying disease, risk from other medications, lack of pre-defined outcome in regard to malignancy reporting. Individualized monitoring of patients on anti-TNF treatments based on their past medical history, other significant co-morbidities and medications that may influence the risk of malignancy is of value to mitigate such concern.

We treat exact patient of RA with biologic therapy as suggested by treatment recommendation guidelines. However, the step-down therapy does not assure complete cure and may sometimes achieve sustained remission. Hence during the course of therapy, based on patient's response, the medicine dose is either increased or reduced. It is evidenced in some studies that when patients stop taking the biologics, the severity of RA is often observed more than usual (18–20). On the other hand, observational studies and treatment recommendation guidelines raise the possibility of narrowing down the biologic use in treatment strategies has reduced the dose to the lowest effect in patients achieving sustained remission. Several studies have demonstrated a large interindividual pharmacokinetic variability which translates to unpredictability in clinical response among individuals (21).

Conclusion

Rheumatoid arthritis (RA) is a common disease that mainly effects the joints and causes destruction and complications or may even leave a patient with immobility and disability. Recent treatment options depending on the better understanding of disease pathology have led to immense changes in the management of this disease. The aggressive use of biologic DMARD therapy has allowed patients to achieve improved function and decreased joint destruction. To treat rheumatoid arthritis (RA) patients the use of biologics has sometimes lead to the risk and progression of opportunistic infections like tuberculosis (TB), urinary tract infection (UTI) and skin diseases. Based on the results it is clear that the awareness of biologics and their complications in the arthritis patients requires more effort, especially T.B, UTI. skin diseases and other side effects of biologics being used, which may cause potential adverse effects in patients.

Irrespective of already existing drugs for treating RA by controlling TNF-alpha level circulation in patients' body, it is also recommended that other crucial ILs such as IL-17 and receptor kinase involving Janus kinase (JAKs), which mediates signal transduction of cell surface receptors for cytokines involved in the pathogenesis of inflammatory diseases such as RA. However, the biologic response modifiers are expensive and may be beyond the financial means of some patients who are in need of these effective treatments. The development of biosimilars over the next several years may help to provide more affordable versions of these successful therapies.

An understanding of these pitfalls will allow for the optimal patient care in both the medical and surgical settings. Bringing awareness on these critical obstacles might help in advancement in the treatment strategy.

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Appendix-I

Questions were asked to patients included in the study

- 1. Awareness on biologics they are using and their side effects.
- 2. Are they aware that biologics are teratogenic in nature?
- 3. What will they do if they have Urinary Tract Infection (UTI)? Do they stop medication, continue the medication or seek medical help and none?
- 4. Where do they store the medicine? Fridge door, inside the fridge or Room temperature.
- 5. Do they know the proper way of transporting the medicines?
- 6. Aware of Global assessments from 1-10?
- 7. Does the disease affect their daily activity?
- 8. Are they aware of the duration of the treatment plan?
- 9. Are they aware of taking vaccination before the treatment?
- 10. Do they use anti-TB medication?
- 11. Are they aware of purpose of using anti-TB medication?
- 12. Are they aware of the complications of using anti-TB medication?
- 13. Are they aware of previous history of TB?
- 14. Do they have any history of TB exposure?
- 15. Do they have any family history of TB?
- 16. Are they aware of the side effects of anti-TB medication?
- 17. Whether PPD skin test, CXR and LFT were performed and aware of these test timings and results?