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Safety Profile of Biologics at Pediatrics Rheumatology Clinic, at Children Hospital in Tripoli City, (2009-2019)

Soad Hashad[1,2], Iman Almisllati[2], Majeda Altfeel[2], Halah Etayari[2], Zuhyrah Awhaidah[2] and Aya Etwati[2]

[1] Department of Pediatric, Faculty of Medicine, University of Tripoli
[2]Pediatric Rheumatology Clinic, Tripoli Children Hospital

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ABSTRACT

The advent of biological drugs has revolutionized the management of various pediatric rheumatologic diseases, primarily juvenile idiopathic arthritis (JIA). These drugs enable better disease control and prevent or retard damage due to active disease in a substantial number of children. The study conducted to evaluate the risk of infection, (mild and sever), anaphylaxis, malignancy and autoimmunity among pediatric rheumatology patients treated with biologics. This was a case series retrospective study; carried out in Rheumatology unit Tripoli Children Hospital, including all children receiving biologics. The six biologics studied were etanercept, adalimumab, anakinira, infliximab, rituximab and tocilizumb. Medical records were reviewed demographic data; information related therapy, infections, anaphylaxis, malignancy, autoimmune diseases, and reason of discontinuation were collected. Data analyzed by using the Statistical Program for Social Sciences version 16.

All 92 patients treated with six different biologics between 2009 and 2019 were included, 53(58%) were females. The majority of patients had JIA 66(71.7%). Most common side effect was mild to moderate infection in 49 patients (33.3%) in all biologics,and no cases of TB or meningitis. The most common type of infection was mild upper respiratory tract infections, pneumonia that does not require hospitalization. Injection site reaction only noted in 16 patients treated with anakinra .

New onset uveitis in two patients in Etanercept group, hypersensitivity reaction was recorded in 4(4.3%) patients. Abnormal LFT in form of high transaminase or bilirubin registered noted in 17 patients most of them (75%) among cases receiving Tocilizumab. Biologics discontinued in 47(51%) of the cases for different reasons, remission and inefficacy were most common causes.

The safety profiles of the six available studied biologics, are highly acceptable and encouraging. However, more long-time data is needed for sever adverse events.

Keywords- *JIA; Biologics; Rheumatology; Pediatrics; Safety.*

INTRODUCTION

Juvenile idiopathic arthritis (JIA) affects between 1:1000-1:2000 children, untreated JIA can last well into adulthood, causing significant long-term functional impairment.[1]

Juvenile idiopathic arthritis is the most common chronic rheumatic disease of unknown aetiology in childhood and predominantly presents with peripheral arthritis. The disease is divided into several subgroups, according to demographic characteristics, clinical features, treatment modalities and disease prognosis.[2]International League of Associations for Rheumatology (ILAR) classified JIA to seven subtypes: systemic (SoJIA), oligoarthritis (oligoJIA), rheumatoid factor positive poly articular (RF+ve poly JIA) rheumatoid factor negative polyarthritis (RF-ve poly JIA), Enthesitis related juvenile (ERA) psoriatic (JPsa) and undifferentiated arthritis.[2]

Improved understanding of the pathogenesis of rheumatoid arthritis has led to the development of various rheumatoid arthritis (RA) treatments. The current therapies for RA are divided into four categories: non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, non-biologic disease-modifying anti-rheumatic drugs (DMARDs) and biologic DMARDs.[3]

Biologic agents are molecules that specifically target cytokines or cell surface antigens and different from traditional immunosuppressive or disease- modifying antiheumatic drugs (DMARs), as they target to and selectively block only one inflammatory pathway such as tumor necrosis factor (TNF-α) blockers (etanercept, adalimumab, infliximab), interlukin-1 (IL-1) inhibitors (anakinra), IL-6 receptor blockers (tocilizumab), and anti-CD20-antibodies (rituximab). In contrast traditional DMARs act on multiple pathways and cause generalized immune suppression.[4,5]

With the increasing use of anti-TNF agents, a number of common concerns have arisen.one of which is the increased risk of infection, particularly tuberculosis; fungal infections, including histoplasmosis; and other opportunistic infection. Infusion and injection reactions, the occurrence and aggravation of infections, the occurrence of a second autoimmune diseases, including uveitis, psoriasis, chronic inflammatory bowel disease, multiple sclerosis, diabetes mellitus, and the development of

@ Author to whom correspondence should be addressed: Dr Soad Hashad; *Tel:* 00218923064018*; E-mail*: soadhashad@hotmail.com

malignancies are major concerns regarding treatment with biologics.[6]

Biological agents have been shown to be efficient and safe in JIA patients, despite reports of increased frequency of infections that sometimes require hospitalization and sporadic reports of autoimmune diseases. There is some evidence that treatment with TNF blockers could increase the risk of malignancy in children. However, a clear causal relationship has not been established since underlying illnesses and the use of concomitant immunosuppressants bear a risk of malignancy as well.[2]

The efficacy of BAs has now been well demonstrated in various subtypes of juvenile idiopathic arthritis (JIA)[7-9], indifferent pediatrics rheumatological disease; however, there are only a few observational studies that have been conducted in children with rheumatic diseases to evaluate the risk of infection and serious side effect.[10,11] Hence, we conducted this study to evaluate the risk of infection, (mild and sever), anaphylaxis, malignancy and autoimmunity among our patient.

MATERIALS AND METHODS

This was a case series, retrospective study, conducted in Rheumatology unit at Tripoli Children Hospital. A ninety two patients treated with the six different biologics, between 2009 and 2019 were included in the study, receiving biologics for any diagnosis in clinic mainly JIA subtypes, systemic lupus erythramtous (SLE), Behçet disease, chronic uveitis, childhood vasculitis, autoinflammatory disease, and inflammatory bowel disease. The six biologics studied were etanercept, adalimumab, anakinira, infliximab, rituximab and tocilizumb. A case sheet was used to collect the information about the patients from the medical record of the infusion unit. Medical records were reviewed for age at diagnosis, age at starting of treatment, disease phenotype, therapy, infusion dates, dose, and intervals, duration of disease before start biologics, previous steroids and disease modifying drugs, failed previous biologics and Co- treatment with methotrexate, or other disease modifying agents.

Outcomes measure included adverse events: sever adverse events (serious side effect anaphylactic reaction, serious infection, death) or other milder form of side effect, macrophage activating syndrome (MAS), development of autoimmune disease, tolerability and reason of discontinuation.

Statistical analysis was done by using the Statistical Program for Social Sciences SPSS version 16. Descriptive statistics were used and the results are presented as frequencies, means ± standard deviation, and percentages.

RESULTS

Total number of cases attending rheumatology clinic at Tripoli children hospital were 749 children, of which 241(32%) were JIA, and 508(68%) were non JIA. Total number of cases who received biological drugs was 92 children. Out of 92 cases that treated with biological drugs, there were 39(42%) males and 53(58%) females; male to female ratio was 1:1.4. Most of the treated patients 37 (40.2%) were diagnosed after 10 years of age, and 39.1% were diagnosed between 4-10years of age.

About half (56.5%) of the patients started the treatment after 10 years of age, and 8.7% started the treatment less than 4 years of age (Table 1).

Among 92 cases, JIA was reported in 66(71.7%) of them. Systemic juvenile idiopathic arthritis was most frequent subtype of JIA 26(28.3%), followed by seronegative polyarticular juvenile idiopathic arthritis 12(13%) and enthesitis-related arthritis 11(12%). Chronic uveitis was reported in 7(7.6%) of the cases and 6 (6.5%) of patients with childhood vasculitis. Concerning the duration of disease before biologics, 54 (58.7%) patients treated with biologics within first 2 years of disease; while 38 (34.8%) patients were received the biologics after 2 years of diagnosis (Table 1).

Table 1: Clinico-demographic characteristics of the cases

Character	No.	%
Age at diagnosis		
<4	19	20.7
4-10	36	39.1
>10	37	40.2
Age at starting treatment		
<4	8	8.7
4-10	32	34.8
>10	52	56.5
Sex		
Male	39	42
Female	53	58
Disease type:		
JIA	66	71.7
Non JIA	26	28.3
JIA subtype:		
OligoarticularJIA	9	9.8
Polyaritcular seropositive JIA	5	5.4
Polyarticularseronegative-JIA	12	13
SOJIA	26	28.3
ERA	11	12
JPsA	2	2.1
Undifferentiated	1	1.1
Non JIA:		
SLE	4	4.3
Behçet disease	2	2.2
Chronic uveitis	7	7.6
Childhood vasculitis	6	6.5
Auto inflammatory disease	5	5.4
Inflammatory bowel disease	2	2.2
Duration of disease before starting treatment		
≤ 2 years	54	58.7
>2 years	38	41.3

ERA: Enthesitis-related arthritis, soJIA : systemic-onset JIA , JPsA : juvenile psoriatic arthritis

According to biologics used; 37(40%) received etanercept, 9(10%) received adalimumab, 16(17%) received anakinira, 11(12%) received infliximab, 7(8%) received rituximab and 12(13%) received tocilizumab (Figure 1).

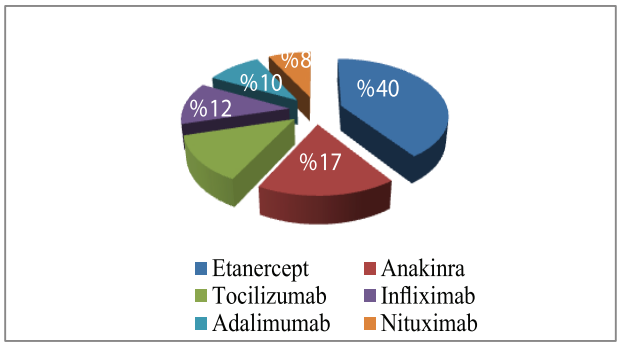

Figure 1: Types of biologics prescribed to the cases

Eleven patients used more than one biologics; six patients used 3 biologics and 5 patients used 2 biologics which represents 6.5%, 5.4% from total patients respectively.

The most commonly used drugs with biologics are Methotrexate (MTX) (69.6%), and prednisolone (46.7%) (Figure 2).

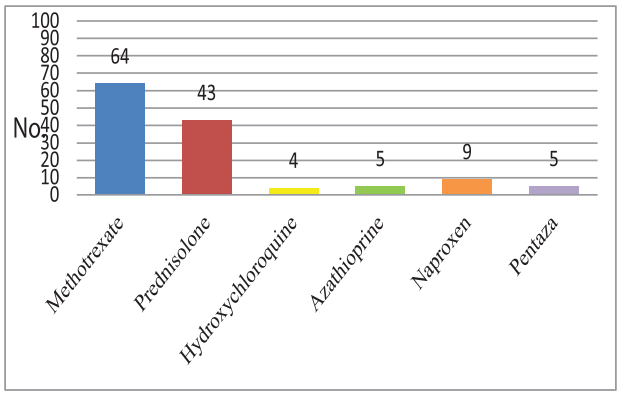

Figure 2: Concurrent treatment with biologics in study population.

The most commonly reported side effect was mild to

Table 2: Adverse drug reactions to biologics among study population

Side effect	Etanercept	Adalimumab	Anakinira	Infliximab	Rituximab	Tocilicumab	Total
	Number %	Number %	Number %	Number %	Number %	Number %	Number %
Infection	22 59.4%	4 44.4%	7 43.75%	8 72.7%	6 85.7%	10 83%	49 53.2%
New onset uveitis	2 5.6%	0 0%	0 0%	0 0%	0 0%	0 0%	2 2.2%
Hypersensitivity reaction	0 0%	0 0%	0 0%	2 18.2%	1 14.3%	1 8.3%	4 4.3%
Injection site reaction	0 0%	0 0%	16 100%	0 0%	0 0%	0 0%	16 17.4%
New ANA positivity	1 2.8%	0 0%	0 0%	0 0%	0 0%	0 0%	1 1.1%
Abnormal LFT	0 0%	4 44.4%	3 18.75%	1 9.1%	0 0%	9 74.9%	17 18.5%
High cholesterol	0 0%	1 5.9%	0 0%	0 0%	0 0%	2 16.7%	3 3.3%
Neutropenia	0 0%	0 0%	0 0%	2 18.2%	0 0%	3 25%	5 5.4%
Lymphopenia	0 0%	0 0%	0 0%	0 0%	1 14.3%	0 0%	1 1.1%
Thrombocytopenia	0 0%	1 5.9%	0 0%	2 18.2%	0 0%	2 16.7%	5 5.4%

Table 3: Reasons of discontinuation of biologics

Reason for discontinuation	Remission	Inefficacy	Infection	Poor compliance	MAS	Anaphylaxis
Etanercept	8	4	1	1	0	0
Adalimumab	5	3	1	0	0	0
Anakinira	12	3	0	0	1	0
Infleximab	0	1	0	0	0	2
Rituximab	0	0	2	0	0	0
Tocilizumab	0	0	0	2	1	0
Total	**25(53%)**	**11(23.4%)**	**4(8.5%)**	**3(6.3%)**	**2 (4.3%)**	**2(4.3%)**

moderate infection, which occurred in 49(53.2%) of the treated patients then abnormal liver function tests (LFT), occurred in 17(18.5%) of the treated patients; injection side reaction 16(17.4%) which documented only with anakinra administration. Most common side effects with administration of Etanercept were infection and new onset uveitis. Hypersensitivity reaction was noted with Infliximab, Rituximab and Tocilizumab use. There were no reported malignancies (Table 2).

The infections that reported are: 27 episode of upper respiratory tract infection (URTI), 8 episodes of pneumonia, 5 episodes of varicella, 3 episodes of gastroenteritis, 3 episodes of urinary tract infection (UTI), 3 episodes paronychia and 2 episodes of valvovaginitis. No reported cases of meningitis or TB (Figure 3).

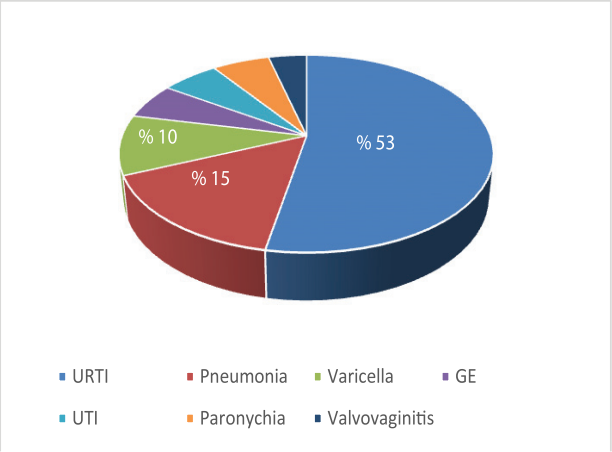

Figure 3: Types of infections with biologics use.

Biologics were discontinued in 47(51%) of the cases for different reasons: 25(53%) due to disease control, 11(23.4%) were non-effective, 4(8.5%) due to infections, 3(6.3%) poor compliance, 2(4.3%) because of macrophage activating syndrome, and 2 patient developed sever anaphylaxis (Table 3).

DISCUSSION

The advance in biologic therapeutics over the past 15 years has led to marked improvement in JIA treatment. In the biological era, the rate of joint damage decreased, and achieved disease remission increased with an increased number of patients with inactive disease. Despite the promising results of these medications, the blockade of important immunological pathways necessitates detailed safety monitoring.[2]

The study included 92 cases, with female to male ratio of 1.4:1. The most used drug is Etanercept, which reflect its indication for more common subtypes, and its practical S/C weekly administration, which is in accordance with Bethencourt Baute et al results.[12] Followed by Anakinra and tocilizumzb, and infliximab. Eleven of the patients used more than one biologics due to non-efficacy, side effect, or non-availability of previous biologics.

Regarding subclasses of JIA, the most common are systemic onset JIA followed by rheumatoid factor sero-positive poly JIA which reflect disease severity and less response to methotrexate in these subclasses. For non JIA group, biologics used as third line for sever disease refractory to standard therapy, and primary vasculitis, BD and idiopathic uveitis are the most common indication consequently.

In general, with the six used biologics, the rates of serious adverse events (AES) were low and No deaths occurred with all drugs, which is comparable with Dutch national biologics registry.[4]

Anaphylaxis reaction occurred in four patients with intravenous biologics and, two on infliximab; sever enough to discontinue the drug. The other two mild allergic reactions and the drug continued. Injection site reaction, in form of erythema and itching at site of S/C injection, documented in all Anakinra treated patients which can be minimized by modifying injection technique;and not documented in other S/C drugs. Our patients are BCG vaccinated and screened annually for all biologics.

No cases of tuberculosis or malignancy were detected, similar finding was reported by Tarkiainen et al. [10] Most common side effect documented is infection in 1-2 episodes per patient per year, URT infections were the most common documented infection; one patient got swine influenza treated with antivirus. In this study, the frequency of mild infections was higher on etanercept or infliximab than on adalimumab, which is in accordance with study of Tarkiainen et al.[10]

Food and Drug Administration (FDA) had added a boxed warning with regard to the possible increased risk of malignancy, especially lymphoma in children treated with anti-TNF- agents. There was no malignancy among treated patients after 10 years follow-up, which is compatible with ZahediNiakiet al, and Beukelmanet al studies; did not find an increased incidence of malignancy in patients with JIA children.[13,14] One girl on adalimumab developed recurrent axillary lymphadenitis and abscess which proofed late manifestation of inherited BD rather a complication of biologics. TNF antagonist therapy has been rarely associated with SLE-like syndromes and antibody syndrome, None of the studied patients developed autoimmune disease like thyroid, celiac, or psoriasis.

Treatment with etanercept does not prevent the onset of uveitis in JIA patients, it is still debatable whether etanercept contributes to the occurrence of uveitis[4]. In present study one girl on etanercept developed new onset uveitis after 3 months of etanercept treatment, but she was a young, with oligoJIA and positive ANA which all considered risk factors to develop uveitis. No flare up of old uveitis in studied patients were noted, this comparable with finding in other studies suggest that etanercept does not cause flare up of uveitis.[4]

Although Guillain-Barre syndrome and optic neuritis were developed in patients identified from the FDA database But in the study group where neither multiple

sclerosis nor Gillian bar syndrome were documented, Which is comparable in a registry run by PRCSG, where in north America where no case of demyelination disease were documented.[5]

The biologics discontinued in 47 (51%) patients in current study. Remission was the first leading reason for discontinuation of a biologic agent, which is inconsistence with Horneffet al study, where the most common reason for discontinuation was poor efficacy or unsatisfactory response. [11]our results are comparable with the Biologics and New Drugs Registry of the British Society for Pediatric and Adolescent Rheumatology (BSPAR); that published the reasons for discontinuation of etanercept therapy, where 100 (20.7%) discontinued etanercept, 9 due to disease control and 88 because of treatment failure (53 due to inefficacy, 14 due to noncompliance and 21 due to adverse events).[15]

CONCLUSION

With the six used biologics, no sever side effect, no deaths, and no malignancies. The most frequent side effects were mild to moderate infection, which did not require hospitalizations, and no cases of TB or meningitis. The safety profiles of the six available studied biologics, are highly acceptable and encouraging. However more long-time data is needed for sever adverse events such as, autoimmune events , response to vaccination or malignancies.

RECOMMENDATIONS

MoreStudies on the withdrawal of biologics and the rates of sustained remission of drugs will be needed. In addition, pharmacogenomics will help in more accurately predicting those children who will respond to a particular biologic, require long-term medication or develop major side effects due to a particular drug.

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