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ORIGINAL ARTICLE

The frequency of infections in patients with juvenile idiopathic arthritis on biologic agents: 1-year prospective study

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Abstract

Introduction The most effective and concurrently the safest treatment regimen selection is important to provide early control of juvenile idiopathic arthritis (JIA) and to have an acceptable quality of life. The effectivity of biologic agents as well as standard disease-modifying drugs is well documented in treatment of JIA. In spite of their high benefit, these drugs have the risk of serious infections. Herein, we conducted a prospective study to investigate the infectious complications of biologic agents in patients diagnosed with JIA.

Methods Patients on biologic treatment regimen were examined by the pediatric infectious disease specialist in every 2 months during 1-year long.

Results Throughout the study period, 57% (*n*:175) of the patients developed infection and 43% (*n*:132) of them completed this period without any infection. Upper respiratory tract infections which were treated in outpatient clinic were the most common infection. Only three serious infections (two pneumonia, one pleural effusion), which required hospitalization, developed. The infection rate was highest in systemic JIA and lowest in enthesitis-related arthritis ($p < 0.001$). The total rate of infection development after 1-year period was lowest for etanercept; it was highest for the patients on infliximab treatment ($p < 0.001$).

Conclusion We comment that the altered immune system of JIA can be responsible from the serious infections irrespective of immunosuppressive therapy. Biologic agents can be safely used in JIA evaluating the loss and benefit statement.

Keywords Biologic agents · Etanercept · Infection · Juvenile idiopathic arthritis

Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease of childhood having significant physical disability with high morbidity and mortality. JIA is a clinically heterogeneous condition with seven categories that have different characteristics and outcomes, which are based on the number of joints affected during the first 6 months of disease and extra-articular involvement. The cause of JIA still remains unclear, but the autoimmune and autoinflammatory processes are held to be responsible. Dysregulation in cytokines that mediate innate immune responses is also a strong evidence [1–5]. Selection of the most effective and concurrently the safest treatment regimen is important to provide early disease control and to have an acceptable quality of life and to decrease the systemic complications of the disease [6].

The biologic agents as well as standard disease-modifying anti-rheumatic drugs (DMARDs) are highly effective therapeutic choices in JIA. In spite of their high benefits, biologic agents have the risk of serious bacterial and viral infections as they act as immunosuppressant and immunomodulator thorough cytokine pathways. There are a number of studies evaluating reliability of biologic agents, with various results and counter-view [7–12]. Currently, the association between the increased rate of infection and biologic agent treatment is unclear due to scarcity of clinical and observational data regarding the infectious complications of biologic agents particularly in children with JIA. Besides, there is not also any report yet in our country. In this study, we conducted a prospective study to

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elucidate the infectious complications of biologic agents in patients diagnosed with JIA.

Patients and methods

Study participants

The diagnosis of patients was done according to the International League of Associations for Rheumatology (ILAR) classification criteria for JIA [13].

The treatment of JIA consists of non-biological medical treatment which is composed of non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying anti-rheumatic drugs (DMARDs). The DMARDS include methotrexate, sulphasalazine, leflunomide, and cyclosporine-a. The first treatment protocol of all patients diagnosed with JIA began with NSAIDs and DMARD. According to the local legislations, biologic agents could only be started to the patients whose disease activity remains uncontrolled despite the usage of DMARDs for 3 months.

The biologic agents the patients used in our study were tumor necrosis factor alpha (TNF-α) inhibitors (etanercept, adalimumab, infliximab), IL-1 receptor antagonist (anakinra), IL-1b antibody (canakinumab), and antibody against the IL-6 receptor (tocilizumab).

Development of infection

JIA patients on biologic treatment regimen were examined by the pediatric infectious disease specialist in every 2 months, between January and December 2017, during 1-year long. A serious infection was defined as an infection that needs hospitalization, intravenous antibiotics or antiviral treatment, opportunistic infections including tuberculosis, systemic mycosis, and varicella. All of the patients were routinely analyzed about latent tuberculosis prior to starting biologic treatment, and none of the patients developed active tuberculosis during the course of study. Hepatitis virus B and C infections were also excluded. Serious infections were classified by site as skin or soft tissue, lower respiratory tract, urinary tract, gastrointestinal tract, and central nervous system. Mild infections were defined as symptoms such as fever, rhinorrhea. Upper respiratory tract infections (URTIs) referred to infections of the nasopharynx, larynx, tonsillae, sinuses, ears, including rhinosinusitis, tonsillitis, pharyngitis, laryngitis/laryngotracheitis, and otitis media which were treated at outpatient clinics with oral antibiotics.

The analyzed variables were recorded as patient's age, sex, age at disease onset, JIA category, disease duration until therapy, the name of biologic agent, concomitant steroid, and DMARD treatment. The informed consent form was obtained from parents. SPSS program (version 20.0, IBM Company, SPSS Inc.) was used for statistical analysis. Numerical data were expressed as mean ± standard deviation, categorical data were expressed as frequency (*n*), and percentage (%).The Shapiro-Wilk test was used to show continuous measurement load. The x^2 and Fisher's exact test were used to compare the differences. Mann-Whitney test was used in non-parametric values.

Results

Totally, 307 patients participated in the study. One hundred seventy-one (55.7%) of the patients were female and 136 (44.3%) were male. The mean age of the patients at diagnosis was 6.24 ± 4.37 years (range 2 months–17 years). The mean age of patients at starting to use biologic agents was 9.00 ± 4.33 years (range 1–19 years). The mean length of biologic treatment was 42.11 ± 35.78 months (range 2–380 months). The mean duration of the illness at starting to use biologic agents was 30.58 ± 32.83 months (range 0–179 months).

The distribution of JIA patients according to ILAR criteria were as follows: oligoarticular (*n*:100, 32.6%), seronegative polyarticular (*n*:85, 27.7%), systemic JIA (*n*:52, 16.9%), enthesitis-related arthritis (*n*:42, 13.6%), seropositive (*n*:18, 5.9%), and juvenile psoriatic arthritis (*n*:10, 3.3%). One hundred eighty-nine patients were on etanercept, 60 were on adalimumab, 22 were on anakinra, 11 were on infliximab, 12 were on canakinumab, and 13 were on tocilizumab treatment during the study period. The demographic parameter patients are given in Table 1.

Throughout the study period (1 year), 57% (*n*:175) of the patients developed infection and 43% (*n*:132) of them completed this period without any infection. A total of 157 upper respiratory tract infections (URTI) developed during 1-year of biologic therapy. None of them required hospitalization that was treated in outpatient clinic. We were able to detect viral respiratory pathogens in 62 (40%) of them. In regard to respiratory viruses' subtypes, human rhinovirus (HRV) and respiratory syncytial virus (RSV) were the most common viruses detected in nasopharyngeal swab samples by multiplex polymerase chain reaction (PCR) method. Seasonal influenza virus was determined only in two patients. Most of the viruses were detected in the winter season. Only the two patients having influenza had mild increase in aspartate aminotransferase, alanine aminotransferase, and creatine kinase enzyme levels. Oseltamivir was used as antiviral treatment in both of them.

In forty acute tonsillopharyngitis infections developed, group A *Streptococcus pyogenes* was positive in eight throat culture. In forty-two urinary tract infections, culture positivity was found only in 12 of them, treated by oral cephalosporins without hospitalization. Twenty-four acute gastroenteritis and 20 nonspecific dermatitis were the rest of the infections. We did not determine bacterial culture positivity in acute

Table 1 Demographic Characteristics of Patients

Number of patients	($n = 307$) n (%)/Mean ± S.D.
Gender	
Female	171 (55.7%)
Male	136 (44.3%)
Diagnosis of patients	
Systemic JIA	52 (16.9%)
Seropositive polyarticular JIA	18 (5.9%)
Seronegative polyarticular JIA	85 (27.7%)
Oligoarticular JIA	100 (32.6%)
Juvenile psoriatic arthritis	10 (3.3%)
Enthesitis-related arthritis	42 (13.6%)
The mean age of the patients at diagnosis (years)	2 months–17 years (6.24 ± 4.37)
The mean duration of the illness at starting to use biologic agents(months)	30.58 ± 32.83
The mean length of biologic treatment (months)	42.11 ± 35.78
The patients used to stop biologic treatment	2 (0.6%)
Biologic agents	
Etanercept	189 (61.6%)
Adalimumab	60 (19.5%)
Anakinra	22 (7.2%)
Canakinumab	12 (3.9%)
Infliximab	11 (3.6%)
Tocilizumab	13 (4.2%)

gastroenteritis, 4 of them were rotavirus positive and 2 of them were positive for adenovirus.

Only three serious infections (two pneumonia, one pleural effusion), which required hospitalization, developed. One of them was a four-year-old systemic JIA patient, who was on anakinra treatment with concomitant high-dose steroid. She developed pneumonia and pleural effusion on the second and the sixth month of treatment, respectively. *Streptococcus pneumoniae serotype* 19 A was isolated in the pleural fluid culture of the patient. She was fully vaccinated with seven valent pneumococcal vaccine; however, serotype 19A is not included in the vaccine. The second pneumonia case was also a systemic JIA patient who was also on anakinra treatment. Seven of the patients had varicella infection without any complication requiring hospitalization, none of them had varicella vaccine. Four of the patients were on etanercept, others were on anakinra, infliximab, canakinumab regimen respectively.

The infection rate was highest in systemic JIA and lowest in enthesitis-related arthritis ($p < 0.001$). The total rate of infection development after 1 year period was lowest for etanercept; it was highest for the patients on infliximab treatment ($p < 0.001$).

There was a statistically significant relationship between the risk of infection development and subgroup diagnosis of patients, the type of biologic agents. The P scores were $p < 0.001$, $p < 0.001$, and $p = 0.041$, respectively. The comparison of infection development according to diagnosis of patients and biologic agents is given in Table 2. The various infection rates in JIA patients on biologic agents over a period of 1 year are summarized in Table 3.

Discussion

Juvenile idiopathic arthritis is a complex disorder with severe disability and pain, complicated by linear or localized growth disturbance. DMARDs have been used safely for a long time in controlling disease activity in JIA. Although the effectivity of DMARDs in preventing the damage and decreasing the disease burden is well documented, JIA still continues to result in long-term sequela. In the past 20 years, many new biologic agents are introduced to treatment of JIA. The earlier use of biologic agents has been reported to improve both short and long-term clinical outcomes of patients with JIA. According to the local legislations, biologic agents could only be started to the patients whose disease activity remains uncontrolled despite the usage of DMARDs for 3 months. The agents seem to achieve complete disease remission and normalize physical development in a substantial number of JIA patients [3, 6].

It is necessary to examine the underlying pathogenesis of the disease in order to evaluate the efficacy of these drugs. The innate immune system and the uncontrolled activation of phagocytic cells leading to increased secretion of inflammatory cytokines such as interleukin 1 (IL-1), IL-6, and tumor necrosis factor alpha (TNF-α) are accused mechanisms causing JIA. Increased level of inflammatory cytokines promotes an inflammatory cascade, local injury, and tissue damage [14–17]. Since biologic agents counter the effects of the inflammatory cytokines, suppression of the immune system is a natural process.

There are various clinical studies indicating the safety and benefit of biologic agents in treatment of JIA [18–21]. The URTI followed by gastroenteritis are the most frequently reported infections in majority of them. Herein, at the end of the 1-year period, 57% (n:175) of the patients developed infection and 43% (n:132) of them completed the treatment episode without any infection. Most of the infections were mild URTI and tonsillopharyngitis which were treated at outpatient clinics without hospitalization. The HRV and RSV were the most common respiratory viral pathogens and most of the infections developed during the winter season. These viruses are the common causative respiratory viruses that can also infect healthy subjects all over the world, so we comment that the result was not surprising. Yet, viral infections are common in winter.

Table 2 Comparison of infection development according to diagnosis of patients and biologic agents

	Infection rate in 1 year		*p* value
	Infection did not develop *n* (%)	Infection developed *n* (%)	
Biologic agent			< 0.001
Etanercept	101 (53.4)	88 (46.6)	
Adalimumab	19 (32.2)	40 (67.8)	
Anakinra	6 (27.3)	16 (72.7)	
Canakinumab	2 (16.7)	10 (83.3)	
Infliximab	1 (9.1)	10 (90.9)	
Tocilizumab	2 (15.4)	11 (84.6)	
Diagnosis			< 0.001
Systemic JIA	8 (15.4)	44 (84.6)	
Seropositive polyarticular JIA	8 (44.4)	10 (55.6)	
Seronegative polyarticular JIA	40 (47.1)	45 (52.9)	
Oligoarticular JIA	47 (47.0)	53 (53.0)	
Juvenile psoriatic arthritis	3 (30.0)	7 (70.0)	
Enthesitis-related arthritis	25 (60.9)	16 (39.1)	

The urinary tract infection, acute gastroenteritis, and dermatitis were the other mild infections developed during the course of study. We confirm the safety of biologic agents in JIA that has been described in previous studies.

On the other hand, increased infectious rates of biologic agents are reported in many other reports especially the ones comparing biologic agents with DMARD [11, 12, 22, 23]. Pneumonia, aseptic meningitis, and soft tissue infections were the serious adverse events needing hospitalization. The British Society for Paediatric and Adolescent Rheumatology reported to 2.1-fold increased rate of infection with etanercept compared with methotrexate, as the varicella and pneumonia were the most common infections [24]. We experienced varicella infection in seven of the patients, four of whom were on etanercept treatment, others were on anakinra, infliximab, and canakinumab regimen. None of the varicella cases were hospitalized and developed complication. All of our patients were on concomitant methotrexate, so we were not able to make such a comparison. But varicella developed mainly in patients using etanercept. The varicella infections occurred in the unvaccinated patients who have the risk to develop as high as healthy children, especially in secondary house hold attack. We can comment that the patients diagnosed with JIA should be evaluated and if necessary should be vaccinated for varicella prior to starting biologic agents.

Only 2 of 307 patients required hospitalization. Both of them were systemic JIA patients and were on anakinra treatment. One of them was a 4-year old girl who developed

Table 3 Various infection rates in JIA patients on biologic agents over a period of 1 year

	Etanercept (*n* = 189)	Adalimumab (*n* = 59)	Anakinra (*n* = 22)	Canakinumab (*n* = 12)	Infliximab (*n* = 11)	Tocilizumab (*n* = 13)
URTI	52 (27.5%)	19 (32.2%)	11 (50%)	10 (45.4%)	8 (72.7%)	5 (38.4%)
AT	12 (6.3%)	10 (16.9%)	4 (18.1%)	4 (33.3%)	2 (18.1%)	1 (7.6%)
UTI	32 (16.9%)	14 (23.7%)	6 (27.2%)	1 (8.3%)	2 (18.1%)	3 (23.0%)
Varicella	3 (1.5%)	1 (1.69%)	1 (4.5%)	1 (8.3%)	1 (9.0%)	0
Pneumonia	2 (1.0%)	4 (6.7%)	3 (13.6%)	1 (8.3%)	0	2 (15.3%)
AGE	2 (1.0%)	0	2 (9%)	1 (8.3%)	0	1 (7.6%)
HSV	0	0	0	0	0	1 (7.6%)
Dermatitis	4 (2.1%)	4 (6.7%)	1 (4.5%)	0	0	1 (7.6%)
Perianal abscess	0	1 (1.69%)	0	0	0	1 (7.6%)
Tuberculosis	1 (0.52%)	1 (1.69%)	0	0	0	0

URTI upper respiratory tract infection, *AT* acute tonsillopharyngitis, *UTI* urinary tract infection, *AGE* acute gastroenteritis, *HSV* Herpes Simplex Virus

pneumonia and empyema on the second and the sixth month of treatment. She had been fully vaccinated with seven valent pneumococcal vaccine. *Streptococcus pneumoniae* serotype 19 A was isolated in the pleural fluid culture which is not a serotype that present in vaccine. *Streptococcus pneumoniae* is the leading cause of bacteremia and pneumonia, resulting in significant morbidity and mortality worldwide even in healthy children. At present, over 95 serotypes have been described, with the introduction of pneumococcal vaccine the incidence of pneumococcal diseases associated with vaccine serotypes reduced but non-vaccine serotypes are still of great concern to clinicians. Previously, healthy children also have the risk of infection with various serotypes of *S. pneumoniae.*

Streptococcal bacteremia and pneumonia have been reported with anakinra; the vaccination status of the patients was not noted. Although there are some case reports documenting serious infections with anakinra, there are no published comparative studies.

In addition to systemic JIA, high disease burden and cumulative high-dose steroid were shared characteristics in both of our patients. Systemic JIA is the most related subtype to serious infections due to higher corticosteroid need and concomitant immunosuppressive therapy [12, 23–25]. Compared with the healthy children, patients with JIA already have increased rate of infection even without biologic agents or immunosuppressive therapy, yet the disease itself is the major risk factor [3]. Higher disease activity and longer disease duration were suggested as other risk factors associated with an increased tendency to infections [26]. Anyway, the infection rate was highest in systemic JIA and lowest in enthesitis-related arthritis ($p < 0.001$) in our study.

Tuberculosis and other opportunistic infections are the other serious infections that can develop in the course of JIA patients on biologic therapy. We did not experience any tuberculosis and fungal infection during the 1-year period. However, the short follow-up period in our study hinders to make a more accurate statement regarding the association of biologic agents and tuberculosis/fungal infections.

In the present study, the total rate of infection development after the 1-year period was lowest for etanercept; it was highest for the patients on infliximab treatment ($p < 0.001$).

Our study has some limitations with short follow-up period being the most important. Moreover, we did not compare the infection rates of patients on biologic agents (± DMARDs) with the subjects solely on DMARDs.

Conclusion

But, timely and accurate treatment is important to provide the control of JIA. Early and proper treatment must begin to prevent the permanent disability and complications of the disease. We suggest that biologic agents are quite safe in treatment of JIA patients who could be monitored closely. However, there is still need for comparative studies to better evaluate the safety of biologic agents in terms of infections.

Compliance with ethical standards

The study protocol was in line with the guidelines of the 1975 Declaration of Helsinki. Ethics Committee approval was obtained from Faculty Local Ethics Committee (367966). Written informed consents were taken from all parents before commencing this study.

Disclosures None.

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