

The necessity, efficacy and safety of biologics in juvenile idiopathic arthritis

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ABSTRACT

OBJECTIVE: Juvenile idiopathic arthritis (JIA) is the most common cause of chronic arthritis in children. Biologics have changed the faith of children with rheumatic diseases. The main objective of this study was to demonstrate the rate of usage, efficacy and safety of biologics in JIA subtypes.

METHODS: This retrospective observational cohort study was conducted between May 2010 and September 2017. All children with the diagnosis of JIA and children under a biological agent treatment were recorded into the local registry system. Age, gender, JIA subtype, medications used, the clinical status of the patient, tuberculosis screening results, and side effects observed under biologics were retrieved from the registry.

RESULTS: There were 405 patients with the diagnosis of JIA in the cohort. Biologics were used in 123 (30.3%) JIA patients. Subtype frequencies of JIA patients were as follows: persistent oligoarticular JIA (33.6%), enthesitis-related arthritis (29.2%), systemic JIA (13%), rheumatoid factor (RF)-negative polyarticular JIA (13%), extended oligoarticular JIA (4.2%), RF-positive polyarticular JIA (3.4%), psoriatic arthritis (1.8%) and unclassified arthritis (1.8%). The rate of biologic use was high in extended oligoarticular JIA (64.7% of the cases), RF-positive polyarticular JIA (57.1%), psoriatic arthritis (57.1%), RF-negative polyarticular JIA (41.5%), and in systemic JIA (39.6%). Enthesitis-related arthritis (27.1%), persistent oligoarticular JIA (17.6%) and unclassified arthritis (16.6%) patients were the cases that needed a biologic agent in the last order. At the last control, 78.9% of the cases were in remission, while 21.1% of them were active despite biologic treatment. Isoniazid prophylaxis was used in 30.8% of the patients. None of the patients developed active tuberculosis infection under prophylaxis. Adverse events were observed in 18.6% of patients under biologics as recurrent uncomplicated upper respiratory tract infections being the most common.

CONCLUSION: Biologics are safe and effective treatment options in children with JIA. Most of the JIA patients with polyarticular involvement require biologics earlier in the disease course. The risk of tuberculosis infection seems not to be increased after appropriate screening and prophylaxis.

Keywords: Biologics; juvenile idiopathic arthritis; tuberculosis.

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Juvenile idiopathic arthritis (JIA) is the most common cause of chronic arthritis in children. JIA is arthritis of unknown etiology that begins before the 16th birthday and persists for at least six weeks. JIA is a diagnosis of exclusion and other causes of chronic arthritis should have been excluded before calling a child as having JIA

[1–3]. JIA is not a single disease but rather a group of disorders as having chronic arthritis a common feature. Currently used International League of Associations for Rheumatology (ILAR) classification criteria divides JIA into seven subtypes as follows: oligoarticular (persistent or extended) JIA, enthesitis-related arthritis (ERA),

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rheumatoid factor (RF)-negative polyarticular JIA, RF-positive polyarticular JIA, systemic JIA, psoriatic arthritis and undifferentiated arthritis [1]. The most common types observed in developed countries are oligoarticular JIA, followed by RF-negative polyarticular type [4]. Oligoarticular type is also the most common subtype in our country but just followed by ERA [5, 6].

Cure is not an applicable term in JIA like in many of the rheumatic diseases. However, with the advent of newer treatment modalities remission with or without medication or clinically inactive disease are the main aims of the treatment by treat to target approach in JIA. Especially with the introduction of biologics to the treatment armamentarium of JIA, achieving remission earlier and preventing chronic sequel is more attainable than before [7–9]. Biologics are disease-modifying anti-rheumatic drugs (DMARDs) manufactured based on the cytokines that are involved in the disease pathogenesis. However, the major concerns with biologics are increased risk of infection, especially of tuberculosis and the development of malignancy. Herein, we present the experience of our pediatric rheumatology center with biologics in JIA.

MATERIALS AND METHODS

This retrospective observational cohort study was conducted in the pediatric rheumatology center of Kanuni Sultan Suleyman Training and Research Hospital between May 2010 and September 2017. All JIA patients that biologics were used were sequentially recorded into the registry system. To be included in this study, the patient had to have a diagnosis of JIA and classified according to the ILAR classification system [1], had to be regularly coming to follow-up visits that are made every 1–3 months and had to be using a biological agent for at least three months. Age, gender, JIA subtype, medications used, the clinical status of the patient at the time of enrollment, tuberculosis screening results, side effects observed under biologics were retrieved from the registry. All children in this study were examined in the last month of the study period to be more precise about the clinical status. To define JIA status at the time of enrollment, criteria for clinical inactive disease in select categories of JIA that was defined by Wallace et al. [10] was used. Clinical remission with medication was defined as an inactive disease for a minimum of six consecutive months while the patient is taking medication, and clinical remission without medication was defined as an inactive disease for a minimum of 12 consecutive months while the patient is off all anti-

TABLE 1. Subtype frequencies and the ratio of the biologic use in JIA subtypes

JIA subtype	Frequency in the JIA	Rate of biologic use
Oligoarticular (extended) JIA	17 (4.2%)	11/17 (64.7%)
RF-positive polyarticular JIA	14 (3.4%)	8/14 (57.1%)
Psoriatic arthritis	7 (1.8%)	4/7 (57.1%)
RF-negative polyarticular JIA	53 (13.0%)	22/53 (41.5%)
Systemic JIA	53 (13.0%)	21/53 (39.6%)
ERA	118 (29.2%)	32/118 (27.1%)
Oligoarticular (persistent) JIA	136 (33.6%)	24/136 (17.6%)
Unclassified arthritis	7 (1.8%)	1/7 (16.6%)

JIA: Juvenile idiopathic arthritis; RF: Rheumatoid factor; ERA: Enthesitis-related arthritis.

arthritis and anti-uveitis medications. All children in the cohort were screened for tuberculosis before the start of a biologic by tuberculin skin test (TST) and posteroanterior chest X-ray and by quantiFERON-TB Gold In-Tube test (QFT-GIT) in some. In children with a positive TST (≥ 5 mm), isoniazid (INH) prophylaxis was commenced and used for six months. Informed consent was taken from the legal guardians of the children. This study was approved by the local ethics committee (date: 03.01.2019, number: KAEK/2019.01.03) and was conducted according to the tenets of the declaration of Helsinki.

Statistical Analysis

Clinical and demographic characteristics were summarized by the mean and standard deviation for continuous variables and count and percent for categorical variables. Statistical analyses were performed using the SPSS software package for Windows (version 22.0; SPSS, Chicago, IL, USA).

RESULTS

The cohort in this study consisted of 123 children. There were 405 patients with the diagnosis of JIA during the study period. Thus, the rate of biologic use in JIA was 30.3%. The mean duration of follow-up of JIA patients that biologics was used was 34.6 ± 18.5 months. The cohort consisted of 67 males (54.5%) and 56 females (45.5%). The mean duration of biologics use was 17.3 ± 13.0 months.

Subtype frequencies of JIA patients the rate of biologic use are shown in Table 1. The most common sub-

types were persistent oligoarticular JIA (33.6%), enthesitis-related arthritis (29.2%), systemic JIA (13%) and RF-negative polyarticular JIA (13%). Extended oligoarticular JIA (4.2%), RF-positive polyarticular JIA (3.4%), psoriatic arthritis (1.8%) and unclassified arthritis (1.8%) were the subtypes with less common predominance. The rate of biologic use was the highest in extended oligoarticular JIA (64.7% of the cases), RF-positive polyarticular JIA (57.1%), and psoriatic arthritis (57.1%), followed by RF-negative polyarticular JIA (41.5%), systemic JIA (39.6%) and enthesitis-related arthritis (27.1%). Persistent oligoarticular JIA (17.6%) and unclassified arthritis (16.6%) patients were the cases that least commonly needed a biologic agent during the disease course.

One hundred and fifty-eight biologic agents were used in 123 patients (Table 2). In 78.8% of the patients, only one biologic agent was used and in 21.2% of the patients, two or more biologics were needed. Of 26 patients that needed ≥ 2 biologics, the first agent was discontinued due to side effects in three patients and in 23 of them due to inefficacy (Table 2). Only seven patients (5.6%) needed ≥ 3 biologics and three of them had RF-negative polyarticular JIA and four of them had systemic JIA that followed a polyarticular course during follow-up.

Isoniazid prophylaxis was used in 38 (30.8%) patients. Tuberculin skin test was applied to all patients before the initiation of biologics, and ≥ 5 mm was accepted as a cut-off point to start INH prophylaxis for presumed latent tuberculosis infection. Mean induration was 3.4 ± 5.1 mm. In 67 patients (54.4%), TST was anergic. In 17 patients (13.8%), induration was ≥ 10 mm. None of the patients had abnormal posteroanterior chest X-ray. Also, we have performed a QFT-GIT test in 51 (41.4%) patients before the start of biologics and only in two of them, test results were found to be positive; one of those patients' TST was 0 mm and the others was 13 mm. Thus, in 38 patients that INH prophylaxis was administered, only one of them was due to QFT-GIT positivity. None of the patients developed tuberculosis infection during the follow-up under biological treatment.

Adverse events were observed in 18.6% of the patients as recurrent uncomplicated upper respiratory tract infections being the most common. Two patients had an anaphylactic reaction to biologics (one with infliximab and one with tocilizumab), and one patient had a persistent rash under adalimumab. These were the three cases that needed to change the biologic due to side effect. Other transient side effects were neutropenia (1 patient), lym-

TABLE 2. The number, duration and discontinuation rate of the biologics

Biologic agent	Number of the patients	Duration of the use (months)	Discontinuation rate due to inefficacy or side effect
Etanercept	78 patients	13.5 \pm 8.1	26.9%
Adalimumab	36 patients	13.4 \pm 10.2	8.3%
Tocilizumab	25 patients	15.2 \pm 14.2	20%
Anakinra	14 patients	10.3 \pm 13.8	21.4%
Canakinumab	3 patients	17.6 \pm 13.3	33.3%
Infliximab	2 patients	7.0 \pm 7.0	50.0%

phopenia (2 patients), thrombocytopenia (2 patients), hyperbilirubinemia (1 patient), and hypertransaminasemia (1 patient). Also, two patients had hand-foot-and-mouth disease and three patients had varicella infections and all healed without sequela.

At the last control, 78.9% of the cases were in remission (70.8% of them had remission with medication and 8.1% of them were under remission without medication) and 21.1% (26 patients) of them were active despite biologic treatment. Of the 26 patients, eight had RF-negative polyarticular JIA, six had ERA, five had RF-positive polyarticular JIA, three patients had persistent oligoarticular JIA, two had psoriatic arthritis, and two cases had systemic JIA.

DISCUSSION

The findings obtained in this study suggest that biologics are safe and effective treatment options in JIA. Most of the side effects were transient, and only in three cases (2.4%) medication was changed due to side effects. Reactivation of latent tuberculosis infection is a major concern of biologics, especially in tuberculosis endemic countries like ours. Also, the method of screening for tuberculosis before the start of biologics is a debated topic. This study has shown that TST and posteroanterior chest X-ray seem to be enough for tuberculosis screen and ordering the QFT-GIT test does not provide more information over TST. Initiation of INH prophylaxis in patients with ≥ 5 mm TST seems to be a reasonable cut-off as we have not observed any tuberculosis infection during the study period.

Juvenile idiopathic arthritis is the most common rheumatic disease of the children. It is seen all over the

world, but subtype frequencies change by geography. While oligoarticular subtype and RF-negative polyarticular subtypes are the most frequent ones in the western countries, ERA and oligoarticular subtypes seem to be the most common ones in the developing countries [5, 6, 11]. Our large number of JIA cohort demonstrated that oligoarticular JIA is also the most common subtype in our country but just followed by ERA with nearly equal frequency to oligoarticular subtype.

The introduction of biologics has changed the life of children with rheumatic diseases also approaches of physicians to the treatment of rheumatic diseases by adopting a treat-to-target approach. The main target in JIA treatment is achieving remission as soon as possible, but in patients with long-standing disease achieving low disease activity is also accepted as a reasonable target [9]. Etanercept was the first approved biologic in JIA in 1999 [12]. Later, many studies with different biological agents have shown that biologics have improved both physical and functional outcomes and quality of life of the patients and also of the families [8, 13]. Adalimumab and tocilizumab were the second and third biologics that were approved to be used in JIA [13, 14]. Thus, in many studies about biologics in JIA etanercept, adalimumab and tocilizumab were the most commonly employed ones as in our study [11, 15]. As stated previously, JIA is not a single disease and has seven subtypes. Nalbanti et al. looked for predictors of early introduction of biologic treatment during the disease course, and they have found that polyarticular involvement was the most important risk factor for the necessity of biologics [16]. Our study has also shown that patients with polyarticular involvement needed higher rates of biologic usage during the disease course. Also, in this study, patients with polyarticular JIA and sJIA patients with polyarticular involvement were the groups that needed 3rd or 4th biologic agents.

The efficacy of biologics in JIA is indisputable, but every good thing comes with caveats. The major concerns of biologics are side effects that include infections and the development of malignancy. Reactivation of latent tuberculosis infection is also one of the main concerns in patients under biologic therapy. Screening for latent tuberculosis infection before the start of biologics is recommended in all patients [13, 17]. The basic procedures include posteroanterior chest X-ray and TST. The main issue with TST is that it has cross-reactivity with *Bacillus Calmette-Guerin* (BCG) vaccine and non-tuberculous mycobacteria and low sensitivity in patients

with the impaired cellular immune system [17, 18]. Interferon-gamma release assays (IGRAs), as QFT-GIT, the most commonly used one, measure *in vitro* interferon-gamma release by T cells following stimulation with *Mycobacterium tuberculosis* antigens. Some studies showed that IGRAs might work better than TST in detecting latent tuberculosis infection before the start of biologics in patients with rheumatic diseases [17–19]. Camlar et al. looked for TST and QFT-GIT assays in 39 children with JIA and 40 healthy children. TST was defined as positive ≥ 10 mm in children with JIA and ≥ 15 mm in healthy controls. TST was positive in 28% of children with JIA and 32.5% of healthy controls. QFT-GIT assay was positive in 5% of the patients. In two children with QFT-GIT positivity, one child had negative TST. The authors concluded that the combination of the QFT-GIT method with TST would provide successful diagnostic screening for latent tuberculosis infection [17]. Lee et al. from South Korea - in where the prevalence of tuberculosis is intermediate and BCG vaccination is mandatory at birth, just like our country - looked for TST and QFT-GIT results of 342 adult patients with rheumatoid arthritis or ankylosing spondylitis and TST was defined as positive ≥ 10 mm. TST was positive in 35.7% and QFT-GIT was positive in 30.1% of the patients. In QFT-GIT positive patients, 31.5% had negative TST. The authors started tuberculosis prophylaxis only to patients with QFT-GIT positivity and tuberculosis infection developed only in 1.5% of the patients with a median follow-up duration of 41.7 months. The authors concluded that QFT-GIT might be used instead of TST for diagnosing latent tuberculosis infection in patients before starting anti-TNF in countries where BCG vaccination is mandatory [18]. Pharmachild/PRINTO registry, the largest international registry, including 8274 JIA children from Europe, North America and Asia, reported 17 cases (0.2%) of tuberculosis under biologics. Also, in the same study, no case of tuberculosis was observed in 3990 German JIA children receiving biologics [11].

Patients with rheumatic diseases have reduced TST response secondary to inherent immune dysfunction due to underlying primary disease and also secondary to medications used [17, 20–22]. Barut et al. looked for TST response in 234 JIA children receiving biologics, and TST positivity (accepted as ≥ 5 mm) was observed in 41% of the children. Prophylactic INH treatment was administered to all children, and only one child developed tuberculosis infection during follow-up [21]. Brunelli et

al. from Brasil, a tuberculosis endemic country, looked for TST responses of 69 children with JIA on biologics and cut-off value was ≥ 5 mm. They started INH only in three children due to TST positivity and none of the patients developed tuberculosis infection with a median follow-up of 3.8 years [23]. In our study, we have also accepted TST cut-off for INH prophylaxis as ≥ 5 mm and none of the patients developed active tuberculosis infection for a mean follow-up of 17.3 months. QFT-GIT test is not available in most of the government hospitals and even in university hospitals in our country. We were able to study the QFT-GIT test in 51 patients in the cohort in a private laboratory and only in two patients, the test became positive. Only in one case, INH prophylaxis was administered due to the QFT-GIT test.

The overall frequency of adverse events is reported to be around 20% in the largest registry of biologics in JIA. Infections, gastrointestinal disorders and cytopenias were the most common ones [11]. In the meta-analyses of Aeschlimann et al. that included 19 trials on biologics in JIA, only 17 serious infections were reported, as varicella and bronchopulmonary infections the most frequent ones, among 810 children using biologics and 15 among 797 healthy controls. The authors concluded that serious infections were uncommon and not significantly increased among patients with JIA receiving biologics compared with healthy controls. Furthermore, the risk remained nonsignificant when different classes of biologics compared separately [24]. In our cohort, we have observed any adverse event in 18.6% of the patients and uncomplicated upper respiratory tract infections, varicella, transient cytopenias were the most common ones. Horneff et al. reported that in only 4.3% of 729 JIA children under biologics, biologics were discontinued due to intolerance and this ratio was 2.4% in our cohort. In the same study, discontinuation due to inefficacy was observed in 15.2% of JIA cases. In our study, this number was 19.6% and most of them were belonging to patients with polyarticular involvement or sJIA cases with the polyarticular course. The authors concluded that biologics in JIA were not only very effective but also very well tolerated [15]. Another important issue in biological drugs is the development of malignancies. Patients with JIA have increased risk of malignancy compared to their healthy peers, irrespective of treatment received [25]. Beukelman et al. conducted two studies about the risk of malignancy and biologics and the conclusion of two studies was that children with JIA had an increased rate of incident malignancy compared to children without

JIA. However, treatment with biologics did not appear to be further increasing the risk of malignancy [26, 27]. In our cohort, we did not observe any malignancy development or death under biologics.

The major limitations of our study are the low number of some biologic agents and relatively short follow-up time under biologics. The strength of our study comes from the inclusion of all types of JIA.

Conclusion

Our conclusion from this study is that biologics are safe and effective treatment options in JIA. In patients with polyarticular involvement and sJIA patients that follow polyarticular course biologic agents should be considered earlier during the disease course. Screening for tuberculosis with TST and chest X-ray and initiation of INH prophylaxis for six months when TST is ≥ 5 mm seems to be a reasonable approach to protect from tuberculosis infection before the initiation of biologics in JIA.

Ethics Committee Approval: The study was approved by local ethics committee (date: 03.01.2019, number: KAEEK/2019.01.03) and was performed according to the tenets of the declaration of Helsinki.

Conflict of Interest: No conflict of interest was declared by the authors.

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