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RISK OF INFECTION AND DISEASE ACTIVITY OF PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS TREATED WITH AND WITHOUT BIOLOGICS

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ABSTRACT – *Objective:* Juvenile idiopathic arthritis is the most common rheumatic disease children suffer from. Many questions arise regarding the risk of infection related to the disease and to the treatments with conventional and biological DMARDs. We aimed to assess the rate of infection in JIA patients treated with and without biologics and confirm the link between the infection and the disease activity.

Patients and Methods: The risk of infection was evaluated in 2 groups (biological vs. conventional DMARDs). JIA activity was assessed using JADAS-10, physician and parent VAS.

Results: Two minimal infections were noted under conventional DMARDs and 5 infections under biologics giving an infection rate ratio of 1.9. No correlation was found between the disease activity assessed by JADAS-10 and the risk of infection. The infection rate was higher in the biological group compared to the conventional DMARDs group (62.5% *vs.* 33%), but the difference was not statistically significant (p=0.6).

Conclusions: Our results suggest no significant difference in infection rates between JIA subjects treated with and without biologics. Larger scale studies of the relationship between infection rates, type of treatment and disease activity are needed.

KEYWORDS: Infection, Biologic DMARDs, Juvenile idiopathic arthritis.

INTRODUCTION

Juvenile idiopathic arthritis, previously known as Chronic Juvenile Arthritis (CJD), is the most common rheumatic disease children suffer from. It is defined by the presence of arthritis for more than 6 weeks in patients under 16 with no etiology[1]. Its prevalence ratio is between 3.8 and 400 out of 100,000 children. After excluding a large number of other etiologies, the diagnosis is made based on a set of clinical criteria[2]. There are 7 categories (subtypes) according to the International League of Rheumatology Associations (ILAR): systemic, oligoarticular, polyarticular without rheumatoid factor, polyarticular with rheumatoid factor, arthritis with enthesitis, psoriatic arthritis and undifferentiated arthritis[3]. The exact etiopathogenesis of different clinical diseases related to JIA is not fully understood. However, immunological predisposition (some cell-surface antigens such as HLA-B27 and HLA-DR4) and environmental factors (mainly infections) are the most relevant causes studies focus on[4,5]. The relationship between arthritis and infections is not as clear and understood for children as it is for adults[5]. Immunosuppres-

sive agents, frequently used for the treatment of JIA, as well as the disease itself can predispose children with JIA to an increased risk of infection[6-8]. In some cases, JIA can be clinically detected following enteric infections: Parvovirus B19, Rubella, Mumps, Hepatitis B virus (HBV), Epstein-Barr virus c(EBV), Chlamydophila pneumoniae and Mycoplasma pneumoniae infections. The study by Aslan et al[5] aimed to search for microorganisms which might be responsible for the pathogenesis of JIA (a total of 70 patients, 26 with primer JIA, 20 with recurrent JIA, 24 healthy control were included). Infection was detected in 39.13% of patients. They noticed that some microorganisms like Mycoplasma pneumoniae, Chlamydophila pneumoniae and C. Jejuni can trigger or worsen the clinical course of JIA cases. They also stressed on the importance of pre-diagnosis of microorganisms as well as adding specific antimicrobial therapy to the standard JIA therapy[5]. Another study was conducted in the Pediatrics Rheumatology Ward of Imam Khomeini Hospital in Tehran during the period 2001-2002 and included 50 patients with JIA. These patients were assessed serologically (IgM and IgG specific viral capsid antigens) for EBV infection and their response to therapy was evaluated. Ebstein Barr Virus (EBV) infection was detected in 44 (88%) patients: 33 cases, 6, 4 and 1 case in the polyarticular, pauciarticular, systemic and spondylitis group, respectively. Fifty four percent of EBV-positive patients with JIA did not respond to the classical therapy. They suggested EBV virus was involved in the pathogenesis of JIA and patients with EBV were in a greater risk of developing JIA[9]. A third study was conducted to evaluate the prevalence of recent parvovirus B19 infection in a cohort of 150 children (75 with acute arthropathy and 75 healthy controls) and to determine the prevalence of a JIA diagnosis. Parvovirus B19 IgM antibody was investigated in all patients who were followed up for a period of at least 6 weeks. The patients with chronic progression of joint complaints were followed for at least 6 more months to determine their evolution. Parvovirus B19 IgM was detected in 16 out of 74 patients (21.6%) with acute arthropathy *vs.* 3 out of 74 (4.1%) in the healthy group. The parvovirus B19 positive patients with arthropathy were more likely to become chronic and develop JIA than the IgM negative group with arthropathy. This study supports the hypothesis that for some patients, parvovirus B19 infection may be associated with the onset of JIA[10]. Many questions currently arise regarding the risk of infection related to the activity of the disease and to treatments with conventional and biologic DMARDs. The objective of our study was to assess the rate of infection in patients with juvenile idiopathic arthritis treated with and without biological antirheumatic drugs and to search for a correlation with the infection rate and the activity of the disease.

PATIENTS AND METHODS

This is a monocentric observational study involving 14 patients followed up for juvenile idiopathic arthritis in our unit. The patients were diagnosed using the International League of Associations for Rheumatology (ILAR) classification criteria for JIA. The socio-demographic, clinical and biological characteristics of the patients included in the study were collected. The vaccination status was not noted. The patients on biologic agents (bDMARDs) were studied in the biological group. The biologic agents used in our study were tumor necrosis factor alpha (TNF-α) inhibitors (etanercept, adalimumab, infliximab) and antibody against the IL-6 receptor (tocilizumab). The patients treated with conventional DMARDs in the « non-biological group ». The DMARDS include methotrexate, sulphasalazine, leflunomide, and cyclosporinea. The risk of infection was evaluated within the 2 groups. The activity of the JIA was assessed by the JADAS-10 score (Junevile Arthritis Diseas Score 10), the doctor VAS and the patient VAS (analog visual scale).

RESULTS

Our study included 14 patients with juvenile idiopathic arthritis: 4 children had a systemic subtype, 4 had a polyarticular subtype, 2 persistent oligoarticular subtype, an extended oligoarticular subtype and 3 arthritis with enthesitis. Patients' average age was 13.8 +/- 4 years with a sex ratio of 1. The clinical examination revealed an average joint index at 5.3 (0-14) and an average synovitis index at 1.3 (0-7). The inflammatory tests showed an average erythrocyte sedimentation rate at 32.3. JIA activity was assessed by the JADAS 10 (Juvenile Arthritis Diseas Activity Score) in average equal to 15.4 (9.2-22.6) (Table 1). The patients were divided in 2 groups: a group receiving conventional DMARDs (43%) and a group receiving biological antirheumatic drugs (57%). Two cases of minimal Ear Nose Throat (ENT) infections with conventional DMARDs have been reported. In the biological subgroup, 5 cases of infections were reported: a case of ENT infection, one of dental abscess, one of the urinary tract, one pulmonary tuberculosis and one case of severe varicella which required the hospitalization of a girl receiving biological treatment of type Infliximab (Table 2). In numerical terms, the rate of infection in the classical and biological DMARDs

Table 1. Sociodemographic, clinical characteristics of the population.

	Children with JIA (N=14)
Age[1]	13.8 y ± 4
Female sex[2]	7 (50%)
Joint Index[3]	5.3 (0-14)
Synovitis Index[3]	1.3 (0-7)
Erythrocyte Sedimentation Rate[1]	32.3
JADAS 10[1]	15.4 (9.2-22.6)
JIA subgroups	
systemic	4
polyarticular	4
persistent oligoarticular	2
extended oligoarticular	1
arthritis and enthesitis	3

1: Average and standard deviation; 2: Number and percentage; 3: maximum and minimum.

Table 2. Type of infection in the 2 JIA groups.

	Children JIA (N=14)	
	Classic DMARD	**Biologicals**
Varicella	-	1
ENT infections	2	1
Dental abscess	-	1
Urinary tract infection	-	1
Pulmonary Tuberculosis	-	1

groups were respectively 33% and 62.5%, and the infection rate ratio was 1.9 (95% CI, 0.2-24.7) for subjects in the biological *vs.* non-biological group. In addition, the average JADAS 10 score in our patients was 15.4 (9.2-22.6). No correlation was found between the activity of the disease evaluated by this score and the infection (the correlation was 0.223 (p = 0.465)). The infection rate was higher in the biological group compared to the conventional DMARDs group (62.5% *vs.* 33%), but the difference was not statistically significant (p=0.6) (Table 3).

Table 3. Infection rate in the 2 groups.

	Children JIA (N=14)	
	Classic DMARD group	**Biological group**
Number of patients	6	8
	2 (33%)	5 (62.5%)

DISCUSSION

In spite of the high benefit provided by biologic agents as well as standard disease-modifying anti-rheumatic drugs (DMARDs) in the treatment of JIA, these drugs might be associated with the risk of developing serious infections. Many studies are still evaluating this correlation, with conflicting results, in particular in children with JIA[11]. Infection rates vary considerably between different studies: the incidence of mild infections varies

between 8 and 97%[12,13] while the incidence of serious infections is low in all clinical trials involving JIA patients and varies between 0 and 9%[14,15]. Furthermore, our study suggests that there is no statistically significant difference in infection rates between subjects followed for JIA treated with and without biological antirheumatic drugs. The infection rate ratio was 1.9 (0.2-24.7) for subjects in the biological *vs.* non-biological group. Our finding corroborates with the results reported by the American study conducted by Walters et al[16] who have prospectively evaluated the rate of infection in two groups of JIA with and without anti-TNF. After a follow-up of 12 months, they noted that the average rate of infection/month was 0.29 in the anti TNF group and 0.24 in the non anti TNF group and that the ratio of the infection rate in the anti TNF group compared to non anti TNF group was 1.14 (Confidence Interval = 95%, 0.78-1.66 $p = 0.51$). No serious infection was reported in the 2 groups. The German BIKER register[17] also worked on the link between anti TNF agents and the risk of infection: 82% of the 3350 patients included in the study were under MTX and 56.6% were under biological treatments. 28 infections were noted (6 under MTX and 22 under biological treatments). The study revealed that the patients followed for JIA under MTX had a low infectious risk unlike the patients under biological treatments which have a slightly higher risk but without statistically significant difference. This finding was confirmed by the study conducted by Nagy et al[18]. Aygun et al[11] conducted a prospective study to investigate the risk of infectious complications of biologic agents in patients with JIA. Patients on biologic antirheumatic drugs were examined by a pediatric specialist every 2 months during a whole year. 57% of the patients developed an infection (upper respiratory tract infections were the most common). Only three patients developed serious infections (two pneumonia, one pleural effusion) and required hospitalization. Because of a higher corticosteroid need and concomitant immunosuppressive therapy, systemic JIA was the subtype mostly related to serious infections ($p < 0.001$). Other comparative studies are needed to better evaluate the safety of biologic agents in terms of infections. We have also investigated the potential relationship between the disease activity and the risk of infection, a relationship which has previously been studied for adults exclusively. In that regard, the activity of the Rheumatoid Arthritis disease can influence the risk of infection regardless of the therapeutic strategy[19]. Our study did not show any correlation between JADAS-10-assessing the JIA activity and the infection rate (the correlation was 0.223 ($p = 0.465$)). The German BIKER register has shown in a multivariate analysis that the risk of infection is high in patients on anti TNF and in patients with a high initial JADAS 10. Patients with an initial JADAS10 > 20 have 6.7 times higher risk of infection compared with patients with a JADAS10 < 10. The risk for patients having a JADAS between 10 and 20 remains slightly higher compared to those with JADAS < 10 with no statistically significant difference though[17]. Walters et al[16] also sought a correlation between the activity of the disease (evaluated by the CHAQ: Child Health Assessment Questionnaire and the VAS reported by the doctor/ patient) and the infectious risk and they noted that the increase in the CHAQ score and the VAS was correlated with the increase of infection rates. Therefore, JIA activity could increase the risk of infection for these patients regardless of immunosuppressive therapy[11]. However, the various studies conducted in this area have not clarified whether JIA patients are at risk of infections due to the disease itself (by immune dysfunction) or to the activity of the disease which could contribute in the absence of immunosuppressive therapy. Vaccination is a powerful mean to reduce the burden of infectious diseases in patients with JIA. Live attenuated vaccines are not recommended for extremely immunosuppressed patients, but non-live vaccines are generally considered to be safe and immunogenic[20,21]. Patients should be vaccinated, if possible, before starting a biologic therapy. For optimal immune protection, administration of inactivated vaccines should ideally be performed at least 2 weeks before starting immunosuppressive therapy. If therapy has already been initiated, it is recommended to wait for a stable phase with a low disease activity before vaccinating patients. This should be done in close collaboration with an experienced pediatric rheumatology center. In general, there is no need to interrupt biologic therapy[20,22]. As patients on immunosuppressive therapy have a higher risk of complications from pneumonia and influenza, they should receive the conjugate pneumococcal vaccine (no age restriction) and the polysaccharide pneumococcal vaccine (if over 2 years old), as well as a yearly inactivated influenza vaccine[22,23].

In addition, anti-TNF therapy as well as other biological agents and rheumatic diseases themselves have been associated with a greater risk of active tuberculosis[24,25].

Latent tuberculosis infection (LTBI) screening and short course INH primary prophylaxis before an anti-TNF treatment appear to be effective in preventing tuberculosis activation in JIA patients of a high TB risk country. However, more studies with larger cohorts and longer follow-up periods are necessary to confirm these findings[24,26].

Some authors consider the Tuberculin Skin Test (TST) as the most sensitive parameter to identify patients eligible for LTBI treatment[24]. Others recommend performing both TST and IGRA (interferon-gamma releasing assays) as screening tools to provide successful diagnosis screening for LTBI in JIA before starting a biologic treatment[27-30]. Our study has some limitations, namely the small size of our sample. Furthermore, this is a monocentric observational study, and therefore, the therapeutic strategy of the patients included in the study was not checked at inclusion. In addition, the comparison of the infectious risk between the various anti TNF agents as well as the impact of associated treatments, notably

corticosteroid therapy, were missing in our study. Unlike most studies which focused on evaluating the effectiveness of biological treatments on the activity of JIAs, our study is one of the few which aimed at assessing the infectious risk of these biological treatments and determining the relationship between the disease activity and the risk of infection.

CONCLUSIONS

Our results suggest that JIA patients under biological treatment have a slightly higher infectious risk than the patients under conventional DMARDs but without statistically significant difference. Also, no correlation was found between the disease activity and the infection. Large-scale studies focusing on the relationship between the disease activity, infection rate and the treatment strategy could shed the light on the potential mechanisms and predictors of infectious risk in patients followed for JIA.

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Authors contribution:
S. Bouayad performed the statistical analysis and the interpretation of the results and prepared the manuscript. M. Eddaoudi participated actively in the data collection. S. Rostom participated in article writing and critical review of the manuscript. B. Amine and R. Bahiri participated in the critical review of the manuscript. All authors read and approved the final manuscript.

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