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REVIEW

Biologics in juvenile idiopathic arthritis-main advantages and major challenges: A narrative review

Amra Adrovic, Mehmet Yıldız, Oya Köker, Sezgin Şahin, Kenan Barut, Özgür Kasapçopur

Department of Pediatrics, Division of Pediatric Rheumatology, Istanbul University-Cerrahpasa, Cerrahpasa Medical School, Istanbul, Turkey

ABSTRACT

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in childhood. The disease is divided in different subtypes based on main clinical features and disease course. Emergence of biological agents targeting specific pro-inflammatory cytokines responsible for the disease pathogenesis represents the revolution in the JIA treatment. Discovery and widespread usage of biological agents have led to significant improvement in JIA patients' treatment, with evidently increased functionality and decreased disease sequel. Increased risk of infections remains the main discussion topic for years. Despite the slightly increased frequency of upper respiratory tract infections reported in some studies, the general safety of drugs is acceptable with rare reports of severe adverse effects (SAEs). Tuberculosis (TBC) represents the important threat in regions with increased TBC prevalence. Therefore, routine screening for TBC should not be neglected when prescribing and during the follow-up of biological treatment. Malignancy represents a hypothetical complication that sometimes causes hesitations for physicians and patients in its prescription and usage. On the other hand, current reports from the literature do not support the increased risk for malignancy among JIA patients treated with biological agents. A multidisciplinary approach including a pediatric rheumatologist and an infectious disease specialist is mandatory in the follow-up of JIA patients. Although the efficacy and safety of biological agents have been proven in different studies, there is still a need for long-term, multicentric evaluation providing relevant data.

Keywords: Anakinra, canakinumab, etanercept, juvenile idiopathic arthritis, tocilizumab.

Juvenile idiopathic arthritis (JIA) is the most frequent chronic entity in pediatric rheumatology. Diagnosis of JIA is based on criteria which include disease onset prior to the age of 16 years and arthritis lasting longer than six weeks.[1-4] According to the International League of Associations for Rheumatology, JIA is divided into seven different subtypes: seropositive polyarticular JIA (pJIA), seronegative pJIA, systemic-onset JIA (sJIA), oligoarticular JIA, enthesitis-related arthritis, juvenile psoriatic arthritis and undifferentiated JIA.[5] The decision on initial classification is established regarding clinical features during the first six months of the disease course. The newly onset of additional clinical features further in the disease course defines the final subtype of the disease.[1-5] Definitions and subtypes of JIA are shown in Table 1.

The etiology of the disease is still not completely clear. A variety of endogenous and exogenous factors have been blamed for the disease appearance: genetic predisposition, epigenetic factors, environmental influences, infections etc. Underlying inflammation leads to clinical features of arthritis, resulting in pain and limited functional abilities.[1-4]

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Correspondence: Özgür Kasapçopur, MD. İstanbul Üniversitesi - Cerrahpaşa, Cerrahpaşa Tıp Fakültesi Çocuk Hastalıkları Anabilim Dalı, Çocuk Romatoloji Bilim Dalı, 34098 Fatih, İstanbul, Türkiye. Tel: +90 212 - 414 32 01 e-mail: ozgurkasapcopur@hotmail.com

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Table 1. International League of Associations for Rheumatology classification of subtypes of juvenile idiopathic arthritis[1,4]

JIA subtype	Definition and exclusion	
1. Systemic onset JIA	Fever ≥2 weeks and arthritis in ≥1 joint, plus at least 1 of the following: 1. Evanescent, non-fixed, erythematous rash, 2. Generalized lymphadenopathy, 3. Hepatomegaly and/or splenomegaly, 4. Serositis.	
2. Oligoarticular JIA	Arthritis in ≤4 joints during the first 6 months	(Exclusion criteria: a,b,c,d)
a. Persistent oligoarticular JIA	Arthritis in ≤4 joints throughout the disease course	
b. Extended oligoarticular JIA	Arthritis in >4 joints after the first 6 months	
3. Polyarticular JIA	Arthritis in ≤4 joints during the first 6 months.	(Exclusion criteria: a,b,c,d,e)
a. Rheumatoid factor +	RF positive for at least 2 times with interval of ≥3 months	(Exclusion criteria: a,b,c,e)
b. Rheumatoid factor -	RF negative	(Exclusion criteria: a,b,c,d,e)
4. Psoriatic arthritis	Arthritis + psoriasis or arthritis + at least 2 of the following: 1. Dactylitis, 2. Nail pitting or onycholysis, 3. Psoriasis in a first-degree relative.	(Exclusion criteria: b,c,d,e)
5. Enthesitis-related arthritis	Arthritis and/or enthesitis + at least 2 of the following: 1. Presence/history of sacroiliac joint tenderness and/or lumbosacral pain, 2. HLA-B27 positivity, 3. Arthritis onset in a >6 years old male patient, 4. Acute anterior uveitis, 5. History of 1 of the following in a first-degree relative: a. Ankylosing spondylitis, b. Enthesitis-related arthritis, c. Sacroiliitis with inflammatory bowel disease, d. Reiter syndrome, e. Acute anterior uveitis.	(Exclusion criteria: a,d,e)
6. Undifferentiated arthritis	Fulfills none of the subsets above or fulfills more than 2 subsets above.	

JIA: Juvenile idiopathic arthritis; RF: Rheumatoid factor; HLA: Human leukocyte antigen; Exclusion criteria for juvenile idiopathic arthritis: (a) psoriasis or a history of psoriasis in patient or first-degree relative; (b) arthritis in a human leukocyte antigen-B27-positive male beginning after sixth birthday; (c) ankylosing spondylitis; enthesitis-related arthritis; sacroiliitis with inflammatory bowel disease; Reiter syndrome; or acute uveitis or history of one of these or in first-degree relative; (d) presence of immunoglobulin M rheumatoid factor on at least two occasions at least three months apart; (e) presence of systemic juvenile idiopathic arthritis in patient.

The prevalence of JIA widely varies across the world. It is hard to report the exact general prevalence of JIA despite the number of JIA studies, due to the diversity of the utilized classification methods for years. A wide range of disease incidence and prevalence has been reported: 1-22 in 100,000 and 7-150 in 100,000,[6-8] respectively. A prevalence of chronic arthritis in childhood has been reported as 64 in 100,000 in a study from Turkey.[9] On the other hand, on the other side of the word, the prevalence of JIA has been reported as high as 400 in 100,000 in a study from Australia.[10] Such a wide range of disease prevalence between different regions supports the influence of genetic predisposition with contribution of environmental factors on JIA development.

The etiopathogenesis of the disease is not fully explained yet. There are a few theories of which each seems to contribute to the disease pathogenesis. The theory of immunogenic mechanisms developed secondary to various genetic and environmental factors is the most widely accepted. It is thought that external triggers (e.g. infections, traumas or stress) induct the inflammatory process that results with clinical signs of inflammation and mandatory arthritis accompanied with systemic features such as fatigue, fever or rash.[1-7] The topic of gut microbiota as a potential causative factor for autoimmune and inflammatory conditions has become popular in recent years.[11] Trigger-induced T-lymphocytes and secreted cytokines represent the main mediators of the underlying inflammation.[1-4,12]

Chronic inflammation of affected joints leads to several complications that may limit patients' functionality and daily activities. Thus, the main goals of treatment are to control pain, preserve functional activity, induce remission, and disable disease complications. The ideal treatment would

be the one that is able to achieve these goals in the most possible low doses and during the most affordable treatment period. In accordance with the major postulate of "primum non nocere", the used drugs should be safe and tolerable, without possible risk for additional disease complications.

Medical treatment of JIA is divided into two main groups: non-biological medical treatment and biological medical treatment. The first group encompasses non-steroidal anti-inflammatory drugs (e.g. ibuprofen, indomethacin, tolmetin, naproxen), corticosteroids, and disease modifying anti-rheumatic drugs (DMARDs) (e.g. methotrexate, sulphasalazine, leflunomide, cyclosporine A). The efficacy and safety of non-biological medical treatment have been shown in many studies before.[7,13-16] Despite the principally safe and efficient usage of mentioned drugs in JIA treatment, there has always been a certain percentage of patients with ongoing disease activity, uncontrolled inflammation, and significant disease complications.

Emergence of biological therapeutics targeted to specific pro-inflammatory cytokines responsible for the pathogenesis of JIA (interleukin [IL]-1, IL-6, and tumor necrosis factor [TNF]) represents a revolution in the JIA treatment. Usage of biological agents in JIA treatment during the last 15 years has led to significant improvement in JIA patients.[1-4] In the current biological era, number of JIA patients with inactive disease and/or minimal disease activity increased while the percentage of joint damage decreased.[13,17-19] However, we must not forget to look at the reverse of the medal. The nature of the activity of biological drugs and their ability to block important immunological pathways rise concerns regarding their safety and possible complications (e.g. infections or malignancy).[20-23] The relatively short duration of the usage of biological agents raises some questions that may be answered in the future.

Given the data mentioned above, the aim of this review is to sum up the data on JIA, focusing on biological treatment. We sought to collect up-to-date data on the efficacy and safety of biological drugs used in treatment of JIA patients.

The preparation of this manuscript was carried out according to the recommendations included in reviews for writing a narrative biomedical paper.[24,25]

BIOLOGICAL AGENTS

Mechanism of action and main characteristics

Biological agents represent a relatively new treatment strategy with great expectations in patients with JIA, particularly for those unresponsive to conventional treatment including steroids and non-biological DMRADs. A number of studies have proven the efficacy of biological agents in patients with JIA. On the other hand, their mechanism of action gives rise to a great concern regarding the risk of infections. Bearing on mind the increased frequency of bacterial infection in JIA patients in general, it is still disputable whether biological drugs contribute to increased infection risk in this group of patients.

Biological agents used for the treatment of JIA are shown in Table 2.

Etanercept

Etanercept represents a fusion protein of the extracellular ligand-binding part of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFR) linked to the fragment crystallizable (Fc) portion of human immunoglobulin (Ig) G1. The molecule binds to soluble TNF-alpha (α), consequently decreasing the downstream TNFR-mediated signaling. Etanercept is a biological drug with proven efficacy and safety in patients with JIA, particularly for those with pJIA subtype.[23,26-32] A study by Prince et al.[33] including the Dutch national registry for JIA patients showed the efficacy and safety of etanercept not only in the treatment of pJIA patients, but also for patients with systemic JIA and other disease subtypes. The drug is used at a dose of 0.8 mg/kg/week.[13,17,26,27] Drug reactions are uncommonly reported, in general. Mild infections that do not require hospitalization are the most commonly reported drug reactions. Among the non-infectious adverse events, local skin reactions at the site of injection are the most frequently reported.[26-28,30-32] Apart from frequent, mild, injection-site reactions, the most frequent adverse events among 95 JIA patients treated with etanercept were neuropsychiatric manifestations observed in 30 patients (23.6%).[27]

Table 2. Biological drugs used in treatment of juvenile idiopathic arthritis[1,2,5,12]

Drugs	Mechanism of actions	Dose
Etanercept	TNF suppression, fusion protein TNF receptor suppression	0.8 mg/kg/week or two times a week 0.4 mg/kg (maximum 50 mg/week)
Infliximab	TNF suppression, anti-TNF monoclonal chimeric antibody	5-10 mg/kg/month (maximum 200 mg/month)
Adalimumab	TNF suppression, anti-TNF monoclonal antibody	<30 kg: 20 mg/every 2 weeks (24 mg/m^2) >30 kg: 40 mg/every 2 weeks
Anakinra	IL-1 receptor antagonist	2-10 mg/kg/day (maximum 200 mg/day)
Canakinumab	Anti IL-1β monoclonal antibody	<40 kg: 4-6 mg/kg/4-8 weeks >40 kg: 150-300 mg/dose/4-8 weeks
Rilonacept	IL-1 suppression; soluble fusion protein	2.2-4.4 mg/kg/week
Tocilizumab	IL-6 receptor antagonist	<30 kg: 12 mg/kg 2-4 weeks >30 kg: 8 mg/kg 2-4 weeks (maximum 400 mg/dose)
Abatacept	T-cell co-stimulator; soluble fusion protein	10 mg/kg/4 weeks + (maximum dose 500 mg)
Rituximab	CD20 antigen suppression	375 mg/m^2/weeks, for 4 weeks (maximum dose 500 mg)

CD: Cluster of differentiation; IL: Interleukin; TNF: Tumor necrosis factor.

Infliximab

Infliximab is a chimeric monoclonal IgG1 antibody consisting of two parts: human constant and murine variable regions. Unlike the other anti-TNF agent (namely, etanercept) that binds only to soluble subunit, infliximab binds to both the soluble part and the membrane-bound precursor of TNF-α. Consequently, it interrupts the interaction between TNF-α and its receptors and cause lysis of cells that produce TNF-α.[1-3] In clinical trials, infliximab led to reduction of features of inflammatory diseases and caused a remission in patients who were unresponsive to first-line treatment options. The standard dose of the drug is 3-6 mg/kg/4-8 weeks (maximum dose 200 mg). It is indicated for the treatment of various pediatric inflammatory disorders such as JIA, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn's disease, ulcerative colitis, and uveitis etc.[1,13,23,34-36] Additionally, the frequency of severe and opportunistic infections were unremarkable in studies among patients treated with infliximab. However, allergic reactions during the intravenous (IV) infusion of infliximab appear to be slightly more common compared to other TNF blockers.[13,19,20]

Adalimumab

Adalimumab is a fully humanized monoclonal antibody targeting TNF-α and inhibiting its interaction with the p55 and p75 cell surface TNFRs. The usual dose of adalimumab is 24 mg/m^2 15 days (maximum 40 mg). Adalimumab is administered subcutaneously (SC), used in the treatment of juvenile rheumatoid arthritis (RA), uveitis, and other chronic debilitating diseases mediated by TNF.[23,37,38] Combined usage of adalimumab with non-biological DMARDs (namely methotrexate) enhances the drug efficiency.[37-39] According to German Biologics Registry, adalimumab is highly effective in children and adolescents with inflammatory conditions. Moreover, the treatment with adalimumab is safe and efficient in patients with JIA.[2,37-40] Apparently, adalimumab was well tolerated, efficient, and safe in young patients with pJIA aged two to four years and those older than four with <15 kg.[41] Seven-Year Interim Results from the STRIVE Registry showed that adalimumab was well tolerated and efficient in the majority of treated children with pJIA. No deaths, malignancies, active TBC, demyelinating disorders or congestive heart failure were reported during 1,855.5 patient-years of observation time in pJIA patients treated with adalimumab.[40] The other relevant register for biologics, The Dutch Register, showed that adalimumab and infliximab were equally effective as a second line therapy in JIA patients (other than systemic disease subtype) who failed to respond to etanercept.[42]

Anakinra

Anakinra is a recombinant human IL-1 receptor antagonist (IL-1Ra). It binds competitively to the IL-1RI, thereby inhibiting the action of elevated levels of IL-1. Anakinra is administered SC in doses of 2-10 mg/kg/day (maximum 200 mg). Multicentric studies showed the efficacy and safety of anakinra in sJIA patients. According to results from the Dutch National ABC registry, anakinra is superior to TNF-α blockers in sJIA patients.[42] It is associated with normalization of blood gene expression profiles and de novo induction of interferon signature in patients with sJIA.[43] The injection site reaction represents the most common adverse reaction that could occasionally make its usage difficult. Still, it is a well-tolerated and easy applicable drug with proven efficacy in sJIA patients.[13,29,42]

Canakinumab

Canakinumab is a recombinant, human anti-human-IL-1 beta (β) monoclonal antibody that belongs to the IgG1/kappa (κ) isotype subclass. It binds to human IL-1α and disables its proinflammatory activity by interrupting its interaction with IL-1Rs. However, it does not bind IL-1α or IL-1ra.[43]

Clinical trials reported safe and effective usage of canakinumab in sJIA patients. Its main advantage over the other anti IL-1 treatment option (anakinra) is its lower frequency of usage (once per months), compared to anakinra's daily injections, which are often poorly tolerated by pediatric patients.[43-46] The recommended dose is 4 mg/kg/day for children <40 kg and 150 mg/day for children >40 kg every four-eight weeks.[1,13] When evaluating the risk for infections, a slightly higher frequency of mild infections has been reported in patients compared to placebo.[29]

Tocilizumab

Tocilizumab is a recombinant, humanized, anti-human IL-6R monoclonal antibody. It is indicated for the treatment of active pJIA and sJIA patients with inadequate response to non-biological DMARDs. The recommended dose is 12 mg/kg in patients <12 kg and 8 mg/kg in patients >12 kg every two-four weeks.[19] In a number of studies, tocilizumab was reported as efficient and safe in severe, persistent sJIA and pJIA patients. Apart from controlling disease activity in sJIA patients, tocilizumab has been reported to have therapeutic benefits in disease complications including secondary amyloidosis.[47-51]

Tocilizumab was approved for IV injections in the treatment of patients with sJIA aged two to 17 years. Recently, tocilizumab treatment was investigated in sJIA patients younger than two years in an open-label phase 1 trial. The mentioned study showed that tocilizumab in a dose of IV 12 mg/kg administered every two weeks provided pharmacokinetics, pharmacodynamics, and efficacy in sJIA patients younger than two years compared to those in patients aged two to 17 years. Moreover, safety of this treatment modality was comparable except for a higher incidence of serious hypersensitivity events in patients younger than two years.[48] For several years, tocilizumab has been available in a SC formulation, which provides its more comfortable usage and increases the quality of patients' life. Several clinical trials have shown the safety and efficacy of SC tocilizumab among adult patients with RA.[52,53] As far as we know, currently, there are no reports on the results of switching from IV to SC form of tocilizumab in patients with JIA. However, there are some reports on usage of SC tocilizumab among patients with uveitis with contradictory results.[54-56] Quesada-Masachs et al.[54] reported four cases with JIA-associated uveitis who were treated with SC tocilizumab after they reached disease remission by IV drug form. All of the four cases experienced disease flare (ocular and/or joint) during the first few months of SC tocilizumab treatment.[54]

It should be kept in mind that some infections may be underestimated and may remain undiagnosed in patients treated with tocilizumab, due to its ability to affect the level of acute-phase markers and to inhibit systemic features of infection (fever).[13,29]

Abatacept

Abatacept is a soluble fusion protein, with ability to link to the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 and to the modified Fc (hinge, CH2, and CH3 domains) portion of human IgG1. The drug acts as a selective co-stimulative modulator and inhibitor of T lymphocytes. The drug is used as injections at a dose of 10 mg/kg/monthly. It is

suggested as a second line therapy in patients with moderately to severely active pJIA, unresponsive to non-biological DMARDs and anti-TNF agents. Except for mild infections, SAEs have not been registered in patients treated with abatacept.[13,29,57]

Rituximab

Rituximab is a chimeric murine/human monoclonal antibody directed against the cluster of differentiation 20 antigen on the surface of B lymphocytes. The proposed dose of the drug is 375 mg/m^2 for three or four doses. At the moment, the drug is indicated in patients with RA, granulomatosis with polyangiitis and microscopic polyangiitis and in some non-rheumatologic conditions (non-Hodgkin's lymphoma). In pediatric patients, it is used as off-label in patients with systemic lupus erythematosus. There are a limited number of studies regarding the usage of rituximab in JIA patients. A single study investigating the efficacy and safety of repeated course of rituximab in patients with different forms of JIA that were refractory to anti-TNF agents (infliximab) and routine immunosuppressive therapy has been published.[51] This study showed the efficacy of rituximab in patients with severe pJIA and sJIA, refractory to other non-biological and biological agents.[58]

It is important to note the mandatory vaccination for encapsulated bacteria prior to rituximab treatment.[13,59]

Adverse effects

Infections

Discovery of biological agents and their expanding usage have led to significant benefits in rheumatologic conditions, in general. On the other side, it has raised a number of questions and discussions regarding the risk for infections. Although biologics have been used for more than 20 years, debates about their association with increased risk for opportunistic and community-acquired infections continue. The majority of data come from studies among adults while studies in pediatric population are scarce.[59-61]

The increased risk for infections among JIA patients has been reported independently from biological usage. It is considered that the disease itself bears an increased risk for infections, due its pathogenesis.[61] Consequently, the adverse events (particularly infections) of biologics in JIA patients should be carefully monitored and interpreted. It is generally discussed that the increased frequency of infections arises from multiple factors, including pathogenesis of the disease, immunosuppressive treatment (both biological and non-biological), and socio-economic factors. Moreover, data from a study by Beukelman et al.[62] suggest that the use of steroid-sparing treatment strategies may reduce the risk of serious infections in children with JIA, regardless of the usage of biologics, emphasizing the significance of steroids in the development of infections.

Etanercept, adalimumab, infliximab, anakinra, canakinumab, and tocilizumab are the most commonly used biological agents in childhood rheumatic diseases. The recommendations for safety monitoring of patients treated with TNF-α inhibitors include evaluation of basic biochemical parameters and screening for TBC initially (prior to initiation of agent) and approximately once per year during the follow-up.[62,63] There are two main studies that represent the major source for the data of efficacy and safety of biologics in pediatric population: the German BIKER and the Dutch registries.[33,60]

The rate of serious infections reported in the German Biologics Registry for Pediatric Rheumatology was low. At the same time, treatment with biological agents (etanercept and/or adalimumab) was associated with slightly increased risk for serious infections, compared to patients treated only with methotrexate. The highest rate of 13.5 per 1,000 patient-years occurred in patients with adalimumab monotherapy, followed by etanercept+methotrexate combination (9.8 per 1,000 patient-years), adalimumab+methotrexate combination (7.6 per 1,000 patient-years) and etanercept monotherapy (5.2 per 1,000 patient-years). The lowest rate of serious infections occurred in those treated with methotrexate monotherapy without a biological agent (1.6 per 1,000 patient-years).[60]

Data from the Dutch registry also reported the safety of etanercept among patients with JIA. During 312 patient-years of etanercept use, 65 adverse effects (AEs) were reported. SAEs occurred in nine patients (the rate was 0.029 per patient-years).[33]

In another study among JIA patients treated with biological agents (84.7% were treated with anti-TNF agent), only three serious infectious events were reported during the one-year follow-up. In the same study, the frequency of infection was lowest in patients treated with etanercept and highest with those treated with infliximab. The authors concluded that changes in the immune system in JIA patients may increase the risk of serious infection, regardless of the biological treatment used, and that these drugs can be used safely in the decision-benefit balance.[21]

In another meta-analyses of serious infections among JIA patients treated with biologics, serious infections were uncommon and not significantly increased regardless of the subtype of the disease and the type of biologics.[64] In the mentioned analysis of 19 trials accounting for 21 individual studies (11 for TNF-α inhibitors [n=814 patients], three for IL-6 inhibitors [n=318], six for IL-1 inhibitors [n=353], and one for selective T-lymphocyte costimulation modulators [n=122]), 32 serious infections were reported: 17 among children receiving biological agents and 15 among children in the control group. The incidence rate of serious infection was 5.56 per 100 patient-years in the biological agents group compared with 4.69 per 100 patient-years in the control group.[64]

In a meta-analysis evaluating the efficacy and safety of biological agents in systemic JIA patients, canakinumab and tocilizumab statistically significantly increased the risk of AEs compared with rilonacept. Also, tocilizumab statistically significantly increased the risk of AEs compared with canakinumab. However, post hoc analysis of AEs-evaluated as the total number of events per total patient-days (where anakinra was eligible for inclusion)-showed that rilonacept statistically significantly decreased the risk of AEs compared with placebo, whereas anakinra, canakinumab, and tocilizumab did not differ from placebo.[65]

Similarly, Amarilyo *et al.*[66] reported no significant difference in the frequency of serious infections in patients with pJIA using different biological agents (etanercept, adalimumab, abatacept, anakinra, and tocilizimab).

In various studies, the most common infections detected during the use of anti-TNF agents were upper respiratory tract infections, pneumonia, cellulitis, abdominal abscess, and varicella infections.[66-71]

Opportunistic infections, including TBC, are rarely reported. Herpes zoster is the main specific infectious agent reported in studies.[29]

Based on data from the literature, the usage of biological agents, which has been shown to be effective in reducing the morbidity and mortality of rheumatologic diseases in childhood, is of great importance for the management of rheumatic diseases. Careful monitoring of children under biological treatment for infections is of paramount importance. A number of studies, systemic reviews, and meta-analyses reported the acceptable safety of biologics in pediatric population.[29] Except for the mild upper-respiratory tract infections, there are no certain arguments for increased risk of SAEs (including severe infections that require hospitalization) among pediatric patients treated with biologics.[21,29,33,60,64,65]

Tuberculosis

Despite the well-organized worldwide vaccination program, TBC remains one of the commonest general infections, particularly in endemic countries. Immunosuppression, due to disease nature and/or secondary to used treatments, represents the additional factor that increases the risk for reactivation of latent TBC in JIA patients. Therefore, the collaboration between rheumatologist and infectious diseases specialist is of crucial importance in management of JIA patients, particularly those treated with biological agents. Close monitoring of patients using biological agents regarding the signs of latent/manifest TBC infection is highly recommended. Several guidelines suggest detailed evaluation for a history of contact to a TBC patient. According to the American Academy of Pediatrics Red Book, an initial tuberculin skin test (TST) or interferon gamma release assay (IGRA) should be performed in children before initiation of immunosuppressive therapy, including prolonged steroid administration, use of TNF-α antagonists, or other immunosuppressive therapy.[72,73] Previously recommended annual screening of children at low risk of TBC with an initial negative TBC test has been accepted as inappropriate according to 2013 Update of the 2011 American College of Rheumatology Recommendations for

the Treatment of Juvenile Idiopathic Arthritis.[19] It has been recommended that patients with an initial negative TBC test prior to starting a biological agent have TBC screening repeated at any point if their risk of TBC changed to moderate or high, as determined by regional infectious disease guidelines.[19] However, repeat routine testing for TBC is not recommended in children who remain at low risk during the immunosuppressive treatment. Only patients with history of exposure or local contact, which is suggestive for exposure, should undergo re-evaluation by the TST and/or IGRA.[72,73]

The TST and chest X-ray should be routinely performed during the follow-up of patients.[74-76] On the other side, the relevance of TST as a TBC screening method is disputable. It should not been forgotten that different host factors could influence the TST results (young age, poor nutrition, immunosuppression).[72] There are some studies reporting the possible irrelevance of TST in patients treated with biological agents.[75-78] Barut et al.[78] reported that in JIA patients under biological treatment, TST was significantly lower compared to the control group. Consequently, TST alone seems inadequate for recognition of latent TBC infection in JIA patients. The IGRA represents the more reliable option but currently is not indicated in children younger than five years.[73]

Prophylactic treatment includes a nine-month course of isoniazid (INH). Alternatively, rifampicin could be used with shorter treatment duration of four months.[72,79,80] Previously ceased anti-TNF treatment should be re-started after one month of INH prophylaxis.[79-81] In a study from Turkey among 144 JIA patients treated with anti-TNF agents, seven patients (4.8%) were treated with INH prophylactically due to positive TST, which was ≥10 mm and only one patient (0.69%) required anti-TBC treatment since he had positive QuantiFERON-TB test while on INH prophylaxis.[20] This frequency is slightly lower compared to data from a previous study from Turkey by Cagatay et al.,[82] who reported the rate of TBC as 0.85% in patients under anti-TNF treatment.

Malignancy

The relationship between chronic autoimmune inflammatory diseases and malignancy is an issue that has been a topic of discussion for years. Chronic inflammation and immune dysregulation as a main pathogenic mechanism of disease (both RA and JIA) play a possible role in development of malignancies.[83-87] The increased incidence of certain types of malignancy in adult patients with RA and its association with high disease activity have been reported. Malignancy rates in adult RA patients have been evaluated in a number of clinical trials and attention has been drawn to a significant relationship between increased lymphoma incidence and the disease activity.[83,84] The United States Food and Drug Administration gave out a warning in 2008 about the possible association between the use of TNF blockers and the development of malignancy in children and young adults.[87] This has led to the idea that the disease modifying and immunosuppressive agents used in the treatment of the disease may also predispose to malignancy. However, a number of limiting factors such as voluntary reporting of the patients, neglect of ethnicity and family history, and the fact that the data were obtained regardless of the treatment duration and dose make the results of the mentioned studies unconvincing. Moreover, the contribution of concomitant medications and the influence of the disease activity need to be further elaborated. At the same time, a certain number of studies among JIA patients reported controversial results.[86,88-90] According to the data from Swedish population-based registers, a significantly higher risk of malignancy among biologic-naïve patients with JIA has been identified during the last 20 years compared with the general population. This risk observed in patients with JIA who have had no exposure to biological therapy has implications for the interpretation of cancer frequency in patients with JIA treated with new therapeutic modalities.[86] Similarly, Nordstrom et al.[88] found a nearly three-fold increased risk of cancer in biologic-naïve JIA patients compared to matched controls.

A multicentric study from Canada reported only one case of malignancy among 1,834 JIA patients during the mean follow-up period of 12.2 years. Accordingly, the risk for malignancy has not increased, at least in the initial years following the diagnosis of JIA.[89]

In conclusion, JIA is the common chronic rheumatic entity in childhood. Discovery and introduction of biological agents represent a

revolution in JIA treatment, leading to significant improvement in treatment response and patients' quality of life. Despite a certain number of studies reporting the efficacy and safety of biological agents in children, the risk for infections has remained as the most frequently discussed topic over the recent years. The collaboration between rheumatologists and infectious disease specialists is mandatory during the follow-up of JIA patients under biological treatment. Current data from the literature report no certain association between biological agents and malignancy. Still, there is a striking need for prospective, long-term multicentric studies that may reveal more convincing data regarding the safety of biological treatment.

Take-home messages

1. Biological agents represent a significant step-forward in JIA treatment with evident efficacy in disease control and prevention of disease complications.
2. Except for the mild upper-respiratory tract infections, there are no certain arguments for increased risk of SAEs (including severe infections that require hospitalization) among pediatric patients treated with biologics.
3. Negativity of TST and IGRA tests does not exclude the latent and/or active TBC of infections in patients treated with biologics.
4. There is no evidence of any association between biologics and malignancy in pediatric patients.
5. Treatment choice should be made in accordance with relevant treatment guidelines while the physician should always establish the final decision respecting the individual circumstances of each patient.

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