

# Treatment in juvenile rheumatoid arthritis and new treatment options

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## Abstract

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of the childhood with the highest risk of disability. Active disease persists in the adulthood in a significant portion of children with juvenile rheumatoid arthritis despite many developments in the diagnosis and treatment. Therefore, initiation of efficient treatment in the early period of the disease may provide faster control of the inflammation and prevention of long-term harms. In recent years, treatment options have also increased in children with juvenile idiopathic arthritis owing to biological medications. All biological medications used in children have been produced to target the etiopathogenesis leading to disease including anti-tumor necrosis factor, anti-interleukin 1 and anti-interleukin 6 drugs. In this review, scientific data about biological medications used in the treatment of rheumatoid arthritis and new treatment options will be discussed.

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**Keywords:** Adalimumab, anakinra, anti-TNF agents, pediatric rheumatology, etanercept, infliximab, juvenile idiopathic arthritis, kanakunimab, treatment

## Introduction

Severe disabilities and morbidity may occur during the course of juvenile idiopathic arthritis (JIA) which is one of the most common chronic diseases in the childhood. The disease is manifested with prominent peripheral joint involvement. Chronic inflammation of the joints markedly limits the patient's mobility and productivity in daily life. The cause of these changes in the joints is the inflammatory process which is present in the patients and which is very difficult to control. The cause of this inflammatory process is inflammatory cytokines including TNF-alpha, interleukin 1 and interleukin 6 which are released in excess. Therefore, these patients who are diagnosed with JIA should be treated rapidly and efficiently (1-3).

As in all rheumatic diseases treatment of JIA requires a team work. A pediatric rheumatologist, physiotherapist, ophthalmologist, orthopedician, pediatric psychiatrist and the patient's family should actively participate in this team. The primary objective in the medical dimen-

sion of treatment is alleviation of pain, inhibition of disease activity and recovery of range of motion which is limited. In the last 10-15 years, the efficiency and feasibility of many drugs has been demonstrated in detail owing to increased number of randomized-controlled studies in the area of pediatric rheumatology. The objective of JIA treatment, the drugs used in treatment and how the different subgroups of these drugs are used will be discussed below (1-3).

## What is the goal of treatment and which methods are used to evaluate the results of treatment?

The primary aim of treatment in juvenile idiopathic arthritis is the suppression of clinical symptoms. Clinical suppression means absence of significant inflammatory disease activity. Although the primary aim is suppression, low disease activity may also be accepted especially in chronic disease. The drug treatment should be adjusted at least every three months until the objective is achieved. The disease activity should be monitored regularly (every 1-6 months). In the follow-up, the disease activity measurement tools which have been shown to

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be valid should be used. In addition to disease activity measurements, structural and functional changes should also be considered. The target treatment objective should be pursued throughout the disease. Factors related with the disease, conditions which increase the disease and drug risks may affect the disease activity tool to be selected and the treatment objective. The patient and his/her family should be informed about this process in detail (4-7).

In our clinical practice, different measurement tools are used to evaluate the treatment results. Definitions including exacerbation, minimally active disease, inactive disease and clinical suppression are used to define activity. Different validity methods have been developed and standardized in the last 10-20 years to evaluate and compare the treatment results in juvenile idiopathic arthritis (3-7). The "American College of Rheumatology Pediatric" (ACR pedi) criteria used for this purpose is a 6-item assessment scale which is applied in combination. The "American College of Rheumatology Pediatric" response is very important especially in evaluation and pursuing of treatment response. The "American College of Rheumatology Pediatric" response was insufficient in comparing the absolute response between the patients, in measurements during active disease and in comparing the studies (4-7). The Juvenile Arthritis Disease Activity Score (JADAS) which is another measurement method used in assessment of treatment outcomes provides continuous assessment of the treatment response, but the limit for defining active disease has not been understood clearly and it includes inadequacies in assessment of oligoarticular JIA (Table 1) (5-10).

#### **Non-biological drugs used in treatment of juvenile idiopathic arthritis**

Among the drugs which constitute the base of medical treatment of juvenile idiopathic arthritis, non-steroid antiinflammatory drugs (NSAID) are the most commonly used drugs. The most widely used NSAIDs include ibuprofen, indomethacin, tolmetin and naproxen sodium. These drugs are primarily used in children below the age of 12 years. These drugs decrease pain by analgesic effect at low doses, but have antiinflammatory effect at higher doses. In the first 1-3 days of treatment, a response in the form of decreased pain is obtained (1-3, 11).

Since NSAIDs are mostly not efficient alone in treatment, other long-acting and more potent antiinflam-

matory drugs are required. Studies have proven the efficiency of sulfasalazine especially in arthritis related with oligoarthritis and enthesitis. Therefore, they are frequently used in patients with arthritis related with oligoarthritis and enthesitis. Response to treatment is obtained at the end of 6-8 weeks. Side effects include allergic reactions, bone marrow suppression, gastrointestinal complaints, reversible decrease in sperm count, hepatic and renal side effects. It is not recommended to be used in systemic JIA, since the risk of side effects is increased. The initial dose is 10-20 mg/kg/day and the dose is increased to 30-50 mg/kg/day in weeks (1-3, 11-14).

Methotrexate has improved the disease course significantly in JIA as well as in rheumatic arthritis. It is a long-acting drug with few side effects and its efficiency in treatment of juvenile idiopathic arthritis has been proven. At low doses, it shows antiinflammatory action by inhibiting interleukin-1 production and many cellular functions. The treatment dose is 0.5-1 mg/kg/week. The treatment response does not change above this dose. It may be administered orally, subcutaneously and intramuscularly. Most patients give response to treatment in the first 2-3 weeks. However, response to treatment may sometimes be delayed. It is absorbed rapidly, when taken on an empty stomach. The most important side effects of methotrexate which is used as weekly doses are related with the liver and bone marrow. Therefore, side effects should be monitored by repeating liver enzymes and complete blood count every 2-3 months. Addition of 1mg/kg/day folic acid or folic acid is recommended to decrease the effects on the bone marrow and control the side effects including nausea, oral ulcers and moderate hair loss (12). However, it should be kept in mind that folic acid may decrease the effect of methotrexate.

Corticosteroids are the most efficient drugs among the antiinflammatory drugs. However, their use is limited because of abundant side effects and inability to prevent destructive joint damage markedly. Intraarticular steroid administration is substantially beneficial in oligoarticular type disease especially in large joint involvement manifested by involvement of a single joint. Long-acting steroids including methyl prednisolone acetate or triamcinolone hexacetonide are used with this objective. Various studies have shown that topical triamcinolone hexacetonide is more efficient. In this way, systemic side effects of steroids are avoided. Response to treatment generally develops slowly, but the clinical

**Table 1. Disease activity measurement methods in pediatric rheumatology practice (7-10)**

Pediatric response criteria	
ACR Pedi 30, 50, 70, 90, 100 responses	Improvement of 30, 50, 70, 90, 100%, respectively, compared to baseline values in at least three of the 6-item set accompanied with no worsening of 30% even in one item set.
ACR Pedi item set:	<ol style="list-style-type: none"> <li>1- General evaluation of the disease efficiency, Physician VAS (10 cm visual analogue scale).</li> <li>2- General evaluation of the disease efficiency, Parent/patient VAS (10 cm visual analogue scale).</li> <li>3- Functional sufficiency-CHAQ (Childhood Health Assessment Questionnaire).</li> <li>4- Number of active joints</li> <li>5- Number of joints with limited motion.</li> <li>6- Erythrocyte sedimentation rate</li> </ol>
JADAS (Juvenile Arthritis Disease Activity Score)	The arithmetic mean of the following measurements. <ol style="list-style-type: none"> <li>1- General evaluation of the disease efficiency, Physician VAS (10 cm visual analogue scale).</li> <li>2- General evaluation of the disease efficiency, Parent/patient VAS (10 cm visual analogue scale).</li> <li>3- Number of active joints (on a basis of 27 joints)</li> <li>4- Erythrocyte sedimentation rate.</li> </ol>
Definitions of disease efficiency	
- Clinically inactive disease (all 6 sets should be met)	<ol style="list-style-type: none"> <li>1- No active joint will be present.</li> <li>2- Fever, erythema, serositis, splenomegaly, diffuse lymphadenopathy will not be present.</li> <li>3- No uveitis will be present.</li> <li>4- ESR and CRP will be normal.</li> <li>5- Morning stiffness will last shorter than 15 minutes.</li> <li>6- Physician VAS will be the lowest value in the scale used.</li> </ol>
- Clinical remission while using medication	- Inactive disease for longer than 6 months under treatment.
- Clinical remission without medication	- Inactive disease for longer than 12 months after the end of treatment.
Quality of life measurement tools	
CHAQ (Childhood Health Assessment Questionnaire).	A disease-specific measurement tool which evaluates the ability to perform daily activities.

ACR Pedi; American College of Rheumatology Pediatric; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; JIA: juvenile idiopathic arthritis; JADAS: Juvenile Arthritis Disease

findings improve in time. When repeated intraarticular steroid injection is required for the same joint, a period of 3-4 months should have passed (1-3, 13).

In the systemic type arthritis group, oral or parenteral administration of steroids markedly improves systemic findings. Findings including pain, swelling, sensitivity in the joints or carditis, hepatitis and lung disease related with the disease and fever, cachexia and anemia give a significant response to steroid treatment, whereas destructive events in the joints mostly persist. Side effects including growth retardation, glucose intolerance, obesity, hirsutism, pathological bone fractures

and compression in the vertebrae related with osteopenia, development of cataract, increased lipid levels, increased blood pressure, immunosuppression, disruption in the psychological status and myopathy may be observed in relation with use of systemic steroids. However, reduced dose or every other day dosage after the active process of the disease is controlled, decreases the frequency of these side effects related with excessive dose of systemic steroids. The dose can be increased to 1-2 mg/kg/day in case of congestive heart failure due to carditis or pericarditis or in case of tamponade. In other instances, it is generally administered at a dose below 1mg/kg/day. The dose may be reduced in relation with

decreased complaints and physical findings. In rare cases, a single high dose of 30mg/kg steroid may be administered parenterally to suppress severe systemic disease and this dose may be repeated when necessary (1-3, 13).

In approximately 40% of the patients, a complete treatment efficiency can not be provided with long-acting drugs. At this point, biological drugs which have been used widely in the last 10 years and shown to be efficient come into question. In this review, the biological drugs which are used in pediatric rheumatology practice will be discussed in order.

### Biological drugs

Inadequate efficiency of the drugs which have been used in treatment of juvenile idiopathic arthritis for years and formation of permanent joint limitations necessitated discovery of new treatment options. Many pediatric patients in adulthood have chronic active disease despite early intensive treatment which has been used in the last 20 years (early use of methotrexate). Therefore, biological drugs have been started to be used in treatment of JIA with the objective of reducing the frequency of chronic sequela and achievement of complete suppression. In fact, it is justified to use biological drugs in any child with JIA if

there is no response to long-acting drugs at the end of a 3-6-month treatment period. The biological drugs used in pediatric rheumatology are summarized in Table 2 (1-3, 11-14).

As in all rheumatic diseases, tissue macrophages are also stimulated in JIA because of an unknown cause. Afterwards, abundant amounts of proinflammatory cytokines are released with disrupted helper T cell response. Among these cytokines, especially tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1) and interleukin-6 (IL-6) are responsible of the inflammatory process created. TNF-alpha is responsible of synovitis and inflammatory events, IL-1 is responsible of joint destruction and IL-6 is responsible of systemic findings including fever and rash. Production of biological drugs against these cytokines gained speed especially after the second half of the 1990s (1-3, 14). This drug group is used more widely in adults and their safety has been proven. These drugs have recently been started to be used in children and the area of usage is limited. Drug selection should be performed according to the subgroup of the disease because of the difference of mechanism of action. In addition, the patient's preference should be considered in terms of the mode of administration and frequency of administration. The limitations for use of these drugs include inadequate

**Table 2. Biological therapies used in treatment of JIA**

Generic name	Trade name	Mechanism	FDA approval	Dose
Etanercept	Enbrel	TNF suppression, fusion protein TNF receptor suppression	Present	0.8 mg/kg/week or two times a week 0.4 mg/kg(maximum 50 mg/week)
Infliximab	Remicade	TNF suppression, anti TNF monoclonal chimeric antibody	Absent (present in uveitis)	5-10 mg/kg/month(maximum 200 mg/month)
Adalimumab	Humira	TNF suppression, anti TNF monoclonal antibody	Present	<30 kg:20 mg/every 2 weeks >30 kg:40 mg/every 2 weeks 24 mg/m <sup>2</sup> /14 days
Anakinra	Kineret	IL1-receptor antagonist	Absent	2-10 mg/kg/day(maximum 200 mg/day)
Kanakinumab	Ilaris	IL-1 inhibitor, anti IL-1 beta monoclonal antibody	Present	<40 kg:4-6 mg/kg/4-8 weeks, >40 kg:150-300 mg/dose/4-8weeks
Rilonacept	Arcalyst	IL-1 suppression; soluble fusion protein	Present	2.2-4.4 mg/kg/week
Tosilizumab	Actemra	Il-6 receptor antagonist	Present	≤30 kg, 12 mg/kg/2-4 weeks ≥30 kg, 8 mg/kg/2-4 weeks (maximum dose 400 mg)
Abatacept	Orencia	T cell costimulator; soluble fusion protein	Present	10 mg/kg/4 weeks (maximum dose 500 mg)
Rituximab	MabThera	CD20 antigen suppression	Present	375 mg/m <sup>2</sup> /weeks, for 4 weeks, (maximum dose 500 mg)

FDA: Food and Drug Administration; JIA: juvenile idiopathic arthritis

long-term safety data and cost, though they are efficient drugs (1-3, 11-14).

**TNF - alpha antaonists:** TNF which is a cytokine was associated with rheumatic arthritis (RA) in 1980 for the first time and was found to be increased also in JIA. Tumor necrosis factor-alpha (TNF- $\alpha$ ) is a cytokine which has a significant role in the pathogenesis of JIA and is found at increased levels both in the serum and synovial fluid. In addition, the serum level of soluble TNF receptors has been shown to be associated with the activity of the disease (1-3, 11-14).

**Etanercept:** Etanercept (Enbrel) is a dimeric fusion protein which was produced against human TNF receptor. It is the first biological drug produced. It inhibits human IgG by binding to human IgG by way of p75 TNF receptor expressed on Fc receptor. It also inhibits TNF-beta. It is produced by way of recombinant DNA technology. Other inflammatory cytokine levels, leukocyte migration and production of matrix metalloproteinases are also inhibited with inhibition of tumor necrosis factor-alpha pathway. It was approved for use in polyarticular JIA in children by the Food and Drug Administration (FDA) in 1999. Its efficiency was shown by Lovell et al. (15) for the first time in a multi-center, randomized study conducted with patients with polyarticular JIA. A dose of 0,4mg/kg was administered for two times a week for three months. Patients who gave response to treatment were randomized again for placebo. Better results were obtained in the etanercept group in terms of disease exacerbation and mean exacerbation time. Etanercept is very efficient especially on peripheral joint arthritis. It is the most efficient treatment option in patients with polyarticular JIA. A dose of 0,8mg/kg/week was shown to be efficient and safe in other studies. The efficiency of the drug occurs prominently after the second or third dose (16).

The most important side effect of etanercept is local reactions in the injection site. Therefore, it is safer to administer the drug in different sites. Recurrent upper respiratory tract infections may be observed with a lesser frequency (17).

**Infliximab:** Infliximab (Remicade) is an anti-TNF human/mouse chimeric monoclonal antibody. It binds to all TNF-alpha receptors on the cellular surface. In contrast to etanercept, infliximab affects both soluble TNF receptors and TNF receptors found on the cellular

surface. Its efficiency in treatment of juvenile idiopathic arthritis has been demonstrated. In contrast to the other drugs, it is administered at a dose of 3–6 mg/kg (maximum dose 100 mg) intravenously every 4-8 weeks. The efficiency of the drug is observed at about the first month. Infliximab is especially efficient in spondyloarthropathies which involve the axial skeletal system, inflammatory bowel diseases, psoriatic arthritis and uveitis (1-3, 12-14, 18, 19, 20). Combined use of infliximab with methotrexate markedly increased its efficiency (21). Administration of infliximab is rather troublesome. Tremor, urticaria, contraction and fever spells reflecting anaphylactic reactions may be observed during infusion. Benadryl, paracetamol and steroid may be administered before or during infusion to prevent these reactions. Formation of autoantibodies may be observed in long-term administration (21).

**Adalimumab:** Adalimumab (Humira) is a human monoclonal antibody produced against TNF-alpha. Adalimumab is less immunogenic and has a longer half-life compared to infliximab. The drug is used at a dose of 40 mg every two weeks by way of subcutaneous injection. The dose used in children is 24 mg/m<sup>2</sup>/15 days. Use of the drug in combination with methotrexate markedly increases its efficiency (22). These results show the benefit of changing drugs when there is no response to the TNF alpha antagonist drug used. It has been recently approved in USA by FDA for use in polyarticular JIA at the age of 4 years and above (23). In our country, it has been approved for use at the age of 13 years and above.

#### **Interleukin-1 antagonists**

**Anakinra:** Anakinra (Kineret) is a human recombinant IL-1 receptor antagonist. It decreases IL-1 activity by binding to IL-1 receptor. It is used at a dose of 1-2 mg/kg/day by way of subcutaneous injection in children. The maximum dose is 100 mg/day. Since its half life is 4-6 hours, daily injections should be performed. It is preferred in treatment of systemic JIA (sJIA), since IL-1 has a significant role in the pathogenesis. The most important difficulty in administration of anakinra is daily administration and local reactions which may occur in the injection sites (1-3, 12-14, 24). In another multi-center, double-blind study, 24 patients were compared with placebo and treatment response was observed in 84% of the patients in the first month. However, a reduction in drug response was observed in the patients who had a diagnosis of polyarticular JIA

(25). In one study, it was observed that response was obtained with a rate of 40% with anakinra in the patient group with systemic JIA. In the patient group in whom no responses could be obtained, systemic findings improved, but arthritis findings did not improve (26). Anakinra is generally tolerated well and severe side effects are observed rarely. Its disadvantage is requirement of daily injections and itchy rash may be observed in the injection site. Although the rash spontaneously improves in time, improvement can be provided more rapidly with cold application. Rare cases of neutropenia and hepatotoxicity have been reported (27). Opportunistic infection has not been reported so far; pneumonia, bacteriemia, local skin infections and herpes simplex virus infections have been reported (28). In a study conducted with a patient group with rheumatoid arthritis, injection site reaction, severe bacterial infection and neutropenia were found with a higher rate with anakinra used in combination with etanercept compared to use of anakinra alone (29).

**Kanakunimab (ACZ885):** Kanakunimab (Ilaris) is a monoclonal IgG1 antibody and decreases molecular efficiency by acting as an isoform of interleukin-1  $\beta$ . Phase II studies have shown its efficiency in patients with systemic JIA (30). It was approved by FDA in USA in 2013 for use in patients with active systemic JIA aged 2 years and older. In the study conducted by Ruperto et al. (31), a substantially high response was obtained in systemic JIA patients in terms of ACR pedi 30 response and reduction of fever (84%, 10%) compared to placebo. The recommended dose is 4 mg/kg/every 4-8 weeks for children below 40 kg and 150 mg/kg/every 8 weeks for children above 40 kg. No cancer, tuberculosis or other opportunistic infection cases have been reported; side effects including abdominal pain, vomiting and diarrhea which do not require discontinuation of treatment have been reported. It is the primary anti IL-1 preferred by many clinicians because local injection reaction is observed with a lower rate and the half-life is longer compared to anakinra. In addition, kanakunimab is also reliably used in treatment of many autoinflammatory diseases.

**Rilonacept:** Rilonacept eliminates the efficiency of interleukin-1 receptor protein by acting as a recombinant fusion protein. The dose of usage is 2,2-4,4 mg/kg/week. In a double-blind placebo-controlled study, good response was obtained in patients diagnosed with sJIA (32). Although it is not recommended for the initial treatment of systemic JIA, it is recommended in cases

of unresponsiveness to the other interleukin 1 antagonists and active disease and active arthritis (33).

#### **Interleukin-6 antagonist treatment**

**Tosilizumab:** Tosilizumab (Actemra) is a monoclonal IL-6 receptor antibody. It acts by binding to IL-6 receptor and eliminating IL-6-IL6R bound. In systemic JIA, serum IL-6 levels are related with CRP and fever. In a double-blind, placebo-controlled study conducted with 56 patients diagnosed with systemic JIA, treatment response was observed initially in 91% of the patients (34). In the TENDER study, 61,5% improvement was provided in ACR pedi30 response and 12-week response in the assessment performed after placebo and methotrexate were given compared to tosilizumab and/or methotrexate treatment given for 12 weeks to 112 JIA patients who were not responsive to corticosteroid or NSAIDs (35). Tosilizumab was found to be appropriate for children aged 2 years and older with a diagnosis of active systemic JIA. It may be used alone or in combination with methotrexate. The dose of usage is 12 mg/kg/2-4 weeks below 12 kg and 8 mg/kg/2-4 weeks above 12 kg (36). Double-blind, placebo-controlled studies conducted with tosilizumab showed that there was no significant increase in the risk of infection and no cases of tuberculosis and other opportunistic infections were found. Neutropenia, thrombocytopenia, increased low density lipoprotein, increased alanine aminotransferase and aspartate aminotransferase levels were found with a higher rate in the patients with systemic and polyarticular JIA who were using tosilizumab (37). It was approved by FDA for treatment in cases of systemic JIA unresponsive to previous treatments and especially in cases of active arthritis which do not show improvement and in polyarticular JIA (33).

#### **Treatments targeting T cells and B cells T**

**Abatacept:** Abatacept (Orencia) (CTLA4-Ig) escapes the prior stimulus of the immune response given by activated T cells. Abatacept has been used since 2008 with FDA approval for patients with polyarticular JIA above the age of 6 years. The drug is used as monthly injections at a dose of 10 mg/kg. The efficiency of abatacept in JIA was shown in 190 children with polyarticular JIA in a double-blind, randomized study. In this study, the efficiency of abataceptin (20%, 12/60) was found to be significantly higher compared to placebo (53%, 33/62) (38). In the long-term, open-label part of this study, the rates of ACR Pedi 30, ACR Pedi 50, ACR Pedi 70 and ACR Pedi 100 were found to be 90%, 88%, 57% and 39%, respectively. It was reported to be efficient and to have

no severe side effect in the long-term follow-up. No cancer or tuberculosis infection was reported. However, multiple sclerosis was found in one patient (39). In another study, improvement was shown in the measurements of quality of life (40). It has been recommended by ARC in cases of unresponsiveness to tumor necrosis factor-alpha inhibitors (41). In our country, it is also indicated in cases of TNF unresponsiveness. Currently, only infusion form is available in the pediatric practice. Studies on the subcutaneous form are continuing.

**Rituximab:** Rituximab (Mabthera) is a human monoclonal antibody which increases B cell apoptosis and decreases mature B cells carrying CD20. The main target of rituximab is mature B cells. It is very efficient in all B cell-related diseases. This drug which was initially used in non-Hodgkin lymphomas is being used in resistant rheumatic diseases and especially systemic lupus erythematosus. It is indicated in adult rheumatoid arthritis patients if there is unresponsiveness to the other anti-TNFs. Data about use of rituximab in JIA patients are considerably limited. In one study, improvement in disease activity was reported as a result of treatment of 55 patients who were diagnosed with treatment-resistant polyarticular JIA with rituximab (42). However, it is not indicated for use in JIA patients in our country. When necessary, it may be administered with off-label reporting method. The drug is administered as four infusions weekly at a dose of 375 mg/m<sup>2</sup>. This treatment can be repeated three or four times, if necessary. Before treatment with rituximab, meningococcus, pneumococcus and influenza vaccinations should absolutely be completed.

**Tofacitinib/CP-690,550:** Tofacitinib/CP-690,550 is a selective JAK inhibitor. Tofacitinib acts by inhibiting the activation of JAK 1, JAK 2 and STAT 1. It was approved by FDA for treatment of rheumatoid arthritis (43). Open-label studies are continuing for its use in treatment of juvenile idiopathic arthritis (44).

#### **Points to be considered during use of biological drugs in children**

Decreased immune response and especially inhibition of type IV hypersensitivity response with inhibition of tumor-necrosis factor-alpha response may lead to activation of the diseases related with this response and especially activation of tuberculosis. Therefore, presence of tuberculosis should be absolutely investigated during and before anti-TNF-treatment and efficient anti-tuberculosis treatment should be administered if

the diagnosis is made or if any suspicion is present. In the practice of our group, lung graphy, PPD and fasting gastric juice samples are obtained before treatment. If any sign suggesting tuberculosis infection is found in these data, treatment should be initiated rapidly (1-3, 12-14, 45). Updating these data every 6 months is beneficial in the follow-up. Administration of treatment against tumor necrosis factor-alpha affects vaccine response considerably negatively. Especially live vaccines should be avoided during this process (46). Another long-term problem in administration of anti-TNF is that the possible carcinogenic, reproductive and central nervous system side effects of these drugs. In the final assessment performed by our group, it was demonstrated that use of biological drugs in children was considerably safe in terms of development of tuberculosis (45).

#### **Side effects of biological drugs**

Malignancy was reported by FDA for the first time in 2008 in a few patients who were receiving biological treatment for JIA. There are controversial views about this report, because immunosuppressive drugs used in combination with biological drugs might have contributed to this outcome and there is no clear data about the frequency of malignancy in JIA (47-49). Although it has been proposed that there might be a relation between JIA treatment and development of cancer, a direct causal relationship between biological agents and malignancy has not been established yet (49). Secondary malignancy did not develop in any of more than 300 patients who used biological drugs and who were followed up by our group. It is important to evaluate if the patients have used precancerous drugs and if there is a familial history of cancer before treatment with these drugs (47, 48).

Severe infections including opportunistic infection and tuberculosis have been reported. Generally, prophylactic treatment is not recommended. Tuberculosis screening with PPD is recommended before and during biological treatment (45). Another side effect is development of autoimmune disorders including demyelinating diseases, inflammatory bowel diseases, psoriasis, systemic lupus erythematosus, vasculitic rash and uveitis.

Conclusively, it was observed that biological drugs were considerably efficient and safe in treatment of JIA in the light of all this information. The biological drugs used in treatment of juvenile idiopathic arthritis have significantly changed the course of JIA. These children

will use less medication and especially less steroid, require less surgical treatment, their education will be hindered less and they will be psychologically healthier active individuals. Considering the cost of these drugs, indications for use should be evaluated efficiently. However, frequent and meticulous monitoring of patients is especially important, since there are no long-term results for pediatric patients.

#### Key points in treatment of juvenile idiopathic arthritis

1. Treatment of juvenile idiopathic arthritis is adjusted according to the severity of the disease as combinations of antiinflammatory drugs, long-acting drugs and biological drugs.
2. Early diagnosis and early initiation of efficient treatment is very important.
3. The objective in treatment is to achieve inactive disease or suppression and to maintain this state without using medication.
4. Treatment should be conducted not only by pediatric rheumatologists but by a team composed of pediatricians, physiotherapists, ophthalmologists, child psychiatrists and orthopaedists.
5. These patients should be followed up for long-term even if inactive disease is achieved without medication.

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