Turkish Journal of Pediatric Disease
Türkiye Çocuk Hastalıkları Dergisi

Comparison of Biologic Monotherapy Versus Biologic and Disease-Modifying Anti-Rheumatic Drug Combination in the Treatment of Non-Systemic Juvenile Idiopathic Arthritis

Sistemik Olmayan Juvenil İdiyopatik Artrit Tedavisinde Biyolojik Monoterapi ile Biyolojik ve Hastalık Modifiye Edici Anti-Romatizmal İlaç Kombinasyonunun Karşılaştırılması

Fatma Gül DEMİRKAN, Nuray AKTAY AYAZ

Department of Pediatric Rheumatology, İstanbul University, İstanbul School of Medicine, İstanbul, Turkey

ABSTRACT

Objective: To explore the efficacy of biologics as mono- or combination therapy with conventional disease modifying anti-rheumatic drugs (cDMARDs) in the treatment of juvenile idiopathic arthritis (JIA).

Material and Methods: Medical records of patients with JIA followed-up from January 2020 to 2023 who were treated either with biologic drugs as monotherapy or with combination of cDMARD were reviewed retrospectively. Data of demographic features, clinical scores and treatments were assessed.

Results: Two hundred five cases received etanercept, adalimumab, or tocilizumab alone or in combination with a cDMARD for JIA were included. The male to female ratio of the cohort was almost equal. Oligoarticular was the most common subtype of JIA.

Majority (n=128, 62.4%) of the group received biologic drugs as monotherapy, while the remaining third (n=77, 37.6%) used a combination of biologic and a cDMARD. Nearly half of the group (57.1%) were treated with etanercept and etanercept monotherapy was the most commonly used one among all JIA subtypes except juvenile psoriatic arthritis. Adalimumab combination therapy was prescribed in most of the children with juvenile psoriatic arthritis. Adalimumab, alone or in combination with methotrexate, was preferred for all 8 patients with uveitis at the onset of the disease. Adalimumab combined (n=9) and tocilizumab monotherapy (n=4) were the most common biologics in those who developed uveitis during follow-up.

Conclusion: Etanercept, adalimumab, or tocilizumab are effective and safe biologics in treatment of JIA. Prescribing biologic drugs timely as combined or monotherapy in certain cases is effective in preventing early and late sequelae of JIA.

Key Words: Biologics, Disease-modifying anti-rheumatic drugs, Juvenile idiopathic arthritis

ÖZ

Amaç: Jüvenil idiyopatik artrit (JİA) tedavisinde konvansiyonel hastalık modifiye edici anti-romatizmal ilaçlar (cDMARD'lar) ile mono veya kombinasyon tedavisi olarak biyolojiklerin etkinliğini karşılaştırmak.

Gereç ve Yöntemler: Ocak 2020- 2023 arasında kadar izlenen monoterapi olarak biyolojik ilaçlarla veya cDMARD kombinasyonuyla tedavi edilen hastaların tıbbi kayıtları retrospektif olarak incelendi. Demografik özellikler, klinik skorlar ve tedavi verileri değerlendirildi.

0000-0001-9950-2489 : DEMİRKAN FG
0000-0003-3594-7387 : AKTAY AYAZ N

Conflict of Interest / *Çıkar Çatışması*: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by the Istanbul Faculty of Medicine, Clinical Research Ethics Committee (17.05.2022-871316).

Contribution of the Authors / Yazarların katkısı*: DEMİRKAN FG:** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***AKTAY AYAZ N: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

How to cite / *Atıf yazım şekli*: Demirkan FG and Aktay Ayaz N. Comparison of Biologic Monotherapy Versus Biologic and Disease-Modifying Anti-Rheumatic Drug Combination in the Treatment of Non-Systemic Juvenile Idiopathic Arthritis. Turkish J Pediatr Dis 2023;17:405-411.

Correspondence Address / Yazışma Adresi:

Nuray AKTAY AYAZ
Department of Pediatric Rheumatology, İstanbul University, İstanbul School of Medicine, İstanbul, Türkiye
E-posta: nurayaktay@gmail.com

Received / Geliş tarihi : 17.08.2023
Accepted / Kabul tarihi : 18.09.2023
Online published : 19.09.2023
Elektronik yayın tarihi
DOI: 10.12956/tchd.1345189

Bulgular: Tek başına veya JIA için bir cDMARD ile kombinasyon halinde etanersept, adalimumab veya tosilizumab alan 205 vaka dahil edildi. Grubun kadın erkek oranı hemen hemen eşitti. Oligoartiküler JİA'nın en yaygın alt tipiydi.

Grubun büyük çoğunluğu (n=128, %62.4) biyolojik ilaçları monoterapi olarak alırken, geri kalan üçte birlik kısım (n=77, %37.6) biyolojik ve bir cDMARD kombinasyonu kullanmıştı. Grubun yaklaşık yarısı (%57.1) etanersept ile tedavi edilmişti ve jüvenil psoriatik artrit dışında tüm JİA alt tipleri arasında en sık kullanılan etanersept monoterapisiydi. Jüvenil psoriatik artritli çocukların çoğuna adalimumab kombinasyon tedavisi verildi. Hastalığın başlangıcında üveitli 8 hastanın hepsinde tek başına veya metotreksat ile kombinasyon halinde adalimumab tercih edildi. Takip sırasında üveit gelişenlerde adalimumab kombine (n=9) ve tosilizumab monoterapisi (n=4) en yaygın biyolojik ilaçlardı.

Sonuç: Etanersept, adalimumab ve tosilizumab JİA tedavisinde etkili ve güvenli biyolojik ilaçlardır. Biyolojik ilaçların zamanında ve uygun hastalarda kombine veya monoterapi olarak seçilmesi, JİA'nın erken ve geç sekellerini önlemede etkilidir.

Anahtar Sözcükler: Biyolojikler, Hastalık modifiye edici anti-romatizmal ilaçlar, Juvenil idiyopatik artrit

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common cause of chronic inflammatory arthritis seen under the age of 16 and can cause severe disability. The incidence of the disease has been reported as 19.8 per 100,000 children (1, 2).

Currently, treatment strategies of JIA includes non-steroidal anti-inflammatory drugs (NSAIDs) as the first-line therapy. Corticosteroids and conventional disease-modifying anti-rheumatic drugs (cDMARDs) are required in nonresponsive cases. Treatment response may vary according to the subtype of the disease and accompanying complications.

The introduction of biologic drugs have revolutionized improving patients' quality of life as they reduces the Juvenile Arthritis Disease Activity Score (JADAS) and the number of joints affected. In addition, with the widespread use of biologics in the treatment of JIA, the dose of other conventional medications used together with biologics drugs can be reduced and the harmful effects of those with long-term side effects such as corticosteroids can be prevented (3, 4).

In Türkiye, etanercept (ETA), adalimumab (ADA), and tocilizumab (TCZ) are the main licensed biologics and recommended for children with systemic and non-systemic JIA subtypes in case of inadequate response or intolerance to DMARDs. Previous reports have revealed that 80% of children with JIA are treated by combination of biologics and methotrexate rather than replacing methotrexate with biologics (3,5,6). According to the literature, depending on the molecular structure of biologic drugs, JIA subtype or complications of the disease such as uveitis, monotherapy of biologics or combination with DMARDs can be preferred. However, centers continue to determine their preferences according to their own experiences and the rules of healthcare systems of countries (7, 8).

The aim of this observational study is to evaluate the efficacy of combination versus mono-therapy of biologics licensed in Türkiye for children with non-systemic JIA.

MATERIALS and METHODS

The study was approved by the Istanbul Faculty of Medicine, Clinical Research Ethics Committee (17.05.2022-871316). All patients and their parents gave written informed consent in accordance with the Declaration of Helsinki.

The medical charts of 205 patients treated with biologic agents out of 856 JIA patients with JIA were reviewed retrospectively. Patients who were followed-up between January 2019 and January 2023 enrolled to the study according to being eligible for the following criteria: 1) Meeting the International Association of Rheumatology Societies (ILAR) criteria for JIA, 2) No history of comorbid rheumatologic disease, 3) Negative scanning results for tuberculosis, and 4) Absence of a systemic symptom leading to systemic JIA (sJIA). Because sJIA is the only subtype recognized as an autoinflammatory disease rather than an autoimmune disease, it is distinguished from other subtypes by its more severe disease course, different and challenging treatment strategies. For these reasons, patients with a diagnosis of sJIA, which is often considered a separate disease, were excluded from this study. 5) Patients receiving abatacept, etc., which are relatively less preferred in the treatment of JIA, were excluded from the study.

Demographic and clinical features, laboratory variables, family history, received medications, and periodic outcome measures were collected retrospectively.

Intermittent recording of the juvenile arthritis disease activity score-27 (JADAS-27) assessed the efficacy of the main treatment (9). The Wallace criteria was accepted for the definition of inactive disease. Components of this criteria were as follows: No active arthritis or uveitis; a physician's global assessment indicating no disease activity; no fever, rash, serositis, splenomegaly, or lymphadenopathy; and no elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level (10).

The cohort was divided into 2 groups: Those who received biologic monotherapy (ETA, ADA, or TCZ) and those who received biologic and cDMARDs combination therapy. All groups involve patients who had the respective treatments for at least 3 months and follow-up of >6 months. Firstly, the main comparison was between TCZ and tumor necrosis factor (TNF)-alpha inhibitors (TNFi) used as monotherapy or in combination with a DMARD. Secondly, patients received TNFi were categorised by concomitant conventional (methotrexate, sulfasalazine, or leflunomide) therapy. The period of drug

exposure terminated either at the recorded discontinuation date, the final available visit, or when switching to another DMARD or biologic, whichever took place earlier.

Reasons for discontinuation of treatment or resumption of the discontinued drug were recorded. The corticosteroid sparing effect of the main treatment was determined by recording discontinuation data and the duration of steroid use.

Statistical Analysis

Descriptive statistics were expressed as frequencies or percentages for categorical variables. Continuous variables are stated with mean±standard deviation (SD) or median with interquartile range (IQR) according to the normality of the data. To compare groups Pearson's chi-squared test, Fisher's exact test, independent-samples t-test and Mann– Whitney U test were used depending on type of the data processed. The p-values less than 0.05 were considered as statistically significant. Statistical analyses were performed utilizing SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Overall, 205 of 856 children with non-systemic JIA aged 2 to 18 years and receiving biologic drugs were enrolled to the study. The male to female ratio of the cohort was almost equal. Oligoarticular was the most common subtype of JIA. Patient characteristics and the distribution of patients by JIA subtype according to ILAR criteria is summarized in Table I.

As a complication of JIA, uveitis developed in 24 patients during the course of the disease. Eight (3.9%) of them were diagnosed incidentally at the onset of JIA, and 16 (7.8%) of them were diagnosed with uveitis during periodic visits for JIA. ADA alone or in combination with methotrexate was preferred for all patients with uveitis at the onset of the disease. ADA combined therapy (n=9) was the most common, and TCZ monotherapy (n=4) was the second most common in those who developed uveitis during follow-up.

Majority (n=128, 62.4%) of the group received biologic drugs as monotherapy, while the remaining third (n=77, 37.6%) used a combination of biologic and cDMARD. Nearly half of the group (57.1%) were treated with ETA in the entire cohort and ETA monotherapy was the most commonly used drug among all JIA subtypes except juvenile psoriatic arthritis. ADA combination therapy was prescribed in most of children with juvenile psoriatic arthritis. At the last visit, while 20 (9.8%) patients had discontinued biologic therapy, 185 (90.2%) were still under biologic therapy. Among the whole group baseline disease characteristics (median VAS, PGA, CRP, and ESR values) were slightly more severe in children received either TCZ mono or TCZ combination therapy than the other groups. Comparison of the groups by index drugs at study enrolment can be seen table II.

Fifteen patients were under systemic corticosteroid therapy at the time of biologic initiation and at the last visit one case with juvenile psoriatic arthritis required corticosteroid therapy with adalimumab and leflunomide.

Methotrexate was the major cDMARD most preferred when combination of biologics was required. In TCZ combination group leflunomide and methotrexate were prescribed at similar rates.

When comparing the medications for discontinuation, the most common cause was achieving inactive disease (19, 9.3%) for

Table I: The demographic features and the distribution of disease subgroups

Features	
Gender (female/male)*	101/104 (49.3 / 50.7)
Age, years†	14.2 (10.6-18)
Age at diagnosis, years†	9 (4.2-12.6)
The delay in diagnosis, months†	2.4 (1-8.5)
Follow-up period, years†	3.8 (2-6.3)
Age at biologic onset, years†	11 (6.7-14.5)
The disease duration at initiation of biologic therapy, months†	23.7 (10.5-40.5)
The duration of biologic therapy usage, months†	20.7 (10.2-40.7)
Family history of rheumatologic disease*	
Rheumatoid arthritis	21 (10.2)
Psoriazis	5 (2.4)
JIA	3 (1.4)
JIA subtypes	
Oligoarticular JIA*	115 (56.1)
Persistent*	107 (52.2)
Extended*	8 (3.9)
RF-negative polyarticular JIA*	35 (17.1)
Enthesitis-related arthritis JIA*	35 (17.1)
Psoriatic arthritis*	11 (5.4)
RF-positive polyarticular JIA*	9 (4.4)

:** *n(%),* **†:** *(median, IQR),* ***JIA: *juvenile idiopathic arthritis,* ***RF:*** *rheumatoid factor,* ***IQR:*** *interquartile range*

Table II: Comparison of the groups by index drugs at study enrolment

	Index drug at study enrolment					
	ETA mono (n=81)	**ETA combo (n=36)**	**ADA mono (n=31)**	**ADA combo (n=35)**	**TCZ mono (n=16)**	**TCZ combo (n=6)**
JIA category*						
Oligoarticular						
Persistent	46 (43)	22 (20.6)	16 (15)	17 (15.9)	5 (4.7)	1 (0.9)
Extended	3 (37.5)	2 (25)	0	1 (12.5)	2 (25)	0
RF-negative polyarticular	16 (45.7)	2 (5.7)	4 (11.4)	4 (11.4)	6 (17.1)	3 (8.6)
Enthesitis-related	11 (31.4)	7 (20)	8 (22.9)	7 (20)	1 (2.9)	1 (2.9)
Psoriatic	2 (18.2)	1 (9.1)	2 (18.2)	4 (36.4)	1 (9.1)	1 (9.1)
RF-positive polyarticular	3 (33.3)	2 (22.2)	1 (11.1)	2 (22.2)	1 (11.1)	0
ANA positivity*	28 (41.2)	11 (34.4)	12 (41.4)	17 (54.8)	3 (20)	2 (33.3)
Seropositivity (RF and/or anti-CCP)*	3 (3.7)	3 (8.3)	2 (6.4)	3 (8.5)	1 (6.2)	1 (16.6)
HLA-B27 positivity*	6 (7.4)	3 (8.3)	5 (16)	4 (11.4)	0	1 (16.6)
ESR (mm/hour)†	10 (23)	8 (19)	18 (19)	10 (24)	20 (40)	7.5 (30)
CRP (mg/L)†	1.7 (6.4)	1.8 (6.4)	3.7 (18.5)	2 (13.6)	7.4 (57.5)	6.6 (23.1)
Patient/parent global assessment†	6 (2)	5 (3)	6 (3)	5 (4)	8 (3)	6.5 (3)
Physician global assessment†	5 (2)	5 (2)	5 (3)	5 (3)	6 (3)	6 (5)
Concomitant cDMARD*						
MTX		27 (75)		27 (77.1)		3 (50)
SAZ	-	5 (13.8)	-	3 (8.5)	-	0
LEF		2 (5.5)		4 (11.4)		3 (50)

***:** *n(%),* **†:** *median (IQR),* ***DMARDs:** Disease-modifying antirheumatic drugs,* ***JIA:** juvenile idiopathic arthritis,* ***RF:** rheumatoid factor,* ***IQR:** interquartile range,* ***ETA:** Etanercept,* ***ADA:** Adalimumab,* ***TCZ:** Tocilizumab,* ***ANA:** Antinuclear antibody,* ***CCP:** Cyclic citrullinated peptide,* ***HLA:** Human leukocyte antigen,* ***ESR:** Erythrocyte sedimentation rate,* ***CRP:** C-reactive protein,* ***MTX**: Methotrexate,* ***SAZ:** Sulfasalizne,* ***LEF:** Leflunomide*

all groups. TCZ-mono (31.3%) and ETA-monotherapy (11.1%) groups were the two in which treatments were stopped most frequently due to inactive disease. Patients' failure to comply with follow-up periods and drug administration (10, 4.9%) were among the other reasons for discontinuation. Discontinuation was usually noted for adverse events in children treated with TCZ mono- and ADA combination therapy (4% vs. 3%). Shorter disease duration, RF- polyarticular JIA subtype, concomitant steroid treatment and higher JADAS-27 levels at baseline were significantly associated with greater risk of discontinuation.

Ineffectiveness (29, 14.1%) and uveitis (8, 3.9%) were the leading causes of switching biologic therapies. TCZ mono- (7%, 43.8%) and combination (5%, 83.3%) treatments were switched significantly more often than other groups due to poor efficacy (p=0.01).

At the first year evaluation, significant improvement in disease activity parameters was observed in patients in all groups. Remission in JADAS-27 was achieved in 65%, 61.2%, and 50.7% in the ETA, ADA, and TCZ combination cohorts, respectively. In monotherapy cohorts JADAS-27 remission rates were 60%, 58%, and 41.7% for ETA, ADA, and TCZ groups, respectively. Although less improvement was observed in the JADAS-27 scores of the patients who received TCZ monotherapy, there was no significant difference between groups (p=0.7).

DISCUSSION

This is a comprehensive retrospective observational study comparing ETA, ADA, and TCZ, which are currently used in the treatment of JIA. Previous reports are mostly associated with effectiveness of cDMARD monotherapy and combination of them with biologic medications in JIA. Our study stands out for comprehensively comparing the use of the most commonly used biologics as monotherapy and in combination with cDMARDs.

Within a span of decade, biologic medications became widespread in treatment of JIA. In cases where cDMARDs are insufficient to provide remission, bDMARDs are preferred as both mono- and combination therapy. In clinical practice, TNFi such as ETA are the first-line biologics that are the most frequently used in JIA (11,12). Data of the German registry regarding ETA use in JIA revealed that ETA is safe and effective for treatment of JIA (13). A prospective, open-label, multicenter registry evaluating the long-term safety and efficacy of ETA mono- or in combination with methotrexate reported that all these drugs might be preferred in JIA because they are effective (14). In another study comparing combination versus monotherapy of ETA, cases receiving combination therapy with methotrexate showed greater ACR Pedi 70 response at the end of the first year, than patients receiving ETA alone (62% vs 45%; $p < 0.010$) (15). In the present study, there was no significant

difference between ETA mono- and combination therapies in terms of median JADAS-27 scores, PGA, or VAS. Patients who received ETA and methotrexate concomitantly and ETA monotherapy showed significant improvement in JADAS-27 scores at the end of first year ($p<0.001$). However, there is still insufficient evidence about the accurate time of discontinuation of ETA in JIA.

ADA, a fully human monoclonal anti-TNFi, is accepted for being effective and safe in the treatment of JIA. In German BIKER registry, long-term data was reported regarding ADA versus ADA and methotrexate for JIA management. In patients with ADA monotherapy, ERA ($p = 0.004$) was documented more often. No differences in treatment response or adherence to treatment between groups were declared (16). ADA is frequently preferred in JIA associated uveitis. A study determining the role of ADA in the treatment of JIA-uveitis in children showed that the combination of ADA with methotrexate is safe and effective (17). ADA was the second most common bDMARD prescribed in all groups of our cohort following ETA. It was the most important choice in our cases that develop uveitis during the course of the disease and at the onset of the disease. All uveitis subjects were in remission under ADA mono- and combination therapy in our study at the first year of biologic initiation.

It is known that the neutralizing antibody against bDMARDs may have a negative effect on the functional drug level indirectly by increasing drug clearance through the formation of immune complexes (18, 19). Secondary failure and adverse events of bDMARDs can be related to the anti-drug antibodies. ETA is a non-immunogenic anti-TNFi. Although antibodies are produced in the immune system against ETA, they are not neutralizing and do not affect drug efficacy or safety. However, the use of ADA carries the risk of developing anti-drug antibodies leading to neutralization and related effects (19). Studies have shown that methotrexate has a protective effect on the formation of anti-drug antibodies, which is a major challenge especially for the use of anti-TNFi. In our study, methotrexate was the most common cDMARD prescribed for combination with biologics. Although we did not evaluate anti-drug antibody levels, our study shows that the combination of bDMARDS with methotrexate is as effective as monotherapy and is often preferred by rheumatologists in clinical practice.

TCZ is a recombinant humanized monoclonal antibody whose mechanism of action is an interleukin-6 receptor antagonist. It has been frequently prescribed for the treatment of systemic and polyarticular forms of JIA (20). Moreover, recent literature provides promising outcomes regarding the efficacy of intravenous and subcutaneous TCZ in the management of JIA associated uveitis (21, 22). In previous studies, in contrast with anti-TNFi, no improvement in outcome has been observed by combining TCZ with cDMARD. So, TCZ was identified as being highly effective as a monotherapy (6, 23). In this study, TCZ mono- and combination therapies were most commonly preferred for the treatment of RF-polyarticular JIA and JIA-associated uveitis, and were effective and well tolerated. Because our data included a small number of cases receiving TCZ, it was difficult to make comparisons for the TCZ alone and the combined treatment groups.

This study also has some limitations. Clinical data were collected retrospectively from patient records and this was not an inception cohort. At the same time, it was very difficult to make an optimal evaluation because there was not a homogeneous number of patients in all groups. However, such data are valuable for clinicians as they are real-life data.

In conclusion, bDMARDs, which can be used in combination or alone, are critically important drugs in the treatment of JIA. Considering their cost-effective properties, choosing them as combined or monotherapy timely is effective in preventing early and late sequelae of JIA. Prospective, controlled randomized studies based on real-life data with larger patient groups on these drugs would be of great value.

REFERENCES

1. Petty RE, Southwood TR, Manners P,Baum J, Glass DN, Goldenburg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390-2.
2. Danner S, Sordet C, Terzic J, Donato L, Velten M, Fischbach M, et al. Epidemiology of juvenile idiopathic arthritis in Alsace, France. J Rheumatol 2006;33:1377-81.
3. Horneff G, De Bock F, Foeldvari I, Girschick H J, Michels H, Moebius D, et al. Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA Registry. Ann Rheum Dis 2009;68:519-25.
4. Zhang T, Huang S, Guo Y, Jin J, Yan W, Wang P, et al. Effectiveness of tumor necrosis factor inhibitors in children with enthesitis-related arthritis: a single-center retrospective analysis. Front Pediatr 2023;11:1122233.
5. Krüger K. Combination therapy using methotrexate with DMARDs or biologics--current status. Z Rheumatol 2011;70:114-22.
6. Klein A. Biologics in the treatment of juvenile idiopathic arthritis : A comparison of mono- and combination therapy with synthetic DMARDs. Z Rheumatol 2019;78:599-609.
7. Alexeeva E, Dvoryakovskaya T, Denisova R, Sleptsova T, Isaeva K, Chomahhidze A, et al. Dynamics of concomitant therapy in children with juvenile idiopathic arthritis treated with etanercept and methotrexate. Pediatr Neonatol 2019;60:549-55.
8. Alexeeva E, Horneff G, Dvoryakovskaya T, Denisova R, Nikishina I, Zholobova E, et al. Early combination therapy with etanercept and methotrexate in JIA patients shortens the time to reach an inactive disease state and remission: results of a double-blind placebo-controlled trial. Pediatr Rheumatol Online J 2021;19:5.
9. Bulatović Ćalasan M, de Vries LD, Vastert SJ, Heijstek MW, Wulffraat NM. Interpretation of the Juvenile Arthritis Disease Activity Score: responsiveness, clinically important differences and levels of disease activity in prospective cohorts of patients with juvenile idiopathic arthritis. Rheumatology 2013;53:307-12.
10. Wallace CA, Ruperto N, Giannini E. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. J Rheumatol 2004;31:2290-4.

11. Levälampi T, Kärki J, Rebane K, Vahasalo P, Malin M, Kroger L, et al. Etanercept for patients with juvenile idiopathic arthritis: drug levels and influence of concomitant methotrexate: observational study. Pediatr Rheumatol Online J 2023;21:27.
12. Verstegen RHJ, Shrader P, Balevic SJ, Beukelman T, Correll C, Dennos A, et al. Dosing Variation at Initiation of Adalimumab and Etanercept and Clinical Outcomes in Juvenile Idiopathic Arthritis: A Childhood Arthritis and Rheumatology Research Alliance Registry Study. Arthritis Care Res (Hoboken) 2023;75:410-22.
13. Horneff G, Schmeling H, Biedermann T, Foeldvari I, Ganser G, Girschinck HJ, et al. The German etanercept registry for treatment of juvenile idiopathic arthritis. Ann Rheum Dis 2004;63:1638-44.
14. Giannini EH, Ilowite NT, Lovell DJ, Wallace CA, Rabinovich CE, Reiff A, et al. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum 2009;60:2794-804.
15. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med 2000;342:763-9.
16. Klein A, Becker I, Minden K, Foeldvari I, Haas JP, Horneff G. Adalimumab versus adalimumab and methotrexate for the treatment of juvenile idiopathic arthritis: long-term data from the German BIKER registry. Scand J Rheumatol 2019;48:95-104.
17. Ramanan AV, Dick AD, Jones AP, Hughes D, Mckay A, Hallas AR, et al. Adalimumab in combination with methotrexate for refractory uveitis associated with juvenile idiopathic arthritis: a RCT. Health Technol Assess 2019;23:1-140.
18. Nassar-Sheikh Rashid A, Schonenberg-Meinema D, Bergkamp SC, Bakhlakh S, Vries A, Rispens T, et al. Therapeutic drug monitoring of anti-TNF drugs: an overview of applicability in daily clinical practice in the era of treatment with biologics in juvenile idiopathic arthritis (JIA). Pediatr Rheumatol Online J 2021;19:59.
19. Atiqi S, Hooijberg F, Loeff FC, Rispens T, Wolbink GJ. Immunogenicity of TNF-Inhibitors. Front Immunol 2020;11:312.
20. Machado SH, Xavier RM. Safety of tocilizumab in the treatment of juvenile idiopathic arthritis. Expert Opin Drug Saf 2017;16:493-500.
21. Iannone C, Marelli L, Costi S, Pellico MR, La Franca L, Caporali R, et al. Tocilizumab in Juvenile Idiopathic Arthritis Associated Uveitis, a Narrative Review. Children (Basel) 2023;10: 434.
22. Frampton JE. Tocilizumab: A Review of Its Use in the Treatment of Juvenile Idiopathic Arthritis. Pediatric Drugs 2013;15:515-31.
23. Thiele F, Klein A, Klotsche J, Windschall D, Dressler F, Kuemmerle Deschner J, et al. Biologics with or without methotrexate in treatment of polyarticular juvenile idiopathic arthritis: effectiveness, safety and drug survival. Rheumatology (Oxford) 2023;62:2230-8.