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Comparative efficacy and safety of etanercept and adalimumab in the treatment of polyarticular juvenile idiopathic arthritis

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Abstract

Objective This study aims to evaluate the efficacy and safety of Etanercept and Adalimumab in the treatment of polyarticular juvenile idiopathic arthritis (pJIA).

Methods From Jan 2021 to Oct 2023, 66 pJIA patients were prospectively randomized into Etanercept ($n=33$) and Adalimumab ($n=33$) groups at our hospital. Efficacy, via Juvenile Arthritis Disease Activity Score 10 (JADAS-10), and anti-cyclic citrullinated peptide (CCP), tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell count (WBC) were assessed pre-treatment and at 1-, 3-, 6-month intervals post-treatment. Adverse reactions were monitored.

Results Two groups showed comparable efficacy ($P>0.05$) at baseline in anti-CCP, TNF-α, CRP, ESR, WBC, and JADAS-10 score. Treatment for a period of 1 to 3 months led to statistically significant reductions in these markers over time ($P<0.05$). Adalimumab group was found significantly lower levels of mentioned markers than Etanercept group at 1–3 months ($P<0.05$), but after 6 months, statistical differences vanished ($P>0.05$). Normal total bilirubin, alanine transaminase, aspartate aminotransferase, serum creatinine levels were detected post-3 months in both groups; with similar adverse reaction rates ($P>0.05$).

Conclusion Both Etanercept and Adalimumab are effective and safe for managing pJIA, demonstrating significant reductions in inflammatory markers and disease activity with no significant difference in efficacy or safety profiles.

Clinical trial number Not applicable.

Keywords Etanercept, Adalimumab, Polyarticularjuvenile idiopathic arthritis, Efficacy, Safety

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Introduction

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease affecting children under 16 years of age, characterized by persistent arthritis lasting for more than six weeks with no identifiable cause [1–3]. The incidence of JIA varies widely, ranging from 16 to 150 cases per 100,000 children [2, 4]. The International League of Associations for Rheumatology (ILAR) classification, updated in 2001, categorizes JIA into seven distinct types, among which oligoarticular, polyarticular, and systemic forms are most prevalent. Polyarticular JIA (pJIA), defined by the involvement of five or more joints within six months of disease onset, can lead to severe outcomes such as irreversible joint damage, deformities, systemic symptoms, and multi-organ involvement [5, 6]. These complications significantly affect the growth, development, and overall quality of life in affected children [7].

Recent advances in understanding the pathophysiology of pJIA and the development of targeted therapies have revolutionized disease management. Among the various treatment options, biologic agents targeting tumor necrosis factor-alpha (TNF-α) have shown promising results [8, 9]. TNF-α plays a pivotal role in the inflammatory process of pJIA, making it a key therapeutic target [10].

Adalimumab, a fully human recombinant IgG1 monoclonal antibody targeting TNF-α, is globally recognized for its efficacy in treating various inflammatory conditions, including pJIA [11]. Etanercept, a recombinant human TNF receptor-Fc fusion protein, is another TNF-α inhibitor with structural and functional similarities to infliximab. Approved by the China Food and Drug Administration (CFDA) for rheumatoid arthritis in 2005, Etanercept has been widely used in clinical practice [12]. Despite the widespread use of both agents, comparative clinical research specifically evaluating their efficacy and safety in the treatment of pJIA remains limited. Therefore, this study aims to provide a comprehensive evaluation of the efficacy and safety profiles of Etanercept and Adalimumab in managing pJIA.

By analyzing clinical outcomes and laboratory parameters, this study seeks to contribute valuable insights into the comparative effectiveness of these two biologic agents, ultimately guiding optimal therapeutic strategies for children suffering from pJIA.

Methods

Participants

This prospective study enrolled 66 patients diagnosed with pJIA treated at our hospital from January 2021 to October 2023. The patients were randomly assigned to either the Etanercept group or the Adalimumab group, with 33 patients in each group. The inclusion criteria were: (1) diagnosis of pJIA according to the revised ILAR criteria (2001) [13], which include children under 16 years old with unexplained arthritis persisting for more than six weeks; (2) inadequate response to conventional oral medications (nonsteroidal anti-inflammatory drugs and methotrexate) for more than three months; (3) presence of poor prognostic factors, such as young age at onset, recurrent joint symptoms, and evidence of bone and joint destruction; (4) signed informed consent from all participants or their guardians. Exclusion criteria included: (1) potential tuberculosis infection as confirmed by tuberculin purified protein derivative skin test, chest X-ray or high-resolution CT, and T-cell enzyme-linked immunospot assay or lymphocyte culture interferon-gamma release assay; (2) acute or chronic active infections as determined by comprehensive bacterial, viral, fungal, and parasitic tests; (3) male patients over 16 years old with HLA-B27 positive arthritis; (4) presence of psoriasis; (5) first-degree relatives with HLA-B27 associated diseases including ankylosing spondylitis, arthritis associated with enthesitis, acute anterior uveitis, or sacroiliitis; (6) diagnosis of systemic juvenile arthritis.

Treatment protocols

Patients in the conventional antirheumatic drug treatment group received standard antirheumatic therapy, which included nonsteroidal anti-inflammatory drugs (NSAIDs), methotrexate, sulfasalazine, and prednisone, along with functional exercises and physical therapy.

Etanercept Group: Patients received conventional antirheumatic drugs in combination with subcutaneous injections of Etanercept at a dose of 0.4 mg/kg, administered twice weekly for three months.

Adalimumab Group: Patients received regular antirheumatic drugs in addition to Adalimumab. For patients weighing between 15 and 30 kg, Adalimumab was administered at a dose of 20 mg every two weeks. For patients weighing ≥ 30 kg, the dose was 40 mg every two weeks. Treatment continued for three months.

Outcome measures

Efficacy evaluation

The Juvenile Arthritis Disease Activity Score 10 (JADAS-10) system was used to assess treatment efficacy [14]. The criteria for efficacy were: (1) Complete remission: JADAS-10 score of ≤ 1 following treatment. (2) Partial remission: A reduction of ≥ 30% in the JADAS-10 score compared to baseline, with no recurrence within six months. (3) Incomplete effective: a decrease of less than 30% in the JADAS-10 score relative to baseline, accompanied by fluctuating disease activity within six months, without achieving a stable state of partial remission. (4) Ineffectiveness: No change or an increase in the JADAS-10 score.

The effective rate was calculated as the percentage of patients achieving complete or partial remission.

Laboratory tests

One day before treatment, and at one month, three months, and six months post-treatment, blood samples (3 mL) were collected from each patient, centrifuged, and analyzed. Levels of anti-cyclic citrullinated peptide (anti-CCP) antibody, TNF-α, and C-reactive protein (CRP) were measured using enzyme-linked immunosorbent assay (ELISA). Erythrocyte sedimentation rate (ESR) was assessed with an ALIFAX fully automated rapid ESR analyzer (Test1), and white blood cell counts were determined using a Sysmex XN-1000 hematology analyzer via flow cytometry.

JADAS 10 [15]

The JADAS-10 was applied before treatment, 1 month and 3 months post-treatment. The JADAS-10 comprises 4 components: Active Joint Count (AJC), Physician Global Assessment of Disease Activity (PhGA), Parent/Patient Global Assessment of Well-being (PaGA), and ESR. Evaluators were required to assess ten specific pairs of joints, including the bilateral cervical spine, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints, hips, knees, and ankles. The AJC score was calculated based on the number of joints exhibiting active disease. Each joint received a score of 1 for active inflammation and 0 for no inflammation. For the PhGA, physicians rated disease activity on a visual analog scale from 0 to 10, where 0 indicated no disease activity and 10 represented the highest level of disease activity. For the PaGA, patients or parents evaluated the patient's health status on a similar 0–10 scale, with 0 indicating optimal health and 10 representing the worst health status. ESR values less than 20 mm/h were assigned 0 points, ESR values greater than 120 mm/h were assigned 12 points, and ESR values between 20 and 120 mm/h were scored using the formula (ESR − 20) / 10. The total ESR score ranged from 0 to 12 points.

The sum of the scores from these 4 components yielded a total JADAS-10 score ranging from 0 to 47, with higher scores indicating greater disease activity. Generally, a total score < 10 indicates low disease activity, a score of 10–20 indicates moderate activity, and a score > 20 indicates high disease activity.

Safety assessment

Three months post-treatment, liver function parameters (total bilirubin [TBil], alanine aminotransferase [ALT], aspartate aminotransferase [AST]) and serum creatinine (Scr) were measured. Adverse reactions were meticulously documented throughout the treatment period.

Statistical analysis

Data were analyzed using SPSS 21.0 software. All measurement data were assessed for normal distribution (Supplementary Table 1). Measurement data that followed normal distribution were presented as mean ± standard deviation (mean ± SD). Comparisons between two independent groups were analyzed using the independent samples t-test, while comparisons within the same group were analyzed using the paired samples t-test. For skewed data, results were expressed as median and interquartile range (IQR), and the Wilcoxon rank-sum test was utilized. Repeated measures data at different time points within the same group were analyzed using one-way ANOVA. Categorical variables were expressed as percentages (%) and analyzed with the chi-square (χ^2) te**st.** A p-value of less than 0.05 was considered statistically significant.

Results

Comparison of baseline characteristics

The baseline characteristics of the patients in the Etanercept and Adalimumab groups were comparable. There were no statistically significant differences between the two groups regarding age, body mass index (BMI), gender distribution, or disease duration ($P > 0.05$) (Table 1).

Comparison of efficacy

The overall efficacy, as determined by the JADAS-27 system, showed no significant difference between the two groups. The total effective rates were 81.82% for the Etanercept group and 78.79% for the Adalimumab group ($P > 0.05$) (Table 1).

Comparison of laboratory indicators and JADAS-10 scores

One day before treatment, there were no statistically significant differences between the two groups in terms of anti-cyclic citrullinated peptide antibodies, TNF-α, CRP, ESR, white blood cell count, and JADAS-10 scores ($P > 0.05$). After 1 month, 3 months, and 6 months of treatment, both groups showed a reduction in anti-cyclic citrullinated peptide antibodies, TNF-α, CRP, ESR, white blood cell count, and JADAS-10 scores, with more pronounced decreases over time ($P < 0.05$). However, after 1 month and 3 months of treatment, the Adalimumab group had significantly lower levels of anti-cyclic citrullinated peptide antibodies, TNF-α, CRP, ESR, white blood cell count, and JADAS-10 scores compared to the Etanercept group ($P < 0.05$). After 6 months of treatment, there were no statistically significant differences between the two groups in anti-cyclic citrullinated peptide antibodies, TNF-α, CRP, ESR, white blood cell count, and JADAS-10 scores ($P > 0.05$) (Table 2).

Table 1 Comparison of general information between the two groups

Indicator	Etanercept group (*n* = 33)	Adalimumab group (*n* = 33)	χ^2/t	*P*	Significant difference in normal distribution (*P*)
Age (years)	6.84 ± 1.23	6.79 ± 1.19	-0.237	0.813	0.526
BMI (kg/m^2)	20.87 ± 2.18	20.72 ± 2.09	-0.404	0.687	0.298
Gender (M/F)	38/28	36/30	0.123	0.726	0.156
Disease duration (months)	7.65 ± 1.03	7.57 ± 1.16	-0.419	0.676	0.270
Rheumatoid rheumatoid Positive (n)	2	1	0.341	0.559	0.076
Total effective rate (%)	54(81.82)	49(74.24)	1.105	0.293	0.526
Complete remission (n)	30	28			0.298
Partial remission (n)	24	21			0.156
Incomplete effective (n)	10	13			0.270
Ineffective (n)	2	4			0.076

Note: BMI, body mass index

Table 2 Comparison of laboratory indicators and JADAS-10 scores between the two groups (n, %)

Indicator	Time	Etanercept Group (*n* = 33)	Adalimumab Group (*n* = 33)	t	*P*	Significant difference in normal distribution (*P*)
CCP (RU/mL)	1 day before treatment	26.76 ± 2.32	26.47 ± 2.17	-0.716	0.475	0.553
	1 month after treatment	9.87 ± 1.03	6.93 ± 1.08	-16.004	<0.001	0.260
	3 months after treatment	4.39 ± 0.41	3.42 ± 0.37	-16.004	<0.001	0.096
TNF-α (ng/mL)	1 day before treatment	8.76 ± 1.37	8.68 ± 1.42	-0.329	0.742	0.343
	1 month after treatment	5.19 ± 0.76	4.03 ± 0.81	-8.484	<0.001	0.193
	3 months after treatment	4.18 ± 0.72	3.76 ± 0.69	-3.422	0.001	0.174
CRP (ng/mL)	1 day before treatment	12.39 ± 1.32	12.45 ± 1.24	0.269	0.788	0.315
	1 month after treatment	5.03 ± 1.06	4.09 ± 1.08	-5.046	<0.001	0.263
	3 months after treatment	4.14 ± 1.09	3.53 ± 1.14	-3.142	0.021	0.275
ESR (mm/H)	1 day before treatment	22.18 ± 2.13	22.36 ± 2.09	0.490	0.625	0.519
	1 month after treatment	15.56 ± 1.09	13.74 ± 1.05	-9.769	<0.001	0.263
	3 months after treatment	13.87 ± 1.14	13.08 ± 1.32	-3.680	<0.001	0.304
White blood cell count (10×10^9/L)	1 day before treatment	10.63 ± 1.45	10.56 ± 1.54	-0.269	0.789	0.368
	1 month after treatment	5.76 ± 0.74	4.31 ± 1.55	-6.858	<0.001	0.301
	3 months after treatment	3.87 ± 0.67	3.45 ± 0.63	-3.710	<0.001	0.160
JADAS-10 (score)	1 day before treatment	23.87 ± 0.45	23.82 ± 0.53	-0.584	0.560	0.121
	1 month after treatment	8.34 ± 0.42	6.39 ± 0.39	-27.640	<0.001	0.100
	3 months after treatment	7.42 ± 0.17	5.89 ± 0.13	-58.081	<0.001	0.076

Note: CCP, Cyclic Citrullinated Peptide; TNF-α, Tumor Necrosis Factor-alpha; CRP, C-Reactive Protein; ESR, Erythrocyte Sedimentation Rate; JADAS-10, Juvenile Arthritis Disease Activity Score in 10 joints

Table 3 Comparison of adverse reactions between the two groups (n, %)

Indicator	Etanercept group (*n* = 33)	Adalimumab group (*n* = 33)	χ^2	*P*	Significant difference in normal distribution (*P*)
erythema	1	1			
pruritus	2	2			
pain	0	0			
swell	1	2			
Total adverse reaction rate (%)	4	5	0.129	0.719	0.092

Comparison of adverse reactions

After three months of treatment, liver function parameters (TBil, ALT, AST) and serum creatinine (Scr) levels remained within normal ranges for both groups. There were no significant differences in the number of infection-related adverse reactions and the total incidence of adverse reactions between the two groups ($P > 0.05$) (Table 3).

Discussion

pJIA presents a significant clinical challenge due to its chronic course, recurrent joint symptoms, progressive bone and joint damage, poor prognosis, and substantial

impact on the quality of life of affected children. Treating pJIA is a priority for both patients and healthcare providers alike [16]. While the precise pathogenesis of pJIA remains unclear, it is widely recognized that a combination of genetic predisposition and environmental factors such as infections triggers complex, dysregulated inflammatory responses in affected children [17].

Significant strides have been made in pJIA treatment, including traditional nonsteroidal anti-inflammatory drugs, methotrexate, and immunosuppressants. However, research indicates that some children with pJIA exhibit inadequate responses to traditional therapies, frequent relapses post-remission, or intolerable side effects [18]. Consequently, biologic disease-modifying antirheumatic drugs (DMARDs) have gained increasing attention in managing JIA. TNF-α, a pivotal pro-inflammatory cytokine, plays a crucial role in pJIA pathogenesis, secreted by various immune and non-immune cells [19]. TNF-α inhibitors have revolutionized pJIA treatment, offering the potential for long-term maintenance of minimal disease activity or even complete remission. Both Etanercept and Adalimumab, as TNF-α inhibitors, are key players in this therapeutic landscape. Further investigation is warranted to explore the efficacy of both methods in the treatment of pJIA.

Etanercept, a recombinant fusion protein, binds to TNF, blocking its interaction with cell surface receptors and curtailing its activity [20]. The study conducted by Zaripova et al. [21] demonstrated that biological agents are efficacious in the treatment of pJIA and elucidated the underlying mechanisms of their therapeutic effects. Onel et al. [22] proposed that modifications in management strategies, such as earlier initiation of biologics, introduction of biosimilars, and targeted synthetic disease-modifying antirheumatic drugs like tofacitinib, have significantly improved clinical outcomes for patients while identifying potential areas for further improvement and research. Hinze et al. [23] highlighted that the most advanced treatments for pJIA involve biological agents targeting the IL-1 and IL-6 pathways, which effectively control disease onset. Our study's findings of comparable efficacy between the two groups ($P>0.05$) affirm that both Etanercept (81.82%) and Adalimumab (78.79%) can effectively manage clinical symptoms in children with pJIA, consistent with previous research.

In recent years, the discovery of anti-CCP antibodies has highlighted their association with pJIA [24]. These antibodies are recognized as determinants of multiple autoantigens in pJIA, with high sensitivity and specificity, making them valuable for early diagnosis [25]. CRP, an acute-phase reactant, serves as a sensitive indicator of inflammation severity and activity [14]. TNF-α, by binding to its receptors, triggers signaling pathways that increase the expression of cytokines like IL-1 and IL-6, promote cell apoptosis, and facilitate inflammatory cell aggregation and infiltration. The role of TNF-α in the pathogenesis of pJIA is evident [26]. White blood cell count and ESR are also important inflammatory markers in pJIA, reflecting disease severity and activity [27]. Ling [28] demonstrated that the combination therapy of biological agents with other medications for pJIA can effectively manage disease severity. Specifically, this approach significantly reduced the ESR from 40 mm/H before treatment to 5 mm/H after three months of treatment, and CRP levels decreased from 58 mg/L to 3 mg/L over the same period. Chen [29] reported that patients with pJIA exhibited WBC of $(8.74\pm3.38)\times10^9$/L prior to treatment, which increased slightly to $(8.96\pm2.70)\times10^9$/L after three months of therapy. ESR levels decreased from (52.67 ± 38.82) mm/H before treatment to (36.61 ± 34.17) mm/H post-treatment. CRP levels also showed a reduction from (41.15 ± 33.7) mg/L before treatment to (33.91 ± 38.40) mg/L after three months. The JADAS-27 score declined significantly from (27.11 ± 6.72) before treatment to (7.63 ± 5.85) after three months. These findings suggest that the use of biological agents in this patient population is both safe and effective. Research by Simonds et al. [30] supports that both Adalimumab and Etanercept effectively reduce inflammatory factor levels and minimize adverse reactions in pJIA. Liu et al. [31] reported that Etanercept is effective in treating pJIA, demonstrating a reduction in inflammatory markers. Specifically, the ESR decreased from (17.3 ± 5.69) mm/H to (15.10 ± 4.90) mm/H, and CRP levels dropped from (6.80 ± 2.85) mg/L to (5.30 ± 2.47) mg/L after three months of treatment. Additionally, the incidence of adverse reactions was reduced by 15%. The results of this study showed that after 1 month, 3 months, and 6 months of treatment, both groups experienced reductions in anti-cyclic citrullinated peptide antibodies, TNF-α, CRP, ESR, white blood cell count, and JADAS-10 scores, with more pronounced decreases over time ($P<0.05$). However, after 1 month and 3 months of treatment, the Adalimumab group had significantly lower levels of anti-cyclic citrullinated peptide antibodies, TNF-α, CRP, ESR, white blood cell count, and JADAS-10 scores compared to the Etanercept group ($P<0.05$). After 6 months of treatment, there were no statistically significant differences between the two groups in these parameters ($P>0.05$), indicating that both Adalimumab and Etanercept effectively and rapidly reduced anti-cyclic citrullinated peptide antibodies, TNF-α, CRP, ESR, white blood cell count, and JADAS-10 scores, thereby lowering inflammatory factor levels and controlling the disease in patients with polyarticular juvenile idiopathic arthritis. However, by 6 months of treatment, the levels of these parameters were similar between the two groups.

Research by van et al. [32]and Brunner et al. [33] has demonstrated that both Etanercept and Adalimumab reduce the burden of disease and improve overall well-being in children with pJIA. Van et al. [32] indicated that the estimated mean difference in the reduction of active joint count was −0.36 (95% CI: -1.02 to 0.30; $P=0.28$), and the odds ratio for adverse events was 0.48 (95% CI: 0.16 to 1.44; $P=0.19$). Lovell et al. [34] observed no increase in severe adverse events over a long-term follow-up of children treated with Adalimumab. Our study's findings, showing that TBil, ALT, AST, and Scr levels remained within normal ranges and no significant difference in adverse reactions between the groups, align with these studies, suggesting a high safety profile for both medications. Nonetheless, prolonged use of biologics requires close monitoring due to potential secondary infections and drug resistance, impacting long-term treatment outcomes. Regular follow-up is essential to ensure the safety and effectiveness of therapy in children.

In conclusion, both Etanercept and Adalimumab are effective in controlling the clinical symptoms of children with pJIA, showing comparable efficacy. Adalimumab has been shown to rapidly and effectively reduce anti-cyclic citrullinated peptide antibodies, TNF-α, CRP, ESR, white blood cell count, and JADAS-10 scores in patients with pJIA. This indicates a significant reduction in inflammatory factor levels and effective disease control. Furthermore, Adalimumab's bi-weekly dosing schedule requires fewer injections, resulting in less discomfort for patients. Importantly, neither medication increases adverse reactions, showcasing a high safety profile. However, this study is limited by a small sample size and short follow-up period. Further research is warranted to explore the long-term efficacy and safety of these treatments and to investigate the maintenance of remission after dose reduction or discontinuation.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12887-025-05594-9.

Supplementary Material 1

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None.

Author contributions
LG and YG contributed to the conception and design of the study. XC and JG contributed to the acquisition of data. YY, DZ contributed to the analysis of data. LG and YG wrote the manuscript. YY revised the manuscript. All authors approved the final version of the manuscript.

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Data availability
Data is provided within the manuscript files.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Ethics Committee of Children's Hospital of Hebei Province(NO.2022-143B), and the study was performed in accordance with the Helsinki II declaration. Signed informed consent from all participants or their guardians.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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