Etanercept treatment for children with refractory juvenile idiopathic arthritis

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Background: Etanercept has been shown to be an effective treatment for juvenile idiopathic arthritis (JIA). In this study, we evaluated the effectiveness of etanercept therapy in the treatment of refractory JIA.

Methods: This was a retrospective analysis of 11 patients with refractory JIA (polyarticular type n = 7; pauciarticular type, n = 2; systemic type, n = 2) who received treatment with etanercept during the period 2005–2009 in a medical center. The indications for etanercept treatment included persistent fever, arthritis/arthralgia, or elevated levels of inflammatory mediators after treatment with methotrexate and/or prednisolone for more than 6 months. The patients were treated with etanercept (0.4 mg/kg, with maximal 25 mg, subcutaneously, twice a week) for a total of 12 months.

Results: The degree of arthritis/arthralgia improved (range of motion and painful sensation of involved joints), and the levels of inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) decreased progressively in 10 of the 11 patients (p < 0.05) at 1-, 3-, 5-, and 12-month follow-up after treatment with etanercept. Mean hemoglobin levels significantly increased, whereas mean platelet counts decreased after etanercept treatment (p < 0.05). Only one patient with systemic type of JIA failed to respond to the treatment after 6 weeks of etanercept therapy. Methotrexate, prednisolone, and other immunosuppressive drugs were successfully discontinued after a mean of 2.5 months (range, 1–5 months) of etanercept therapy in the 10 patients who responded to etanercept treatment.

KEYWORDS
Etanercept; Juvenile idiopathic arthritis; Tumor necrosis factor-alpha

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in childhood. It is a diagnosis of exclusion and defined as arthritic symptoms of unknown etiology lasting for at least 6 weeks in patients younger than 16 years. Approximately 30% of patients respond to the nonsteroidal anti-inflammatory drugs and an appropriate program of physical therapy. Most patients, however, require more aggressive therapy with antimicrobial drugs. JIA can lead to severe disability and is associated with life-threatening complications, particularly in patients who do not respond to conventional treatment. Although JIA has been divided into subtypes, we are still unable to identify those children who will benefit from more aggressive therapy. Most patients with systemic- or polyarticular-onset JIA need other second-line medications. Hydroxychloroquine and methotrexate (MTX) have been shown to be effective alternatives to nonsteroidal anti-inflammatory drugs. Although glucocorticoids are effective in treating JIA, long-term administration can lead to undesired side effects such as short stature. MTX (10 mg/m²/wk) is the standard treatment regimen for JIA. The patients who do not respond to MTX after 6 months of treatment are classified as having refractory JIA. In such cases, therapies involving combinations of MTX with corticosteroids or other immunosuppressive drugs, such as o-penicillamine, gold compounds, or cyclophosphamide, should be considered.

Biological agents, such as etanercept and infliximab, have recently been shown to be effective in the treatment of refractory JIA. Etanercept, a recombinant human soluble p75 tumor necrosis factor receptor that binds to tumor necrosis factor-alpha and renders it biologically unavailable, has been shown to be effective and well tolerated in patients with rheumatoid arthritis. Results from a multicenter pediatric trial performed in the United States showed that etanercept was effective and well tolerated in 74% of children (n = 69) with JIA regardless of the subtypes of disease.

In the present study, we retrospectively evaluated the effectiveness of etanercept treatment in Taiwanese patients with JIA refractory to MTX and/or prednisolone. We also evaluated when MTX and/or prednisolone should be tapered or discontinued after initiation of etanercept treatment. The effectiveness of etanercept was determined by comparing the dynamic changes in inflammatory markers (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and complete blood counts at baseline with those at 1, 3, 5, and 12 months after etanercept treatment.

Methods

We evaluated the effectiveness of etanercept in 11 consecutive patients in whom refractory JIA had been diagnosed at the Chang Gung Memorial Hospital—Kaohsiung Medical Center based on the International League of Associations for Rheumatology classification criteria for JIA. Among the 11 children, 7 patients had polyarticular type of JIA, 2 patients had pauciarticular type of JIA, and 2 patients had systemic onset of JIA. All the children had systemic features, arthritis/arthralgia, or high levels of inflammatory mediators (CRP and/or ESR) after treatment with MTX (>10 mg/m²/wk) and/or prednisolone (0.25 mg/d/kg) for more than 6 months. The patients were treated with etanercept (0.4 mg/kg, with maximal 25 mg, subcutaneously, twice a week) for 12 months. Complete blood count (including total white blood cell counts, platelet counts, and hemoglobin levels), aspartate aminotransferase (AST) levels, alanine aminotransferase (ALT) levels, CRP levels, and ESR, which had been measured 1 month before etanercept treatment (baseline) and at 1, 3, 5, and 12 months after the treatment began, were obtained from the medical records. Body height (BH) from one patient who received etanercept for more than 40 months was also included to evaluate the kinetic change in height after etanercept treatment. The study protocol was approved by the institutional review board of the Chang Gung Memorial Hospital.

Statistical analysis

Laboratory values are presented as mean ± standard error. Significant differences in levels of CRP, ESR, AST, ALT, total WBC, hemoglobin, and platelets at baseline and after treatment with etanercept were tested by a paired-sample t test. A p value of less than 0.05 was considered statistically significant. All statistical tests were performed using SPSS 12.0 for Windows XP (SPSS Inc., Chicago, IL, USA).

Results

A total of 11 patients (5 boys and 6 girls) with JIA refractory to MTX and/or prednisolone received etanercept treatment. Rheumatoid factor was positive in two patients (18.2%, 2/11), anti-nuclear antibody was positive in four patients (36.4%, 4/11), and human leukocyte antigen-B27 was positive in three patients (33%, 3/9). The mean age at diagnosis of JIA was 103.6 months, and the mean age of patients when etanercept therapy began was 124.6 months (Table 1).

MTX and/or prednisolone were tapered and discontinued at a mean of 2.52 months (range, 1–5 months) after starting etanercept treatment. At Month 5 of the treatment protocol, all the patients were being treated with etanercept therapy alone. There were no adverse effects and cases of atypical mycobacteria infection, diarrhea, sepsis, or cellulitis during the follow-up period. Elevated liver enzyme levels (AST, 90 U/L; ALT, 86 U/L) were noted after 1.5 months of etanercept therapy in one patient with upper respiratory tract infection (Patient 7). The liver enzyme levels had returned to normal at 3-month follow-up.

Conclusion: Etanercept is beneficial for patients with polyarticular and pauciarticular type of JIA that is refractory to conventional treatment but less beneficial for systemic type of JIA.

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Table 1  Demographic data of juvenile idiopathic arthritis patients who received etanercept treatment

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Subtype</th>
<th>Age (diagnosis)</th>
<th>Age (Enbrel)</th>
<th>DMARDs</th>
<th>Corticosteroid</th>
<th>RF</th>
<th>ANA</th>
<th>HLA-B27</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>Poly</td>
<td>7 yr 5 mo</td>
<td>14 yr 2 mo</td>
<td>MTX</td>
<td>+</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>Poly</td>
<td>9 yr</td>
<td>9 yr 6 mo</td>
<td>MTX</td>
<td>±</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>Systemic</td>
<td>1 yr 9 mo</td>
<td>7 yr 2 mo</td>
<td>MTX + Cyc</td>
<td>+</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>Poly</td>
<td>9 yr 2 mo</td>
<td>9 yr 9 mo</td>
<td>MTX</td>
<td>+</td>
<td></td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>Poly</td>
<td>4 yr 4 mo</td>
<td>6 yr 1 mo</td>
<td>MTX</td>
<td>+</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>Pauci</td>
<td>12 yr 10 mo</td>
<td>13 yr 11 mo</td>
<td>MTX + Aza</td>
<td>+</td>
<td></td>
<td>-</td>
<td>+ intra-articular</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>Systemic</td>
<td>14 yr 11 mo</td>
<td>15 yr 8 mo</td>
<td>MTX</td>
<td>+</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>Poly</td>
<td>10 yr 6 mo</td>
<td>11 yr</td>
<td>MTX</td>
<td>+</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>Poly</td>
<td>4 yr 2 mo</td>
<td>4 yr 8 mo</td>
<td>MTX</td>
<td>+</td>
<td></td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>Poly</td>
<td>5 yr 5 mo</td>
<td>6 yr 8 mo</td>
<td>MTX</td>
<td>+</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>Pauci</td>
<td>14 yr 8 mo</td>
<td>15 yr 10 mo</td>
<td>MTX</td>
<td>+</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

ANA = anti-nuclear antibody; Aza = azathioprine; Cyc = cyclosporine; F = female; HLA-B27 = human leukocyte antigen-B27; Intra-articular = intra-articular corticosteroids injection; M = male; MTX = methotrexate; Pauci = pauciarticular type of JIA; Poly = polyarticular type; RF = rheumatoid factor; Systemic = systemic type of JIA.

There was a marked progressive reduction in CRP levels and ESR during the 12-month follow-up period (p < 0.05; Table 2). Persistent fever and arthritic symptoms at Week 6 of etanercept therapy occurred in one child (Patient 3) with systemic-onset JIA. Etanercept was discontinued, and the patient gained 20 cm in height. In the four patients who had received etanercept treatment for less than 40 months and for whom BH data were available, the gain in height significantly increased from a mean of 3.5 ± 0.96 cm before treatment to a mean of 7.5 ± 0.94 cm 10 months after the initiation of etanercept treatment (p < 0.05).

Discussion

Despite the advantages of MTX over other conventional immunosuppressive agents, many patients receiving MTX experience at least some degree of toxicity.8 The most common adverse events in the pre—folate supplementation era included nausea, vomiting, and mucous membrane ulceration.10 Rare but serious adverse effects, such as hepatotoxicity, pneumonitis, opportunistic infections, and the development of certain types of malignancies (e.g. non-Hodgkin lymphoma) have been shown to be associated with MTX therapy.9–12 Therefore, etanercept provides the opportunity to discontinue MTX and decreases the potential toxicities. Placebo-controlled trials and long-term prospective studies on JIA have shown that MTX is less effective in children than in adults.13–16 MTX is not effective or well tolerated in some patients with JIA, and higher doses of MTX may be associated with greater toxicity.17

Etanercept is safe and well tolerated.18 In our study, there were no deaths and adverse reactions to the drug.

Table 2  The dynamic change of laboratory data before and after etanercept treatment

<table>
<thead>
<tr>
<th></th>
<th>Before etanercept treatment</th>
<th>1 mo after etanercept treatment</th>
<th>p&lt;sup&gt;b&lt;/sup&gt;</th>
<th>3 mo after etanercept treatment</th>
<th>p&lt;sup&gt;b&lt;/sup&gt;</th>
<th>5 mo after etanercept treatment</th>
<th>p&lt;sup&gt;b&lt;/sup&gt;</th>
<th>12 mo after etanercept treatment</th>
<th>p&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (×10&lt;sup&gt;3&lt;/sup&gt;/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>9.0 ± 0.9</td>
<td>6.9 ± 0.6</td>
<td>0.044&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.3 ± 0.5</td>
<td>0.089</td>
<td>7.0 ± 0.7</td>
<td>0.105</td>
<td>7.5 ± 0.3</td>
<td>0.06</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.4 ± 0.44</td>
<td>12.4 ± 0.49</td>
<td>0.009&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12.4 ± 0.52</td>
<td>0.031&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12.4 ± 0.46</td>
<td>0.008&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12.8 ± 0.68</td>
<td>0.037&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Platelet (×10&lt;sup&gt;3&lt;/sup&gt;/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>38.2 ± 2.7</td>
<td>28.7 ± 1.8</td>
<td>0.013&lt;sup&gt;a&lt;/sup&gt;</td>
<td>30.1 ± 2.2</td>
<td>0.012&lt;sup&gt;a&lt;/sup&gt;</td>
<td>27.8 ± 2.0</td>
<td>0.002&lt;sup&gt;a&lt;/sup&gt;</td>
<td>26.5 ± 1.96</td>
<td>0.002&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>35.1 ± 11.3</td>
<td>6.7 ± 3.0</td>
<td>0.002&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.25 ± 1.0</td>
<td>0.017&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.82 ± 0.6</td>
<td>0.016&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.3 ± 0.5</td>
<td>0.03&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>26.4 ± 3.7</td>
<td>14.9 ± 2.5</td>
<td>0.015&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9.6 ± 1.4</td>
<td>0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.0 ± 3.1</td>
<td>0.006&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.1 ± 0.9</td>
<td>0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data are presented as mean ± standard error.

<sup>b</sup> The p values were tested by paired-sample t test and nonparametric test. All the p values were tested with values from before etanercept treatment. (n = 10, excluded Patient 3 who failed to respond to etanercept during 6 weeks of treatment); *p < 0.05, statistical significant.

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; WBC = white blood cell count.
Treatment was discontinued in one patient because of fever and persistent symptoms after etanercept treatment for 6 weeks. In another patient, AST and ALT were elevated after four doses of etanercept; however, the increase in liver enzyme levels was because of underlying upper respiratory tract infection and not because of etanercept treatment. Liver enzyme levels returned to within normal range after the infection resolved. The findings from this study provide further evidence that etanercept is a safe and an effective agent for the treatment of refractory JIA.

To the best of our knowledge, no studies have investigated the optimal timing in which MTX and/or prednisolone can be tapered or discontinued after etanercept treatment. Based on our findings, we suggest that disease-modifying anti-inflammatory drugs and prednisolone can be ceased within 5 months after initiation of etanercept treatment. All the patients who responded to etanercept continued to respond to etanercept after MTX and/or prednisolone had been discontinued. Large-scale multicenter trials are needed to confirm our findings.

Vojvodic et al. reported that etanercept improves body growth in most patients with JIA. In our study, there was a significant increase in mean BH after etanercept treatment. Further investigation with long-term follow-up is needed to clarify the association between etanercept treatment and changes in BH. There were only few case reports of etanercept treatment for refractory JIA in Taiwan; here, we reported our experience of etanercept treatment for 11 refractory JIA.

In conclusion, etanercept is beneficial for patients with polyarticular and pauciarticular type of JIA that is refractory to conventional treatment but less beneficial for systemic type of JIA.

Acknowledgments

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