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REVIEW ARTICLE

Guidelines on the use of etanercept for juvenile idiopathic arthritis in Japan

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Abstract Etanercept is a dimeric fusion protein consisting of the extracellular domain of human tumor necrosis factor receptor II (TNFR II, molecular weight 75 kDa) coupled to the Fc region of human immunoglobulin (IgG1). It is produced by recombinant DNA technology by first introducing the gene into Chinese hamster ovarian cells and then purifying the protein from the culture supernatant. The mechanism of action of etanercept consists of binding to serum TNF-α and lymphotoxin (LT)-α (TNF-β), which prevents TNF-α and LT-α from binding to the TNF-α receptor on the plasma membrane of the target cell. Etanercept is currently approved for treating adult rheumatoid arthritis (RA) in more than 70 countries worldwide. In Japan, it was approved for this target group in January 2005. The USA and Europe were the first to approve entanercept for use in treating juvenile idiopathic arthritis (JIA), initially for the treatment of active polyarticular JIA in patients not responding to disease-modifying antirheumatic drugs (USA in May 1999, followed by the EU in February 2000). Thereafter, the drug received approval for the treatment of JIA in many other countries. In Japan, children who have been diagnosed and treated according to Yokota et al. (Mod Rheumatol 17:353–363, 2007), but who have responded poorly to treatment must move onto the next stage of treatment. Such treatments include biological drugs, which, however, should be used with strict adhesion to the indications and exclusion criteria and should be used, for the time being, only by physicians trained on how to use them. In Japan, etanercept was approved in July 2009 for use in children. Although this drug has brought about a revolutionary advance in the treatment of JIA, it is our task to maximize its therapeutic effects and minimize its toxic effects. The guidelines presented here define the indications, exclusion criteria, usage, and evaluation criteria of etanercept for the treatment of polyarticular JIA.

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Keywords Juvenile idiopathic arthritis · Methotrexate · Soluble TNF-α receptor (etanercept) · Steroids

Introduction

Children who have been diagnosed and treated according to the *Proposal for juvenile idiopathic arthritis guidance on diagnosis and treatment for primary care pediatricians and nonpediatric rheumatologists (2007)* [1] but respond poorly to treatment must move onto the next stage of treatment. Such treatments include biological drugs which, however, should be used with strict adhesion to the indications and exclusion criteria and should be used, for the time being, only by physicians trained in how to use them. In Japan, two biological drugs, tocilizumab and etanercept, were approved in July 2009 for use in children. Although these drugs have brought about a revolutionary advance in the treatment of juvenile idiopathic arthritis (JIA), it is our task to maximize their therapeutic effects and minimize their toxic effects.

These guidelines presented here define the indications, exclusion criteria, usage, and evaluation criteria of etanercept for the treatment of polyarticular JIA.

General information and mechanism of action

Etanercept is a dimeric fusion protein consisting of the extracellular domain of human tumor necrosis factor receptor II (TNFR II, molecular weight 75 kDa) coupled to the Fc region of human immunoglobulin (Ig)G1. It is produced by recombinant DNA technology by first introducing the gene into Chinese hamster ovarian cells and then purifying the protein from the culture supernatant. The mechanism of action of etanercept consists of binding to serum TNF-α and lymphotoxin (LT)-α (TNF-β), thereby preventing TNF-α and LT-α from binding to the TNF-α receptor on the plasma membrane of the target cell [2–6].

A clinical study of etanercept was commenced by Immunex Corp. (currently, Amgen, Thousand Oaks, CA) in the USA, and the Food and Drug Administration approved the use of etanercept for treating rheumatoid arthritis (RA) in adults in November 1998. The drug soon thereafter (February 2000) also received approval from the European Union (EU) for treating RA in adults. Etanercept is currently approved in more than 70 countries worldwide. In Japan, etanercept was approved for treating adult RA in January 2005 [7, 8].

Entanercept was first approved for treatment of active polyarticular JIA in patients not responding to disease-modifying antirheumatic drugs (DMARD) in the USA in May 1999 followed by the EU in February 2000. The drug has since received approval for the treatment of JIA in many countries [9, 10].

Although it has not been fully elucidated whether JIA has the same pathology as RA in adults, it is commonly believed that rheumatoid factor (RF)-positive polyarticular JIA and RA share the same pathogenesis [11, 12]. The positive rate for RF in polyarticular JIA cases is 20–30%, which is lower than in RA cases (approximately 80%). However, both conditions share the same pathology in that they are characterized by articular symptoms. The expression of TNF-α and LT-α and cells expressing TNF receptors are found in the synovial fluid and synovial membrane of JIA patients, similar to their occurrence in adult RA patients, suggesting the involvement of TNF in the pathology of JIA [13, 14].

The generic name of this drug is etanercept; it is marketed under the trade name Enbrel.

Guidelines for the use of etanercept in patients with polyarticular JIA

Indication criteria

Patients will be diagnosed with JIA if the onset is before the age of 16 years and there are manifestations of arthritis of unknown cause that persist for more than 6 months. JIA is further classified into systemic JIA, characterized by arthritis together with fever, rash, pericarditis, and other systemic symptoms, and articular JIA (polyarticular or pauciarticular depending on the number of affected joints), which is predominantly characterized by arthritis. In addition, there is psoriasis-related arthritis and enthesitis-related arthritis grouped together as symptomatic JIA [15].

Indication for etanercept

Etanercept should be used in patients with JIA who manifest disease activity in multiple joints and who do not respond to treatment as recommended by the *Proposal for juvenile idiopathic arthritis guidance on diagnosis and treatment for primary care pediatricians and nonpediatric rheumatologists (2007)* [1]. This lack of response includes showing a poor response to existing therapies, such as nonsteroidal antiinflammatory drugs (NSAIDs), steroids, and methotrexate, and being unable to tolerate treatment with anti-rheumatism drugs, such as methotrexate.

The safety and efficacy of etanercept in treating systemic JIA has not been established. Furthermore, several uncontrolled studies have suggested that etanercept is less effective in patients with systemic arthritis and that the initial response is often not sustained [16].

Exclusion criteria (including contraindications) [17]

1. *Patients with septicemia or risk of septicemia*.
2. *Patients with serious infectious diseases*. Etanercept has an immune suppressive effect and thus may affect normal immune responses.
3. *Patients with active tuberculosis*. Etanercept may cause the manifestation or worsening of symptoms in patients with tuberculosis. In these patients, anti-tuberculosis drugs should be administered prior to the administration of etanercept. After the administration of etanercept, patients should be carefully monitored for the onset of tuberculosis through regular history taking and chest X-rays (preferably once a month during the first 2 months of treatment, as much as possible and at least on an as-needed basis thereafter). Since etanercept has also been associated with extrapulmonary tuberculosis (e.g., the pleural membrane and lymph nodes), monitoring should be performed taking this possibility into consideration.
4. *Patients with a previous history of hypersensitivity to ingredients of etanercept*. Etanercept may cause serious allergic reactions, such as angioedema, anaphylaxis, bronchospasm, and urticaria.
5. *Patients with an existing or previous history of demyelinating diseases (e.g., multiple sclerosis)*. Etanercept may cause demyelinating diseases, such as multiple sclerosis, optic neuritis, and transverse myelitis.
6. *Patients with congestive heart failure*.
7. *Patients with malignancy*.

Pre-treatment tests

1. *Blood test and urinalysis*. Peripheral blood tests [white blood cells (WBCs), platelet counts, and differential count of leukocytes], biochemistry [aspartate transaminase (AST), alanine transaminase (ALT), blood urine nitrogen (BUN), lactate dehydrogenase (LD), creatinine, and creatine phosphokinase], and urinalysis (protein and occult blood).
2. *Imaging*. Chest and abdominal computed tomography/magnetic resonance imaging (CT/MRI; as needed), plain X-ray, or contrast-enhanced MRI of joints.
3. *Infection screening*:
   - eliminate the risk of infectious diseases by thorough history taking;
   - pneumonia: plain chest X-ray and chest CT scan;
   - hepatitis: anti-hepatitis B/C antibody screening;
   - tuberculosis and latent fungal infectious diseases: tuberculin reaction test, Quanti FERON assay (QFT-2G) (as needed), plain chest X-ray, chest CT, measurement of blood β-D glucan level and KL-6 level;
4. *Evaluation of cardiac function*:
   - echocardiography ejection fraction/fractional shortening (EF/FS);
   - plain chest X-ray and measurement of brain natriuretic peptides or NT-proBNP (as needed).

Administration

1. *Dosage and administration*:
   - *For patients with JIA manifesting disease activity in multiple joints*: dissolve etanercept in 1 ml of Japanese Pharmacopoeia (JP) water for injection or choose etanercept 25 mg pre-filled syringes as an alternative option. The usual dose for children is 0.2–0.4 mg/kg etanercept administered subcutaneously twice weekly. The dose for children should not exceed the standard dose for adults (25 mg per administration)
2. *Reference*:
   - *Dosage and administration for treatment of RA in adults*: dissolve etanercept in 1 ml of JP water for injection. The usual adult dose is 10–25 mg of etanercept (recombinant) administered subcutaneously twice weekly.
3. *Instructions to patients regarding self-injection of etanercept*: etanercept may be self-injected twice weekly. Patients or their parents must be given instructions on self-injection techniques.

a. Prior to starting treatment with etanercept, facilitate an understanding of self-injection techniques and drug management using a Starter Kit (video and booklets).
b. Instructions on self-injection should be given by a physician on an outpatient or inpatient basis. The physician must ensure that the patient or his/her parent is able to perform self-injection safely and reliably.
c. Self-injection dose should be determined based on a body weight conversion chart. Changing the dose for any reason, such as changes in body weight, must be decided by a physician.
d. The presence or absence of any adverse event associated with self-injection, such as injection site redness, should be checked monthly on an outpatient basis.

Evaluation of treatment effects

The treatment effect of etanercept on JIA should be evaluated based on inflammatory findings [e.g., C-reactive protein (CRP) and RF] and joint findings (e.g., clinical findings and X-ray findings). Percentage improvement in the American College of Rheumatology Pediatric 30% validated scale [ACR Pedi; scale for the assessment of improvement of JRA/JIA (Appendix 2)] or the Disease Activity Score in

rheumatoid arthritis for 28 joints (DAS28; [18]) should also be used for evaluation of overall treatment effects.

1. *Clinical symptoms*. In addition to clinical findings of arthritis, the visual analog scale (VAS) should also be evaluated by a physician. The Childhood Health Assessment Questionnaire (CHAQ) is also a useful tool for evaluating patients' daily activities.
2. *Laboratory test results* (WBC count, hemoglobin, platelet count, and CRP: every outpatient visit).
3. *Imaging*.
   To evaluate treatment effects on arthritis, perform a plain X-ray and contrast-enhanced MRI of joints before treatment and every 6 months after the start of treatment.

Evaluation of adverse drug reactions

1. *Laboratory test results*: WBC count, AST, ALT, etc.
2. *Evaluation of cardiac function*: echocardiography EF/FS.

Further worsening of cardiac function has been reported in patients with heart failure who were treated with TNF-α blockers. Thus, patients under treatment with etanercept should be monitored by electrocardiography (ECG) or echocardiography on an as-needed basis. Regular ECG and echocardiography are required when administering etanercept to patients with concomitant heart failure.

- Summary of adverse drug reactions (ADRs) reported in clinical studies of etanercept among patients with JIA.
  1. *Domestic clinical study results*: Adverse drug reactions (ADRs) were reported in 35 of 35 (100%) patients included in the safety analysis population in a clinical study among Japanese patients with JIA. Major ADRs reported included infection[1] in 34 patients (97.1%), injection site reaction[2] in 27 patients (77.1%), rash[3] in 18 patients (51.4%), headache in 17 patients (48.6%), and abdominal pain in 13 patients (37.1%). Reported abnormal changes in laboratory test values included increased WBC in eight patients (22.9%) and decreased hemoglobin in six patients (17.1%).
  2. *Foreign clinical study results*: ADRs were reported in 60 of 69 (87.0%) patients included in the safety analysis population in a clinical study among American patients with JIA. Major ADRs reported included infection[4] in 47 patients (68.1%), injection site reaction in 26 patients (37.7%), headache in 11 patients (15.9%), rhinitis in nine patients (13.0%), and vomiting in six patients (8.7%). These results are very similar to those reported in the Japanese study.

How to reduce steroids

Since etanercept suppresses inflammation by blocking TNF-α, the dose of steroids should be reduced to minimize and avoid steroid-related adverse effects in those patients showing improvements in clinical symptoms and laboratory test values in response to treatment with etanercept. Because rapid steroid reduction may cause a worsening of the clinical symptoms, such as flare up of arthritis and generalized malaise, the steroid dose should be gradually reduced, in a step-wise manner, while carefully monitoring patients' clinical symptoms.

Interruption of etanercept therapy

No definitive data have been obtained.

Current status of etanercept therapy (as of July 2009)

Etanercept has received approval by the Pharmaceuticals and Medical Devices Agency following the completion of a clinical study evaluating the efficacy and adverse events of the drug in Japanese patients with JIA. A large-scale, all case-based, post-marketing survey evaluating the safety of etanercept in adult RA patients was conducted and completed in 2008. In Japan, etanercept is indicated for patients with JIA manifesting disease activity in multiple joints (only those responding poorly to existing therapies) [19].

Others

- *Vaccination during treatment with etanercept* [20]: live-virus vaccination during treatment with etanercept should be avoided as it is associated with the risk of growth and the spread of vaccine viruses following vaccination. Pediatric patients should preferably complete the necessary vaccination programs before starting treatment with etanercept. It has been shown that patients treated with etanercept showed a slightly smaller increase in antibody titer following pneumococcal vaccination than those not treated with etanercept.
- *Federal Drug Administration warnings for malignancies in childhood and adolescence patients treated with anti-TNF agents*: in pediatric reports published to date in Japan (up to September 20, 2009), no incidence of

[1] Includes nasopharyngitis, influenza, upper respiratory tract infection, impetigo, pharyngitis, hordeolum, and tonsillitis.

[2] Injection site reaction and infection site hemorrhage.

[3] Cumulative total of eczema, dermatitis, erythema, and other skin lesions.

[4] Includes common infectious diseases, such as upper respiratory tract infection, pharyngitis, gastroenteritis, otitis, influenza, skin infection, sinusitis, and conjunctivitis infective.

malignancy or psoriasis has been reported in patients exposed to anti-TNF treatment, including those who participated in JIA clinical trials. However, when considering the use of anti-TNF agents, it is highly imperative to carry out adequate screening tests and monitor patient conditions, and treatment should be initiated only after a thorough assessment of associated risks and benefits.

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Conflict of interest statement None.

Appendix 1

Diagnostic and classification criteria for juvenile idiopathic arthritis by ILAR [11]

Diagnostic and classification criteria for juvenile idiopathic arthritis by ILAR [11]

Systemic

1. Systemic arthritis
   Arthritis with remittent fever lasting for more than 2 weeks and one or more of the following signs and symptoms:
   1) Transient erythema
   2) Systemic lymph node swelling
   3) Hepatomegaly or splenomegaly
   4) Serositis

Articular

2. Pauciarticular arthritis:
   Arthritis that becomes localized in 1–4 joints during the first 6 months of disease. Can be divided into the following two types:
   (a) Persistent arthritis: Arthritis affecting 4 or fewer joints during the entire course of disease
   (b) Extensive arthritis: Arthritis affecting 5 or more joints after the first 6 months of disease
3. Polyarthritis (Rheumatoid factor negative)
   Arthritis affecting 5 or more joints during the first 6 months of disease, with rheumatoid factor being negative
4. Polyarthritis (Rheumatoid factor positive)
   Arthritis affecting 5 or more joints during the first 6 months of disease, with rheumatoid factor being positive in at least two measurements performed at an interval of at least 3 months.

Symptomatic

5. Psoriatic arthritis
   Any of the following:
   1) Arthritis with psoriasis
   2) Patients with at least two of the following signs and symptoms:
      (a) Digital arthritis
      (b) Nail deformity
      (c) Any relative within the second degree of relationship has psoriasis
6. Enthesitis-related arthritis
   Either of the following:
   1) Arthritis and enthesitis
   2) Arthritis or enthesitis with at least two of the following signs and symptoms:
      (a) Tenderness in the sacroiliac joint or inflammatory pain in the spine
      (b) Positive for HLA-B27
      (c) Any relative within the second degree of relationship has HLA-B27-related disease
      (d) Anterior uveitis with occasional eye pain, redness and photophobia
      (e) A boy aged 8 years or older has developed arthritis
7. Other:
   Arthritis of unknown cause that begins during childhood and persists for at least 6 weeks

Appendix 2

JIA core set (ACR Pedi)

The JIA core set is used to objectively assess response to treatment in patients with JIA. This method is used to make an overall evaluation using not only clinical and laboratory test findings, such as arthritis and erythrocyte sedimentation rate, but the Childhood Health Assessment Questionnaire (CHAQ) and the physician's global assessment (visual analog scale) as well.

Variables included in the core set are presented below. Each of the following variables is scored.

a) Physician's global assessment
b) Global assessment by patient or patient's legal guardian
c) Number of joints with active arthritis (joints with swelling not due to deformity, or joints with limited motion with pain or tenderness)
d) Number of joints with limitation of motion with pain or tenderness
e) CHAQ assessed by patient or patient's legal guardian
f) Erythrocyte sedimentation rate

Evaluation method: the score for each variable above is calculated to determine disease activity, and any change in the score from the baseline value is used for evaluation purposes.

Reference:

Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum. 1997; 40:1202–9

Appendix 3

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