References

Papers of special note have been highlighted as:
• of interest

1 Cassidy JT, Petty RE. Juvenile idiopathic arthritis. In: *Textbook of Pediatric Rheumatology (5th Edition)*. Cassidy JT, Petty RE (Eds). WB Saunders, PA, USA, 291–303 (2005).

2 Billiau AD, Roskams T, Van Damme-Lombaerts R, Matthys P, Wouters C. Macrophage activation syndrome: characteristic findings on liver biopsy illustrating the key role of activated IFN-γ-producing lymphocytes and IL-6- and TNF-α-producing macrophages. *Blood* 105, 1648–1651 (2005).

3 Packham JC, Hall MA, Pimm TJ. Long-term follow-up of 246 adults with juvenile idiopathic arthritis: predictive factors for mood and pain. *Rheumatology (Oxford)* 41, 1444–1449 (2002).

4 Pascual V, Allantaz F, Patel P *et al.* How the study of children with rheumatic diseases identified interferon α and interleukin 1 as novel therapeutic targets. *Immunol. Rev.* 223, 39–59 (2008).

5 Vastert SJ, van Wijk R, D'Urbano LE *et al.* Mutations in the perforin gene can be linked to macrophage activation syndrome in patients with systemic onset juvenile idiopathic arthritis. *Rheumatology* 49, 441–449 (2010).

• **Macrophage activation syndrome (MAS) in systemic juvenile idiopathic arthritis (JIA) display decreased levels of perforin in NK cells and diminished NK function caused by *PRF1* mutation, which may play a role in the development of MAS.**

6 de Jager W, Vastert SJ, Beekman JM *et al.* Defective phosphorylation of interleukin-18 receptor b causes impaired natural killer cell function in systemic-onset juvenile idiopathic arthritis. *Arthritis Rheum.* 60, 2782–2793 (2009).

7 de Benedetti F, Massa M, Robbioni P. Correlation of interleukin-6 levels with joint involvement and thrombocytosis in patients with systemic juvenile rheumatoid arthritis. *Arthritis Rheum.* 34, 1158–1163 (1991).

8 Lieskovska J, Guo D, Derman E. Growth impairment in IL-6-overexpressing transgenic mice is associated with induction of SOCS3 mRNA. *Growth Horm. IGF Res.* 13, 26–35 (2003).

9 Vastert SJ, Kuis W, Grom AA. Systemic JIA: new development in the understanding of the pathophysiology and therapy. *Best Pract. Res. Clin. Rheumatol.* 23, 655–664 (2009).

10 Harden LM, du Plessis I, Poole S *et al.* Interleukin (IL)-6 and IL-1β act synergistically within the brain to induce sickness behavior and fever in rats. *Brain Behav. Immun.* 22, 838–849 (2008).

11 Raj DSC. Role of interleukin-6 in the anemia of chronic disease. *Semin. Arthritis Rheum.* 38, 382–388 (2009).

• **Inflammation leads to macrophage stimulation of IL-6, which acts on hepatocytes to induce hepcidin production. Hepcidin inhibits macrophage iron release and intestinal iron absorption, leading to hypoferemia and anemia of inflammation.**

12 Fournier T, Medjoubi-N N, Porquet D. α-1-acid glycoprotein. *Biochim. Biophys. Acta* 1482, 157–171 (2000).

13 Hagihara K, Nishikawa T, Sugamata Y *et al.* Essential role of STAT3 in cytokine-driven NF-κB-mediated serum amyloid A gene expression. *Genes Cells* 10, 1051–1063 (2005).

14 Nishikawa T, Hagihara K, Serada S *et al.* Transcriptional complex formation of c-Fos, STAT3, and hepatocyte NF-1α is essential for cytokine-driven C-reactive protein gene expression. *J. Immunol.* 180, 3492–3501 (2008).

• **Molecular mechanism of C-reactive protein (CRP), a serum marker of inflammation, was investigated in terms of synergistic effects of IL-6 and IL-1β, and the essential role of transcriptional complex formation of DNA-binding protein to the CRP gene promoter region was demonstrated.**

15 Houssiau FA, Devogelaer JP, Van Damme J, de Deuxchaisnes CN, Van Snick J. Interleukin-6 in synovial fluid and serum of patients with rheumatoid arthritis and other inflammatory arthritides. *Arthritis Rheum.* 31, 784–788 (1988).

16 Yoshizaki K, Matsuda T, Nishimoto N *et al.* Pathogenic significance of interleukin-6 (IL-6/BSF-2) in Castleman's disease. *Blood* 74, 1360–1367 (1989).

17 Iwamoto M, Nara H, Hirata D, Minota S, Nishimoto N, Yoshizaki K. Humanized monoclonal anti-interleukin-6 receptor antibody for treatment of intractable adult-onset Still's disease. *Arthritis Rheum.* 46, 3388–3389 (2002).

18 Sato K, Tsuchiya, Saldanha J *et al.* Reshaping a human antibody to inhibit the interleukin-6-dependent tumor cell growth. *Cancer Res.* 53, 851–856 (1993).

19 Yokota S, Miyame T, Imagawa T *et al.* Therapeutic efficacy of humanized recombinant anti-interleukin-6 receptor antibody in children with systemic-onset juvenile idiopathic arthritis. *Arthritis Rheum.* 52, 818–825 (2005).

20 Yokota S, Imagawa T, Mori M *et al.* Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomized, double-blind, placebo-controlled, withdrawal Phase III trial. *Lancet* 371, 998–1006 (2008).

• **First report of double-blind, placebo-controlled trial of tocilizumab documenting its efficacy and safety for children with systemic JIA.**

21 de Benedetti F, Martini A. Targeting the interleukin-6 receptor: a new treatment for systemic juvenile idiopathic arthritis? *Arthritis Rheum.* 52, 687–693 (2005).

22 Pascual V, Allantaz F, Arce E *et al.* Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical aspect to IL-1 blockade. *J. Exp. Med.* 201, 1479–1486 (2005).

23 Lurati A, Teruzzi B, Salmaso A *et al.* Macrophage activation syndrome during anti-IL1 receptor therapy (anakinra) in a patient affected by systemic-onset idiopathic juvenile arthritis. *Paed. Rheumatol. Online* 3, 79–85 (2005).

24 Lequerre T, Quarties F, Rosellini D *et al.* Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France. *Ann. Rheum. Dis.* 67, 302–308 (2008).

25 Petty RE, Southwood TR, Manners P *et al.* International League of Association for Rheumatology. International League Association for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J. Rheumatol.* 31, 390–392 (2004).

26 Zak M, Muller J, Karup Pedersen F. Final height, armspan, subischial leg length and body proportion in juvenile chronic arthritis: a long-term follow-up study. *Horm. Res.* 52, 80–85 (1999).

27 Nakajima S, Naruto T, Miyamae T, Imagawa T, Mori M, Nishimaki S, Yokota S. Interleukin-6 inhibits early differentiation of ATDC5 chondrogenic progenitor cells. *Cytokine* 47, 91–97 (2009).

• **Addition of IL-6 to the culture of ATDC5 (a clonal murine chondrogenic cell line) inhibits early chondrogenesis, suggesting that IL-6 may be a cellular-level factor in growth impairment seen in systemic JIA patients.**

28 Immonen K, Savolainen A, Kautiainen H, Hakala M. Longterm outcome of amyloidosis associated with juvenile idiopathic arthritis. *J. Rheumatol.* 35, 907–912 (2008).

29 Cortis E, Insalaco A. Macrophage activation syndrome in juvenile idiopathic arthritis. *Acta Pediatr. Suppl.* 95, 38–41 (2005).

30 Grom AA. Natural killer cell dysfunction: a common pathway in systemic-onset juvenile rheumatoid arthritis, macrophage activation syndrome, and hemophagocytic lymphohistiocytosis? *Arthritis Rheum.* 50, 689–698 (2004).

31 Janka G. Hemophagocytic lymphohistiocytosis: when the immune system runs amok. *Klin. Padiatr.* 221, 278–285 (2009).

32 Kishimoto T, Hirano T. Molecular regulation of B lymphocyte response. *Annu. Rev. Immunol.* 6, 485–512 (1988).

33 Hirano T. Interleukin-6 and its receptor: ten years later. *Int. Rev. Immunol.* 16, 249–284 (1998).

34 Taga T, Kishimoto T. Gp130 and the interleukin-6 family of cytokines. *Annu. Rev. Immunol.* 15, 797–819 (1997).

35 Leaman DW, Leung S, Li X, Stark GR. Regulation of STAT-dependent pathway by growth factors and cytokines. *FASEB J.* 10, 1578–1588 (1996).

36 Taga T, Kishimoto T. Gp130 and the interleukin-6 family of cytokines. *Ann. Rev. Immunol.* 15, 797–819 (1997).

37 De Benedetti F, Pignati P, Gerloni V *et al.* Differences in synovial fluid cytokine levels between juvenile and adult rheumatoid arthritis. *J. Rheumatol.* 24, 1403–1409 (1997).

38 Romanovsky AA, Almeida MC, Aronoff DM *et al.* Fever and hypothermia in systemic inflammation: recent discoveries and revisions. *Front. Biosci.* 10, 2193–2216 (2005).

39 Pignatti P, Vivarelli M, Meazza C, Rizzolo MG, Martini A, De Benedetti F. Abnormal regulation of interleukin 6 in systemic juvenile idiopathic arthritis. *J. Rheumatol.* 28, 1670–1676 (2001).

40 Grom AA. Macrophage activation syndrome and reactive hemophagocytic lymphohistiocytosis: the same entities? *Curr. Opin Rheumatol.* 15, 587–590 (2003).

41 Ravelli A, Caria MC, Buratti S *et al.* Methotrexate as a possible trigger of macrophage activation syndrome in systemic juvenile idiopathic arthritis. *J. Rheumatol.* 28, 865–867 (2001).

42 Bihl F, Emmenegger U, Reichen J *et al.* Macrophage activation syndrome is associated with lobular hepatitis and severe duct injury with cholestasis. *J. Hepatol.* 44, 1208–1212 (2006).

43 Stabile A, Bertoni B, Ansuini V, La Torraca I, Salli A, Rigante D. The clinical spectrum and treatment options of macrophage activation syndrome in the pediatric age. *Eur. Rev. Med. Pharmacol. Sci.* 10, 53–59 (2006).

44 Miller LL, Miller SC, Torti SV, Tsuji Y, Torti FM. Iron-independent induction of ferritin H chain by tumor necrosis factor. *Proc. Natl Acad. Sci. USA* 88, 4946–4950 (1991).

45 Aulitzky WE, Tilg H, Herold M, Berger M, Vogel W, Judmaier G. Enhanced serum levels of β-2-microglobulin, neopterin, and interferon-γ in patients treated with recombinant tumor necrosis factor-α. *J. Interferon Res.* 8, 655–664 (1988).

46 Pucci B, Bertani F, Karpinich NO *et al.* Detailing the role of Bax translocation, cytochrome c release, and perinuclear clustering of the mitochondria in the killing of HeLa cells by TNF. *J. Cell. Physiol.* 217, 442–449 (2008).

- **Mitochondrial permeability transition (MPT) is the initial event of apoptosis by TNF-α. The release of cytochrome c from mitochondria into cytoplasm is proved to depend on the induction of MPT but not ATP content. Cytochrome c activates caspase cascade, and DNA is then degraded.**

47 Soriano ME, Nicolosi L, Bernardi P. Desensitization of the permeability transition pore by cyclosporin a prevents activation of the mitochondrial apoptotic pathway and liver damage by tumor necrosis factor-α. *J. Biol. Chem.* 279, 36803–36808 (2004).

48 Semb H, Peterson J, Tavernier J, Olivecrona T. Multiple effects of tumor necrosis factor on lipoprotein lipase *in vivo*. *J. Biol. Chem.* 262(17), 8390–8394 (1987).

49 Romanovsky AA, Simons CT, Kulchitsky VA. 'Biphasic' fever often consist of more than two phases. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 275, R323–R331 (1998).

50 Takeuchi O, Hoshino K, Kawai T *et al.* Differential roles of TLR2 and TLR4 in recognition of Gram-negative and Gram-positive bacterial cell wall components. *Immunity* 11, 443–451 (1999).

51 Harden LM, du Plessis I, Poole S, Laburn HP. Interleukin-6 and leptin mediate lipopolysaccharide-induced fever and sickness behavior. *Physiol. Behav.* 89, 146–155 (2006).

- **In this experimental system, lipopolysaccharide-induced inflammation can be inhibited by the administration of anti-IL-6 and antileptin sera, but not anti-TNF-α or anti-IL-1β sera, suggesting that IL-6 and leptin are important in regulating fever and sickness behavior such as fatigue and appetite loss.**

52 Oka T, Oka K, Kobayashi T *et al.* Charcteristics of thermoregulatory and febrile responses in mice defiant in prostaglandin EP1 and EP3 receptors. *J. Physiol.* 551, 945–954 (2003).

53 Jones SA, Richards PJ, Scheller J, Rose-John S. IL-6 transsignaling: the *in vivo* consequences. *J. Interferon Cytokine Res.* 25, 241–253 (2005).

54 Jacober ML, Mamoni RL, Lima CS, Dos Anjos BL, Grotto HZ. Anaemia in patients with cancer: role of inflammatory activity on iron metabolism and severity of anaemia. *Med. Oncol.* 24, 323–329 (2007).

55 Veldhuis GJ, Willemse PH, Mulder NH, Limburg PC, De Vries EG. Potential use of recombinant human interleukin-6 in clinical oncology. *Leuk. Lymphoma* 20, 373–379 (1996).

56 Nemeth E, Ganz T. The role of hepcidin in iron metabolism. *Acta Haematol.* 122, 78–86 (2009).

57 Mima T, Nishimoto N. Clinical value of blocking IL-6 receptor. *Curr. Opin Rheumatol.* 21, 224–230 (2009).

58 Nemeth E, Rivera S, Gabayan V, Keller C, Taudorf S, Pedersen BK. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. *J. Clin. Invest.* 113, 1271–1276 (2004).

59 Novick D, Engelmann H, Revel M, Leitner O, Rubinstein M. Monoclonal antibodies to the soluble human IL-6 receptor: affinity purification, ELISA, and inhibition of ligand binding. *Hybridoma* 10, 137–146 (1999).

60 Nishimoto N, Yoshizaki K, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T. Treatment of rheumatoid arthritis with humanized anti-interleukin-6 receptor antibody: a multicenter, double-blind, placebo-controlled trial. *Arthritis Rheum.* 50, 1761–1769 (2004).

61 Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum.* 40, 1202–1209 (1997).

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ORIGINAL ARTICLE

PET assessment of disease activity in children with juvenile idiopathic arthritis

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Abstract
Background The degree of 18-fluorodeoxyglucose (FDG) uptake is previously reported to correlate with physical examination and laboratory tests for evaluating disease activity in patients with rheumatoid arthritis. The clinical validity of ^{18}F-FDG positron emission tomography (PET) has not been evaluated in juvenile idiopathic arthritis (JIA).
Objective To assess the relationship between ^{18}F-FDG PET uptake and disease activity in children with JIA.
Materials and methods A total of 560 joints in 28 children (mean age, 5.4 years; range, 1–16 years) with JIA who had undergone whole-body ^{18}F-FDG PET before treatment were retrospectively assessed clinically, biochemically and radiographically. PET images were assessed independently by two readers. We investigated the relationships between the degree of synovial ^{18}F-FDG uptake and radiographic and clinical symptoms and laboratory findings.
Results Joint tenderness and swelling had a positive association with abnormal ^{18}F-FDG uptake in the joint [odds ratio (OR) 5.37, 7.12, respectively]. The standardized uptake value (SUV) max correlated with the neutrophil count, plasma C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and matrix metalloproteinase (MMP) 3. Joint erosion (OR, 6.17), soft-tissue swelling (OR, 3.77), major joints involvement (OR, 3.50), tenderness (OR, 5.22), and CRP concentration in plasma (OR, 1.81) were positively associated with SUVmax.
Conclusion The degree of ^{18}F-FDG uptake may be associated with the severity of synovitis in children with JIA.

Keywords Juvenile idiopathic arthritis · Disease activity · PET · Child

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Introduction

Juvenile idiopathic arthritis (JIA) is a childhood rheumatic disease defined as clinically heterogeneous arthritides in one or more joints with swelling, pain, or limited range of movement for at least 6 weeks, with age at onset younger than 16 years [1, 2]. Detection of structural changes over time provides valuable prognostic information and helps guide therapy in active JIA. Active arthritis often prompts consideration of commonly referred to disease-modifying antirheumatic drugs (DMARDs), tumour necrosis factor (TNF) inhibitor, interleukin (IL)-1 receptor antagonist, or IL-6 receptor antagonists [3–10].

Although the activity of joint inflammation can be assessed on radiographs, the early radiographic changes are nonspecific and late changes are often irreversible. Despite a close correlation between radiographic score and inflammatory activity, several studies have revealed that MRI is superior to radiography for detecting early changes [11–15]. More importantly, by focusing exclusively on bone erosion and cartilage damage, MRI seems promising in terms of reliability and validity. On the other hand, previous studies have ignored low capability in assessment of weight-bearing major joints because acquisition of small structures in children is limited [13, 14].

Radiographs are insensitive to acute erosive changes in the cartilage. ^{18}F –fluorodeoxyglucose (FDG) is taken up by macrophages and immature granulation tissue [16]. TNF-α, which plays a major role in synovitis in patients with rheumatoid arthritis, regulates glucose transport and metabolism [17]. Becker et al. [18] reported that the degree of ^{18}F-FDG uptake correlated with physical examination and laboratory tests for evaluating disease activity in patients with rheumatoid arthritis. The clinical validity of ^{18}F-FDG PET has not been evaluated in JIA. We hypothesized that ^{18}F-FDG PET helps identify active synovitis and that ^{18}F-FDG uptake correlates with serum markers of inflammation in patients with JIA.

Materials and methods

Patients

Twenty-eight consecutive children with proven JIA who were evaluated for disease activity using PET between 2003 and 2007 at Yokohama City University Hospital, Yokohama were retrospectively enrolled. Diagnostic criteria were based on the International League of Association for Rheumatology (ILAR) classification for JIA [2]. Medical records were reviewed for patient age, gender, treatment history, physical examinations, laboratory tests and imaging studies including radiographs and PET. Evaluation of PET was performed independently by operators who had no knowledge of the results of the other studies. The clinical status and treatment of these children were unaltered during the evaluation period. This study was approved by the Institutional Review Board at our institution and all children provided their informed consent.

Radiographic study

Plain radiographs of 12 major joints: both shoulders, elbows, wrists, hips, knees, and ankles; and minor joints: both temporo-mandibular and sacroiliac joints, both hands and feet were obtained prior to treatment in all children. These had been taken in the posterioanterior projection using a computed radiography system (DRX-866HD or DRX-3535HD; Toshiba Medical Systems, Tokyo, Japan) with general plates and the following setting: 200 mA, 45–80 kVp, and 250 ms. Two radiologists (K.S. and N.K., 12 and 3 years of experience respectively) experienced in musculoskeletal radiography assessed the plain radiographs without knowledge of any information regarding clinical status. They evaluated all joints for five radiological features based on modified criteria [12]: periarticular osteopenia, erosion, joint deformities, soft-tissue swelling, and narrowed joint spaces. Erosion was defined as a cortical defect with an irregular floor. Soft-tissue swelling was defined as an eccentric or irregular fusiform swelling around a joint.

PET study

PET scans were performed before or after radiography with interval mean, 2.6 weeks; range, 0–5 weeks. Children fasted for 6 h before the PET scan. Before injecting ^{18}F-FDG, the blood glucose level was measured in all children (mean, 88 mg/dl). ^{18}F-FDG (3–5 MBq/kg) was injected in the antecubital or a more peripheral vein through an indwelling catheter. The mean injected dose was 120.5 MBq (range: 34.0–228.0 MBq). Whole-body emission and transmission scans were performed in all children. After a 60 min equilibration period during which the child rested, both emission and transmission scans were obtained to generate attenuation corrected images of all table positions. A dedicated PET scanner (SET 2400, Shimadzu, Kyoto, Japan) was used for acquisition with the following parameters: field of view (FOV), 595 mm; single position body-axis length, 20 cm; slice thickness, 3.125 mm; central resolution, 4.2 mm; and half width 5.0 mm. Reconstructed data were rendered in three-dimensional (3-D) imaging using a Butterworth filter with the following parameters: ordered subsets expectation maximization, conversion condition 1.0; subset count 20; cut-off value 10; order 2; and iterations 2. The 3-D image sets were available for review at slice thickness of 12 mm. The maximum standardized uptake value (SUVmax) was analyzed according to the following equation: SUV max = maximal count × calibration factor (kBq/ml)/injected activity (MBq)/body weight (kg).

Image interpretation

PET images were reviewed on a commercially available image viewer (Synapse; Fujifilm Medical, Yokohama, Kanagawa, Japan). Images were analyzed visually and quantitatively by two nuclear medicine physicians (U.T. and T.O., 15 and 3 years of experience) who were unaware of clinical and radiographic findings. They recorded their findings after reaching a consensus. For the visual analysis, abnormal ^{18}F-FDG uptake was defined as substantially greater activity than in the aortic blood on attenuation-corrected images. A region of interest (ROI) was outlined within areas of joints with increased ^{18}F-FDG uptake and measured on each slice. ROIs for determination of regional uptake were hand drawn around the areas of uptake. When the lesion was extensively heterogeneous, the ROI was set so as to cover all of the components of the lesion. When no significant uptake was identified, ROIs were arbitrarily drawn on an axial image in an area thought to represent

synovium. The maximum pixel value in each ROI was recorded for determination of SUVmax. Radiologist (N.K., 3 years of experience) reviewed the medical records. We defined the standard of reference for diagnosis as follow-up imaging findings of conventional radiography based on visual analysis and clinical status.

Clinical evaluation

Two experienced paediatric rheumatologists (>20 years of experience) performed the clinical evaluation. Symptoms at presentation were evaluated based on the International League of Associations of Rheumatology (ILAR) criteria [2]. Recorded details for all children included age at onset, major or minor joint involvement, numbers of involved joints, quotidian fever, tenderness, swelling, limited range of motion, non-fixed erythematous rash, generalized lymphadenopathy, hepatosplenomegaly, pericarditis and macrophage activation syndrome. Routine physical examinations were assessed on the same morning by independent paediatricians 1 day before or after the PET study. Blood samples were taken for biochemical investigations in all children 1 day before or after the PET study. Results of these results were masked to the investigators.

Treatment and follow-up

Treatment consisted of intra-articular corticosteroids (n=24), methylpresonisolone pulse (n=24), immunosuppressants (n=20), DMARDs (n=26), and tocilizumab (n=4). Clinical manifestations were carefully monitored with physical examinations, urinalysis, blood examinations, and screening for active infections in all children during the course of the disease. The follow-up period was dated from the time of diagnosis and the mean follow-up period was 25 months (range 6–60 months). Therapeutic response was evaluated using the American College of Rheumatology Pediatric (ACR Pedi) 30 response and systemic features including quotidian fever, non-fixed erythematous rash, generalized lymphadenopathy, hepatosplenomegaly and pericarditis [19].

Statistical analysis

Comparison of categorical variables between groups was performed using chi-square test and Fisher exact test. Fisher exact test was used when the number of cells was <5. Continuous values were compared with Student's t-test. Simple linear regression was used to compare continuous variables. Univariate regression analyses were performed to assess the variables affecting metabolic activity by comparing categorical distributions with calculation of odds ratio (OR). Multivariate analyses were applied with regression modelling for parameters affecting metabolic activity with marginally significant ($P \leqq 0.1$) variables from univariate analyses offered using a manual step-wise procedure to test the independence of factors for metabolic activity. A priori variables based on previous studies were tested. A P value <0.05 (two-tailed) was considered to

Table 1 Characteristics at presentation in 28 children with JIA

Age, years	5.4±4.0
Boys:girls	12:16
Number of involved joints	
Major joint [a]	6.3±3.6
Minor joint [a]	1.1±0.8
General symptoms	
Quotidian fever	24/28 (86%)
Non-fixed erythematous rash	20/28 (71%)
Macrophage activation syndrome	5/28 (18%)
Pericarditis	4/28 (14%)
Generalized lymphadenopathy	3/28 (11%)
Hepatosplenomegaly	3/28 (11%)

[a] Data are presented as mean ± standard deviation

Table 2 Laboratory results at presentation in 28 children subsequently diagnosed with JIA

	Value	Normal range
Red blood cell, /mm^3	453.8±47.4	Boys:420.0–550.0 Girls:380.0–480.0
Haemoglobin, g/dl	11.8±1.8	Boys:13.5–17.0 Girls:11.5–14.5
Haematocrit, %	35.6±5.0	Boys:40.0–52.0 Girls:34.0–44.0
White blood cells, /mm^3	15,100±9,316	3,500–9,000
Neutrophils, %	75.9±14.2	40.0–70.0
Lymphocytes, %	17.9±10.9	20.0–45.0
Platelets, /mm^3	46.4±16.7	16.0–36.0
Aspartic aminotransferase, U/l	26.4±14.5	10.0–35.0
Creatinine phosphokinase, U/l	30.9±37.9	Boys:55.0–290.0 Girls:40.0–290.0
Lactate dehydrogenase, U/l	281.3±123.0	120.0–240.0
CRP, mg/dl	5.3±4.9	0.0–0.2
Serum amyroid A, μg/ml	513.3±720.5	0.0–10.0
Ferritin, ng/ml	568.9±138.6	Boys:37.0–281.0 Girls:5.0–71.0
ESR, mm/hr	43.6±31.9	Boys:2.0–10.0 Girls:3.0–15.0
MMP 3, ng/ml	239.0±190.5	17.3–59.7
Rheumatoid factor, IU/ml	113.0±383.3	0.0–16.0
Antinuclear antibody, titre	69.6±68.5	<40.0

Data are presented as mean ± standard deviation

indicate a statistically significant difference. Statistical analysis was performed with the PASW Statistics 18 software program (IBM SPSS Inc., Chicago, IL, USA).

Results

Twenty-two out of 28 children (79%) had systemic-onset JIA and 6 (21%) polyarticular JIA (more than four joints affected). The patient characteristics are shown in Table 1. The mean age was 5.4 years, range 1–16 years. The numbers of involved major joints were 6.6±3.3 [mean±standard deviation (SD)] in systemic-onset JIA and 5.2±4.9 in polyarticular JIA. The number of involved minor joints was 1.0±0.9 in systemic-onset JIA and 1.3±0.5 in polyarticular JIA. Extra-articular ^{18}F-FDG accumulations were found in 21/28 children (75%). Frequent locations were spleen in 9/28 (32%) children and bone marrow in 6/28 (21%) children. The results of laboratory tests are summarized in Table 2.

On ^{18}F-FDG PET, 123 of 560 joints (22%) had abnormal uptake (Figs. 1 and 2). The most frequent major joints were shoulder (34/123, 28%), knee (23/123, 19%), hip (21/123, 17%) and wrist (17/123, 14%). Of these, frequencies of joint involvement in each location were similar between children with systemic-onset JIA and children with polyarticular JIA, whereas involvement of joints including ankle, elbow, metacarpophalageal (MCP), metatarsophalangeal (MTP), sacroiliac, and temporo-mandibular (TM) was found only in children with systemic-onset JIA (Table 3). The mean SUVmax of all joints of all cases was 1.0±0.3 (Fig. 3). The SUVmax in clinically involved joints was significantly higher than in unaffected joints (2.0±0.6 versus 0.7±0.3, $P<0.0001$).

Frequent radiographic findings were soft-tissue swelling (104/560, 19%) followed by narrowed joint spaces (46/560, 8%) and joint deformity (40/560, 7%). Significant differences between systemic-onset JIA and polyarticular JIA were found in frequencies of radiographic narrowed joint spaces ($P<0.0001$), joint deformity ($P=0.001$), erosion ($P=0.004$) and soft-tissue swelling ($P=0.008$). However, there was no difference in observed osteopenia ($P=0.198$).

In univariate analyses, non-fixed erythematous rash ($P=0.04$), generalized lymphadenopathy ($P<0.01$), hepatosplenomegaly ($P<0.01$) and macrophage activation syndrome ($P<0.01$) were significantly associated with quantitative ^{18}F-FDG uptake. No association was found with other variables, including age at onset, quotidian fever, pericarditis and extra-articular accumulations. Multiple major or minor joints involvement was associated with quantitative ^{18}F-FDG uptake. The joint-specific symptoms (tenderness and swelling) were also positively correlated with SUVmax, whereas limited range of motion was not (Table 4). Radiographic findings including soft-tissue swelling, nar-

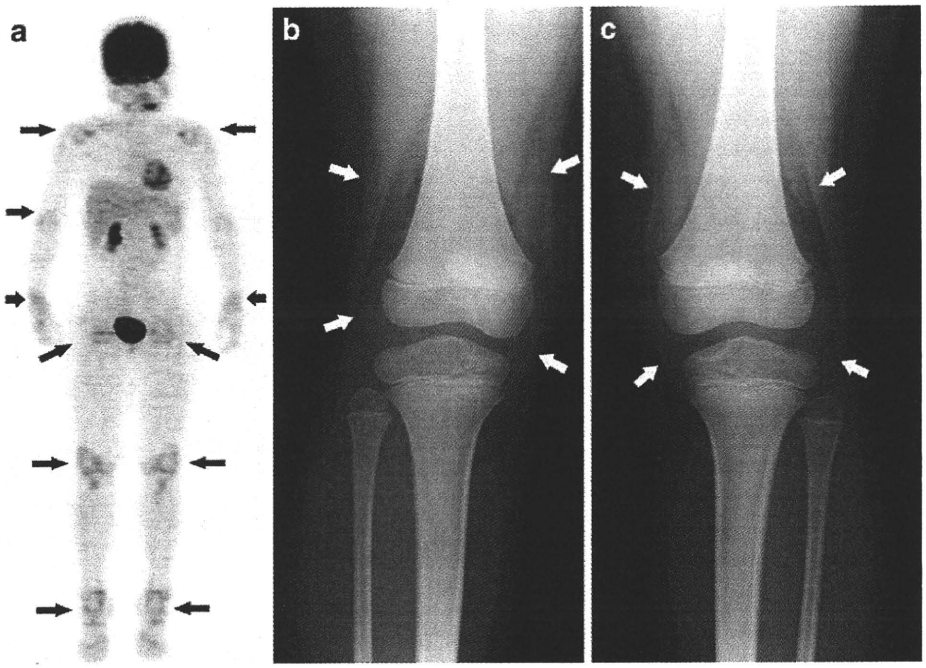

Fig. 1 **a** Whole-body ^{18}F-FDG PET performed at presentation in a 5-year-old girl with systemic-onset JIA shows abnormal uptake of 12 major joints as well as bilateral MCP and MTP joints (*arrows*). The SUVmax of the involved joints ranged from 1.0 (left elbow) to 2.8 (left knee). Physical examination revealed pain and swelling in the wrist, knee, ankle and MCP joints bilaterally. **b**, **c** Radiographs of the knee joints (highest SUVmax) revealed soft-tissue swelling only (*arrows*)

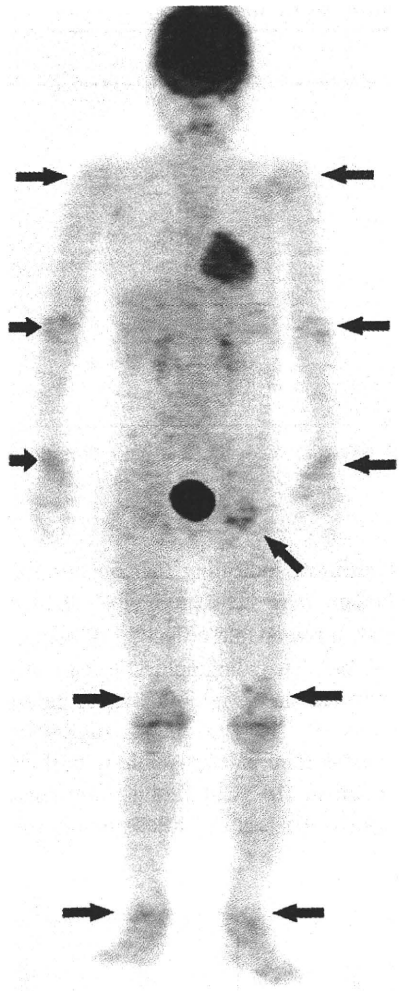

Fig. 2 9-year-old girl with polyarticular JIA. Whole-body ^{18}F-FDG PET performed at presentation shows abnormal uptake of six major joints (*arrows*). The SUVmax of the involved joints ranged from 0.9 (left elbow) to 2.3 (left hip and right ankle). Physical examination revealed tenderness and swelling in elbows, wrists, knees, and ankles as well as limited range of motion in elbows

rowed joint spaces, joint deformity, erosion and osteopenia were associated with higher ^{18}F-FDG uptake. There was a correlation between degree of ^{18}F-FDG uptake and several pathological parameters, including, CRP (r=0.610, P=0.001), neutrophil count (r=0.385, P=0.043), ESR (r=0.376, P=0.049) and MMP 3 (r=0.388, P=0.049) correlated significantly with increased SUVmax (Fig. 4). However, there was no relationship seen between increased SUVmax and other laboratory findings.

Results from the multivariate regression modelling are shown in Fig. 5. Factors associated with increased SUVmax of the joint included erosion [OR, 6.17; 95% confidence interval (CI), 2.60–14.66; P<0.0001], tenderness (OR, 5.22; 95%CI, 2.85–9.57; P<0.0001), soft-tissue swelling (OR, 3.77; 95%CI, 2.22–6.41; P<0.0001), the presence of

Table 3 Clinically involved joints at presentation in 28 children with JIA

Location	Systemic-onset JIA	Polyarticular JIA
Shoulder	26/44 (59%)	7/12 (58%)
Knee	19/44 (43%)	4/12 (33%)
Hip	18/44 (42%)	3/12 (25%)
Wrist	13/44 (30%)	4/12 (33%)
Ankle	10/44 (23%)	0
Elbow	7/44 (16%)	0
MCP	3/44 (7%)	0
MTP	2/44 (5%)	0
Sacroiliac	2/44 (5%)	0
TM	1/44 (2%)	0

multiple major joints involvement (OR, 3.50; 95%CI, 2.10–5.83; P<0.0001) and CRP (OR, 1.81; 95%CI, 1.09–3.02; P=0.022). However, swelling of the joint, the presence of multiple minor joints involvement, osteopenia, joint deformity, narrowed joint spaces, neutrophil count, ESR and MMP 3 were not associated with uptake. During follow-up, 23 children (85%) achieved ACR Pedi 30 response or improvement of systemic features. The remaining 4 children (15%) received subsequent treatment.

Discussion

We found a significant association between the degree of ^{18}F-FDG uptake and typical clinical, radiographic and biochemical findings in JIA. These factors were erosion, soft-tissue swelling, multiple major joint involvement,

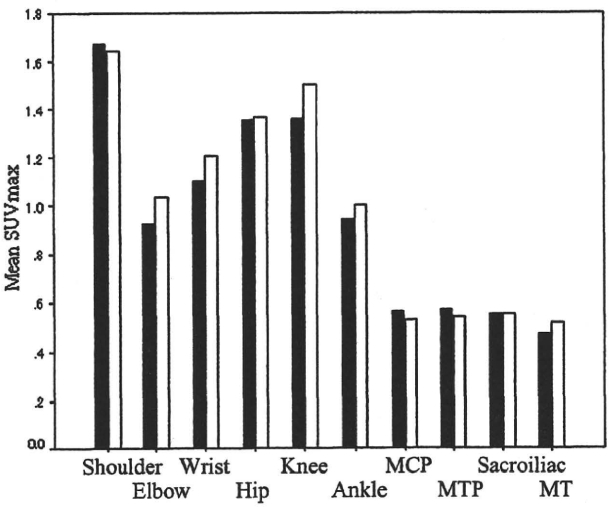

Fig. 3 Graph shows mean SUVmax in 28 children with untreated JIA at ^{18}F-FDG PET. Bar represents right (*black*) and left (*white*) joints. TM, temporo-mandibular

Table 4 Radiographic and clinical findings in major and minor joints at presentation in 28 children with JIA

Variables	*n*	OR	95%CI	*P* value
Radiographic findings				
Soft-tissue swelling	103 (18%)	3.38	2.17–3.27	<0.0001*
Narrowed joint spaces	46 (8%)	4.14	2.32–7.40	<0.0001*
Joint deformity	40 (7%)	3.23	1.72–6.07	<0.0001*
Erosion	29 (5%)	5.68	2.83–11.38	<0.0001*
Osteopenia	6 (1%)	18.47	3.86–88.43	0.002**
Symptoms				
Swelling	63 (11%)	5.37	3.24–8.92	<0.0001*
Tenderness	60 (11%)	7.12	4.27–11.87	<0.0001*
Limited range of motion	32 (6%)	1.67	0.77–3.60	0.191*

Comparisons were performed using chi-square test* or Fisher exact test**. The OR was calculated from the ratio of positive to negative radiographic or clinical findings

tenderness and elevated CRP. In a previous study, the feasibility of glucose metabolism was assessed among patients with rheumatoid arthritis [20]. Quantification of ^{18}F-FDG uptake within joints correlated well with standard clinical measures, suggesting that the degree of ^{18}F-FDG uptake can reflect anatomic and physiologic changes of synovitis and may be used to distinguish active synovitis from chronic change. The intra-individual variability in degree of ^{18}F-FDG uptake was small among patients with rheumatoid arthritis, indicating that quantification of glucose metabolism may be reproducible so that ^{18}F-FDG uptake may be a reasonable reflection of active synovitis.

We also found that radiographic findings of osteopenia, joint deformity and narrowed joint spaces did not correlate with the degree of ^{18}F-FDG uptake, suggesting that PET findings represent joint pathophysiology in the acute phase of inflammation in JIA. Our findings are consistent with previous reports that active inflammation relates to in-

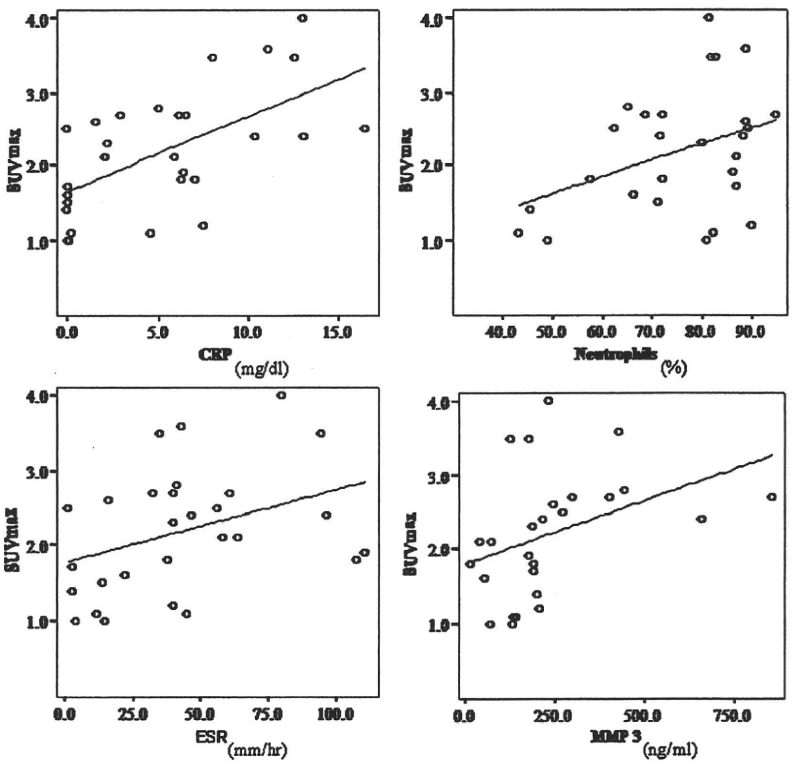

Fig. 4 Scatter plots of SUVmax and CRP, SUVmax and neutrophil, SUVmax and ESR, and SUVmax and MMP 3 with fitted regression lines are shown, whereas no relationship was observed between SUVmax and other laboratory findings. Correlations of SUVmax and CRP [(mg/dl); r=0.610; P=0.001], neutrophil [(%); r=0.385; P=0.043], ESR [(mm/hr); r=0.376; P=0.049] and matrix metalloproteinase MMP 3 [(ng/ml); r=0.388; P=0.049]

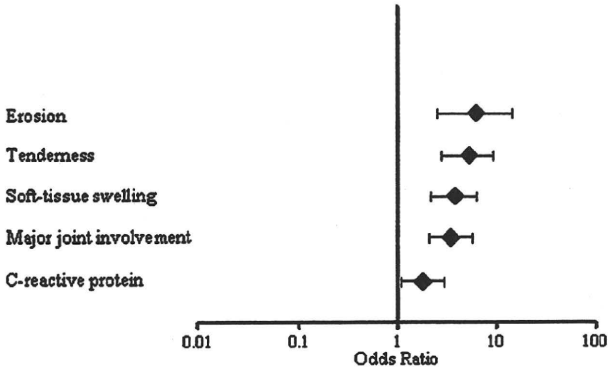

Fig. 5 Graph shows factors associated with SUVmax at ^{18}F-FDG PET in 28 children with JIA. These radiographic findings and symptoms were compared with SUVmax in the same joint. OR was calculated based on positive ratio of radiographic findings and symptoms compared with negative

creased glucose metabolism in patients with rheumatoid arthritis [20, 21]. This suggests that ^{18}F-FDG PET may be helpful in monitoring therapeutic response in JIA.

The association of the degree of ^{18}F-FDG uptake with radiographic erosion was interesting. Erosion may be caused by destruction of bone and cartilage. Elzinga et al. [22] reported increased glucose metabolism due to an inflammatory process involved in the mechanism of cartilage destruction in patients with osteoarthritis. Secondary synovitis in osteoarthritic joints may cause increased metabolic activity. As a result of active inflammation, secondary synovitis may change into fibrotic synovial tissue. Another contributing factor in the relationship between an increased glucose metabolism and erosion may be activated leukocytic infiltration within the pannus admixed with lymphocytes and fibroblasts [20].

Bone erosion is seen in the end stages of the disease process in JIA. Therefore, ^{18}F-FDG PET may underestimate erosive changes because chronic burnt-out erosions may be "cold". The capability of differentiation between acute and chronic erosive changes on ^{18}F-FDG PET is unclear. Irreversible chronic erosive changes could not be precisely evaluated on ^{18}F-FDG PET in our study. Further comparative studies of US, MRI and ^{18}F-FDG PET are required to clarify the relationship between imaging findings and acute or chronic erosive changes.

It has been established that increased glucose metabolism is found in active synovitis in patients with rheumatoid arthritis [20, 21]. The correlations between neutrophil count, CRP, ESR, MMP 3 and increased glucose metabolism in our study confirms results from a previous study on active rheumatic synovitis in which SUV increased in parallel with serum CRP and MMP 3 stimulated by TNF-α [23]. This is further suggestion that ^{18}F-FDG uptake may have a role to guide therapy, and in particular to predict response to anti-TNF-α therapy.

A few reports have investigated therapeutic monitoring by ^{18}F-FDG PET in patients with rheumatoid arthritis. Pollsson et al. [20] reported two patients with rheumatoid arthritis undergoing low-dose prednisone and methotrexate therapy, and showed that ^{18}F-FDG PET correlated well with standard activity scores. Goerres et al. [21] described the feasibility of ^{18}F-FDG PET in the assessment of Infliximab therapy in patients with rheumatoid arthritis. This suggests that a decline in ^{18}F-FDG uptake within a joint on subsequent PET scans may reflect therapeutic response over the course of systemic therapy in patients with JIA. Although our data suggest that changes in the degree of ^{18}F-FDG uptake may be a feasible marker for disease activity, it is necessary to validate these findings through clinical trials with adequate sample size, a wide spectrum of disease severity and duration and with control groups.

Despite consensus that active synovitis within a joint shows a significant degree of ^{18}F-FDG uptake in patients with rheumatoid arthritis, based largely on observational data, it is not clear what threshold values are predictive for active synovitis [24, 25]. Elzinga et al. [22] reported that 76% of joints with synovitis showed increased ^{18}F-FDG uptake, whereas many joints without clinical signs of active disease showed normal uptake in patients with rheumatoid arthritis. In contrast, false-negative and false-positive rates of ^{18}F-FDG PET to detect active synovitis in patients with rheumatoid arthritis were 13% and 11%, respectively [22]. This diagnostic accuracy may be affected by the patient populations, the onset of disease, therapeutic regimens and the presence of subclinical synovitis.

Other limitations of our study were its retrospective nature, the small population enrolled and a low prevalence of chronic erosions. It would have been preferable to compare results with other imaging modalities that measure active synovitis within joint, such as MRI or US. In addition, our interpretation has only surrogate observations for the degree of synovitis without directly measurable gold standard, e.g., biopsy. However, these tests were not feasible. A strength of our study was the availability of a detailed, comprehensive work-up of characteristics in all cases.

Conclusion

We report a possible link between the degree of synovial inflammation and ^{18}F-FDG uptake in children with JIA. We suggest that ^{18}F-FDG PET may have a role in therapeutic management of JIA, pending further validation.

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References

1. Ravelli A, Martini A (2007) Juvenile idiopathic arthritis. Lancet 369:767–778
2. Petty RE, Southwood TR, Manners P et al (2004) International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 31:390–392
3. Lovell DJ, Giannini EH, Reiff A et al (2000) Etarercept in children with polyarticular rheumatoid arthritis. Paediatric Rheumatology Collaborative Study Group. N Engl J Med 342:763–769
4. Russo RA, Katsicas MM, Zalazko M (2002) Etanercept in systemic juvenile idiopathic arthritis. Clin Exp Rheumatol 20:723–726
5. Quartier P, Taupin P, Bourdeaut F et al (2003) Efficacy of etanercept for the treatment of juvenile idiopathic arthritis according to the onset type. Arthritis Rheum 48:1093–1101
6. Gerloni V, Pontikaki I, Gattinara M et al (2005) Efficacy of repeated intravenous infusions of an anti-tumor necrosis factor alpha monoclonal antibody, infliximab, in persistently active, refractory juvenile idiopathic arthritis: results of an open-label prospective study. Arthritis Rheum 52:548–553
7. Katsicas MM, Russo RA (2005) Use of infliximab in patients with systemic juvenile idiopathic arthritis refractory to etanercept. Clin Exp Rheumatol 23:545–548
8. Yokota S, Imagawa T, Miyamae T et al (2004) Long-term therapeutic experience of humanized anti-IL-6 receptor monoclonal antibody (aIL-6R Mab) in systemic-onset juvenile idiopathic arthritis (So-JIA). Arthritis Rheum 50:S438
9. Yokota S, Miyamae T, Imagawa T et al (2005) Clinical study of tocilizumab in children with systemic-onset juvenile idiopathic arthritis. Clin Rev Allergy Immunol 28:231–238
10. Yokota S, Imagawa T, Mori M et al (2008) Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomized, double-blind, placebo-controlled, withdrawal phase II trial. Lancet 371:998–1006
11. Reed MH, Wilmot DM (1991) The radiology of juvenile rheumatoid arthritis. A review of the English language literature. J Rheumatol Suppl 31:2–22
12. Rossi F, Di Dia F, Galipo O et al (2006) Use of Sharp and Larsen scoring methods in the assessment of radiographic progression in juvenile idiopathic arthritis. Arthritis Rheum 55:717–723
13. Doria AS, Babyn P, Feldman B (2006) A critical appraisal of radiographic scoring systems for assessment of juvenile idiopathic arthritis. Pediatr Radiol 36:759–772
14. Malattia C, Damasio MB, Magnaguagno F et al (2008) Magnetic resonance imaging, ultrasonography, and conventional radiography in the assessment of bone erosions in juvenile idiopathic arthritis. Arthritis Rheum 59:1764–1772
15. Pedersen TK, Kuseler A, Gelineck J et al (2008) A prospective study of magnetic resonance and radiographic imaging in relation to symptoms and clinical findings of the temporomandibular joint in children with juvenile idiopathic arthritis. J Rheumatol 35:1668–1675
16. Wipke BT, Wang Z, Kim J et al (2002) Dynamic visualization of joint specific autoimmune response through positron emission tomography. Nat Immunol 3:366–372
17. Fonseca A, Wagner J, Yamaga LI et al (2008) (18) F-FDG PET imaging of rheumatoid articular and extraarticular synovitis. J Clin Rheumatol 14:307
18. Beckers C, Ribbens C, André B et al (2004) Assessment of disease activity in rheumatoid arthritis with (18)F-FDG PET. J Nucl Med 45:956–964
19. Giannini EH, Ruperto N, Ravelli A et al (1997) Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 40:1202–1209
20. Polisson RP, Schoenberg OI, Fischman A et al (1995) Use of magnetic resonance imaging and positron emission tomography in the assessment of synovial volume and glucose metabolism in patients with rheumatoid arthritis. Arthritis Rheum 38:819–825
21. Goerres GW, Forster A, Uebelhart D et al (2006) F-18 FDG whole-body PET for the assessment of disease activity in patients with rheumatoid arthritis. Clin Nucl Med 31:386–390
22. Elzinga EH, van der Laken CJ, Comans EF et al (2007) 2-Deoxy-2-[F-18]fluoro-D-glucose joint uptake on positron emission tomography images: rheumatoid arthritis versus osteoarthritis. Mol Imaging Biol 9:357–360
23. Beckers C, Jeukens X, Ribbens C et al (2006) (18)F-FDG PET imaging of rheumatoid knee synovitis correlates with dynamic magnetic resonance and sonographic assessments as well as with the serum level of metalloproteinase-3. Eur J Nucl Med Mol Imaging 33:275–280
24. Ju JH, Kang KY, Kim IJ et al (2008) Visualization and localization of rheumatoid knee synovitis with FDG-PET/CT images. Clin Rheumatol 27:S39–S41
25. Roivainen A, Parkkola R, Yli-Kerttula T et al (2003) Use of positron emission tomography with methyl-11C-choline and 2-18F-fluoro-2-deoxy-D-glucose in comparison with magnetic resonance imaging for the assessment of inflammatory proliferation of synovium. Arthritis Rheum 48:3077–3084

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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.

All authors are members of the Pediatric Standing Committee of the Japan College of Rheumatology.

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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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References

1. Yokota S, Mori M, Imagawa T, et al. Proposal for juvenile idiopathic arthritis guidance on diagnosis and treatment for primary care pediatricians and nonpediatric rheumatologists. Mod Rheumatol. 2007;17:353–63.
2. Mohler KM, Sleath PR, Fitzner JN, Cerretti DP, et al. Protection against a lethal dose of endotoxin by an inhibitor of tumour necrosis factor processing. Nature. 1994;370:218–20.
3. Mohler KM, orrance DS, Smith CA, et al. Soluble tumor necrosis factor (TNF) receptors are effective therapeutic agents in lethal endotoxemia and function simultaneously as both TNF carriers and TNF antagonists. J Immunol. 1993;151:1548–61.
4. Moreland LW, Baumgartner SW, Schiff MH, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor(p75)-Fc fusion protein. N Engl J Med. 1997;337: 141–7.
5. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis: a randomized, controlled trial. Ann Intern Med. 1999;130:478–86.
6. Weinblatt ME, Kremer JM, Bankhust AD, Bulpitt KJ, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med. 1999;340:253–9.
7. Tanno M, Nakamura I, Ito K, et al. Modeling and cost-effectiveness analysis of etanercept in adults with rheumatoid arthritis in Japan: a preliminary analysis. Mod Rheumatol. 2006;16:77–84.

8. Miyasaka N, Takeuchi T, Eguchi K. Guidelines for the proper use of etanercept in Japan. Mod Rheumatol. 2006;16(2):63–7.
9. 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.
10. Horneff G, Schmeling H, Biedermann T, et al. The German etanercept registry for treatment of juvenile idiopathic arthritis. Ann Rheum Dis. 2004;63:1638–44.
11. Cassidy JT, et al. Chronic arthritis, poly arthritis, oligoarthritis, systemic arthritis. In: Cassidy JT, Petty RE, Laxer RM, Linsley CB, editors. Textbook of pediatric rheumatology. 5th edn. Philadelphia: Elsevier Saunders; 2005. p. 206–303.
12. Harrington J, Kirk A, Newman S. Developmental issues in adolescence and the impact of rheumatic disease. In: Isenberg DA, Miller JJ, editors. Adolescent rheumatology. London: Martin Dunitz; 2000. p. 21–34.
13. Grom AA, Murray KJ, Luyrink L, et al. Pattern of expression of tumor necrosis factor α, tumor necrosis factor β, and their receptors in synovia of patients with juvenile rheumatoid arthritis and juvenile spondyloarthropathy. Arthritis Rheum. 1996;39: 1703–10.
14. Eberhard BA, Laxer RM, Andersson U, Silverman ED. Local synthesis of both macrophage and T cell cytokines by synovial fluid cells from children with juvenile rheumatoid arthritis. Clin Exp Immunol. 1994;96:260–6.
15. Fink CW. Proposal for the development of classification criteria for the idiopathic arthritis of childhood. J Rheumatol. 1995;22: 1566–9.
16. Hashkes PJ, Laxer RM. Medical treatment of juvenile idiopathic arthritis. JAMA. 2005;294:1671–84.
17. Lovell DJ, Giannini EH, Reiff A, Jones OY, Schneider R, Olson. JC, et al. Long-term efficacy and safety of etanercept in children with polyarticular-course juvenile rheumatoid arthritis: interim results from an ongoing multicenter, open-label, extended-treatment trial. Arthritis Rheum. 2003;48:218–26.
18. Prevoo ML. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995;38:44–8.
19. Mori M, akei S, Imagawa T, Imanaka H, Maeno N, et al. Pharmacokinetics, efficacy and safety of short-term (12 weeks) etanercept for the methotrexate-refractory polyarticular juvenile idiopathic arthritis in Japan. Mod Rheumatol. 2005;15:397–404.
20. Elkayam O, Caspi D, Reiblattet T, et al. The effect of tumor necrosis factor blockade on the response to pneumococcal vaccination in patients with rheumatoid arthritis and ankylosing spondylitis. Semin Arthritis Rheum. 2004;33:283–8.