Review Article
International Journal of Basic and Clinical Studies (IJBCS)
2012;1(II): 56-68 Oktayoglu P, Em S, Tahtasiz M

Biologic Therapies in Juvenile Idiopathic Arthritis

Pelin Oktayoglu MD[1], Serda Em MD[1], Mehmet Tahtasiz MD[1], Mehtap Yılmaz Bozkurt MD[1], Demet Ucar MD[1], Mehmet Karakoc MD[1], Kemal Nas MD[1]

1 Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Dicle University, Diyarbakir, Turkey

Abstract

Juvenile idiopathic arthritis (JIA) is the general term of a group of diseases including psoriatic arthritis and other spondyloarthropathies. Although up to date most of drugs are used for the treatment of this disease, an exact cure can not be developed. The targets of the therapy are protecting joint functions, improving clinic symptoms and providing achievement of normal growth and physical development. Disease modifying antirheumatic drugs like methotrexate, sulfasalazine, hydroxychloroquine and corticosteroids, antiinflammatory agents are used for providing these targets. In short and mid term periods promising results are validated from clinical trials related with anti cytokine therapy. Three of these drugs, etanercept, adalimumab and abatacept are approved by FDA for the treatment of JIA. We are expecting long term results of ongoing trials with a great interest. 'Pediatric core set' related with the American College of Rheumatology (ACR) response levels are used for documentation of clinic results in research arena. New treatment researches are still going on and their results are expected hopefully.

Keywords: Juvenile idiopathic arthritis, anticytokine therapy.

Introduction

Juvenile idiopathic arthritis (JIA) is a general term for a group of heterogen diseases that is characterised the arthritis of at least one joint for more than 6 weeks. JIA also includes psoriatic arthritis and other spondyloarthropathies which are not in the spectrum of juvenile rheumatoid arthritis (1).

However the cause and pathogenesis of JIA is not completely understood, both genetic and environmental components appear to play a role (2). A genome-wide scan in affected families supported the view that several genes might affect the development of JIA (3).

There is currently no cure for JIA. The primary aim of medical therapy are to eliminate active disease, to normalize joint function, to preserve normal growth and to prevent longterm joint damage.

JIA is typically treated with disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX), sulfasalazine, and leflunomide, or with biologic agents (4-11). However, not all patients respond to these treatments, and some DMARDs or antiinflammatory agents are associated with toxicities that limit long-term use or diminish compliance (12-15). Thus, there is a need for durable and well-tolerated long-term treatment options for patients with JIA.

Biologic therapies in JIA

With the advent of biologic disease-modifying antirheumatic drugs, commonly referred to as biologics, the treatment options for JIA have changed and improved markedly.

(16). Biologics are genetically engineered drugs that work by selectively blocking the effects of cytokines.

Early JIA trials used a range of outcome variables, including composite scores of individual clinical parameters. Initially for trials, a core set of criteria has been developed through international consensus to facilitate standardization of measures-of-change in JIA (17).

'Pediatric core set' criters include;

1. Number of Active Joints
2. Number of Joints with Loss of Motion
3. Physician's Global Assessment
4. Parent's Global Assessment
5. Childhood Health Assessment Questionnaire
6. ESR

Patient must have at least a 30% improvement in 3/6 items and a worsening of 30% in no more than one component to achieve an American College of Rheumatology Pediatric (ACR Pedi) 30 response . ACR Pedi 50 and 70 require 50 or 70% improvement in 3/6 items with worsening of 30% in no more than one component.

We are going to review some biologic agents those efficacy were evaluated by trials in patients with juvenile idiopathic arthritis.(18).

Etanercept

Etanercept is a recombinant fusion protein in which 2 soluble TNF-a receptors are fused to the Fc portion of human IgG1. Etanercept binds to soluble TNF-a and thus inhibits

inflammatory processes. Lovell et al administrated 0.4 mg of etanercept per kilogram of body weight subcutaneously twice weekly for up to three months in the initial, open-label part of a multicenter trial. At the end of the open-label study, 51 of the 69 patients (74 percent) had had ACR Pedi 30 responses to etanercept treatment. In the double-blind study, patients were randomly assigned to receive either placebo or etanercept for four months or until a flare of the disease occurred. 21 of the 26 patients who received placebo (81 percent) withdrew because of disease flare, as compared with 7 of the 25 patients who received etanercept (28 percent). Authors suggested that etanercept leads to significant improvement in patients with active polyarticular juvenile rheumatoid arthritis (19). Etanercept is one of the TNF α inhibitor approved by FDA for use in JIA.

Infliximab

Infliximab is a chimeric human/mouse monoclonal antibody directed against TNF-α, administered by intravenous infusion. It has a longer half life than etanercept. Ruperto et al randomized one hundred twenty-two children with persistent polyarticular JIA patients despite prior methotrexate (MTX) therapy to receive infliximab or placebo for 14 weeks. Higher proportion of patients in the 3 mg/kg infliximab group than in the placebo group had achieved responses according to the American College of Rheumatology (ACR) Pediatric 30 (Pedi 30) criteria for improvement at week 14 (63.8% and 49.2%, respectively). At the end of 14 weeks, patients in MTX plus 3 mg/kg infliximab group continued to receive therapy but Mtx plus placebo group were turned into MTX plus 6mg/kg infliximab. Infliximab 3 mg/kg appeared less favorable than that of infliximab 6 mg/kg, with more frequent occurrences of serious adverse events, infusion reactions, antibodies to infliximab, and newly induced

antinuclear antibodies and antibodies to double-stranded DNA observed with the 3 mg/kg dose (20).

One of the complications of JIA is a chronic, nongranulomatous uveitis, reported in approximately 15% of patients with persistent oligoarthritis and 5% of patients with polyarticular disease. It appears from some preliminary data that monoclonal antibodies to TNF, especially infliximab, are more effective than the receptor etanercept in the treatment of refractory uveitis (21-23).

Adalimumab

Adalimumab is the first fully human, Ig G1 monoclonal antibody specific for human TNF. Adalimumab binds specifically to TNF and blocks its interaction with the p55 and p75 cell surface TNF receptors, thereby neutralising the activity of this cytokine (24).

Lovell et al. randomized patients underwent stratification according to methotrexate use and received 24 mg of adalimumab per square meter of body-surface area (maximum dose, 40 mg) subcutaneously every other week for 16 weeks. They randomly assigned patients with an American College of Rheumatology Pediatric 30% (ACR Pedi 30) response at week 16 to receive adalimumab or placebo in a double-blind fashion every other week for up to 32 weeks. Seventy-four percent of patients not receiving methotrexate (64 of 86) and 94% of those receiving methotrexate (80 of 85) had an ACR Pedi 30 response at week 16 and were eligible for double-blind treatment. At week 48 among patients receiving methotrexate, flares occurred in 37% of those receiving adalimumab and 65% of those receiving placebo. Adalimumab is the other TNF α inhibitor that is approved by FDA for use of JIA.

Anakinra

It is recombinant form of nonglycosylated human IL-1 receptor antagonist expressed in Escherichia coli. Natural IL- 1 receptor antagonist is produced by macrophages and activated monocytes in response to various inflammatory stimuli. Anakinra competitively binds to both type-I and type-II IL-1 receptors, at least partially blocking cellular responses mediated by IL-1 alpha and IL beta. It has a binding affinity similar to IL-1, but it lacks IL-1 agonist activity (25-27).

In a trial nine systemic onset JIA patients were administered recombinant IL-1 receptor antagonist who were refractory to other therapies. Complete remission was obtained in seven out of nine patients and a partial response was obtained in the other two patients. The authors concluded that IL-1 is a major mediator of the inflammatory cascade that underlies systemic onset JIA and that this cytokine represents a target for therapy in this disease (28).

Rilonacept

Rilonacept is a recombinant fusion protein that combines IL-1 receptor protein components with the Fc portion of the human immunoglobulin molecule. Unlike anakinra, which requires daily dosing, rilonacept is a longer-acting IL-1 blocker and is administered once a week. Preliminary results of a double blind, placebo-controlled study of rilonacept (2.2 to 4.4 mg/kg/week) in systemic onset juvenile idiopathic arthritis followed by an open-label extension trial were reported by Lovell and colleagues in abstract form at the 2007 American College of Rheumatology Scientific Meeting. Of the 21 patients enrolled in the trial, 12

remain in the open-label study and have had good responses to rilonacept – with 10 patients achieving an ACR Pedi 70 response at 42 weeks (29).

Abatacept

Abatacept Soluble fully human fusion protein of the extracellular domain of cytotoxic Tlymphocyte- associated antigen (CTLA)-4, linked to a modified FC portion of the human immunoglobulin G1. It acts as a co-stimulatory signal inhibitor by binding competitively to CD80 or CD86, where it selectively inhibits T-cell activation. Ruperto et al treated 190 patients with JIA by administrating 10 mg/kg abatacept every four weeks. Of the 190 enrolled patients 153 entered the long term extension phase of that study. By day 589, 75%, of patients treated with abatacept during the double-blind and long term extension phases achieved ACR Pedi 50 responses. The authors suggested that abatacept provided clinically significant and durable efficacy in patients with JIA (30). Abatacept was approved for use in JIA by FDA in 2008.

Tocilizumab

Tociluzumab is a humanized anti-human interleukin-6 receptor (IL-6R) monoclonal antibody developed recently in Japan. TCZ binds to the alpha chain of both membranebound and soluble IL-6R, thus blocking IL-6/ IL-6R signaling (31,32)

Yokota et all designed a three phased trial in which 56 children were involved with disease refractory to conventional treatment were given three doses of tocilizumab 8 mg/kg every 2 weeks during a 6-week open-label phase. At the end of the open-label lead-in phase, ACR Pedi 30, 50, and 70 responses were achieved by 51 (91%), 48 (86%), and 38 (68%) patients, respectively. Patients achieving an American College of Rheumatology Pediatric

(ACR Pedi) 30 response and a C-reactive protein concentration (CRP) of less than 5 mg/L were randomly assigned to receive placebo or to continue tocilizumab treatment for 12 weeks or until withdrawal for rescue medication in a double-blind phase. Four (17%) of 23 patients in the placebo group maintained an ACR Pedi 30 response and a CRP concentration of less than 15 mg/L compared with 16 (80%) of 20 in the tocilizumab group. Patients responding to tocilizumab and needing further treatment were enrolled in an open-label extension phase for at least 48 weeks. By week 48 of the open-label extension phase, ACR Pedi 30, 50, and 70 responses were achieved by 47 (98%), 45 (94%), and 43 (90%) of 48 patients, respectively. (33).

Although there are many different drugs available for treating JIA, recent advances in understanding the pathophysiology of arthritis have expanded the treatment of this chronic condition. Anticytokine therapy have changed the treatment of JIA, producing significant clinical improvement. Although promising results have been demonstrated with these medications, the blockade of such important biologic pathways necessitates careful safety monitoring. We are expecting the long term outcomes of these medications hopefully.

References

1. R.E. Petty, T.R. Southland, P. Manners, J. Baum, D.N. Glass, J. Goldenberg et al., International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis: second revision, Edmonton, 2001, *J Rheumatol.* 2004; 31 (2); 390–392.
2. Ravelli A, Martini A. Juvenile idiopathic arthritis. *Lancet*. 2007; 369(9563):767–778

3. Thompson SD, Moroldo MB, Guyer L et al. A genomewide scan for juvenile rheumatoid arthritis in affected sibpair families provides evidence of linkage. *Arthritis Rheum.* 2004; 50 (9):2920–2930
4. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al, for the Pediatric Rheumatology Collaborative Study Group. Etanercept in children with polyarticular juvenile rheumatoid arthritis. *N Engl J Med.* 2000;342:763–9.
5. Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum.* 2007;56:3096–106.
6. Silverman E, Mouy R, Spiegel L, Jung LK, Saurenmann RK, Lahdenne P, et al. Leflunomide or methotrexate for juvenile rheumatoid arthritis. *N Engl J Med.* 2005;352:1655–66.
7. Yokota S, Imagawa T, Mori M, Miyamae T, Aihara Y, Takei S, et al. Efficacy and safety of tocilizumab in patients with systemiconset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. *Lancet.* 2008;371: 998–1006.
8. Van Rossum MA, Fiselier TJ, Franssen MJ, Zwinderman AH, ten Cate R, Suijlekom-Smit LW, et al, for the Dutch Juvenile Chronic Arthritis Study Group. Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. *Arthritis Rheum.* 1998;41:808–16.

9. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med.* 2008;359:810–20.

10. Giannini EH, Brewer EJ, Kuzmina N, Shaikov A, Maximov A, Vorontsov I, et al, for The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. Methotrexate in resistant juvenile rheumatoid arthritis: results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. *N Engl J Med.* 1992;326:1043–9.
11. Ruperto N, Murray KJ, Gerloni V, Wulffraat N, de Oliveira SK, Falcini F, et al. A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to Standard doses of methotrexate. *Arthritis Rheum.* 2004;50:2191–201.
12. Hashkes PJ, Laxer RM. Medical treatment of juvenile idiopathic arthritis. *JAMA.* 2005;294:1671–84.
13. Prince FH, Twilt M, ten Cate R, van Rossum MA, Armbrust W, Hoppenreijs EP, et al. Long-term follow-up on effectiveness and safety of etanercept in JIA: the Dutch national register. *Ann Rheum Dis.* 2009;68:635–41.
14. Flato B, Vinje O, Forre O. Toxicity of antirheumatic and antiinflammatory drugs in children. *Clin Rheumatol.* 1998;17:505–10.

15. Rapof f MA, Belmont JM, Lindsley CB, Olson NY. Electronically monitored adherence to medications by newly diagnosed patients with juvenile rheumatoid arthritis. *Arthritis Rheum.* 2005;53: 905–10.
16. Hashkes PJ, Laxer RM. Medical treatment of juvenile idiopathic arthritis. *JAMA*. 2000; 294(13):1671–1684.
17. Giannini EH, Ruperto N, Ravelli A et al. Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum.* 1997;40:1202–9
18. Oktayoglu P. Tekeoglu İ. Treatment of juvenile idiopathic arthritis and biologic agents. *Sakaryamj.* 2011(3):76-85
19. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, Stein LD, Gedalia A, Ilowite NT, Wallace CA, Whitmore J, Finck BK Etanercept in children with polyarticular juvenile rheumatoid arthritis. *N Engl J Med*. 2000; 16;342(11):763-9.
20. Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G, Wouters C, Silverman ED, Balogh Z, Henrickson M, Apaz MT, Baildam E, Fasth A, Gerloni V, Lahdenne P, Prieur AM, Ravelli A, Saurenmann RK, Gamir ML, Wulffraat N, Marodi L, Petty RE, Joos R, Zulian F, McCurdy D, Myones BL, Nagy K, Reuman P, Szer I, Travers S, Beutler A, Keenan G, Clark J, Visvanathan S, Fasanmade A, Raychaudhuri A, Mendelsohn A, Martini A, Giannini EH.A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum.* 2007; 56(9):3096-106.
21. Richards JC, Tay-Kearney ML, Murray K, Manners P. Infliximab for juvenile idiopathic arthritis-associated uveitis. *Clin Experiment Ophthalmol*. 2005; 33(5):461-8

22. Rajaraman RT, Kimura Y, Li S, et al. Retrospective case review of pediatric patients with uveitis treated with infliximab. *Ophthalmology*. 2006 ;113(2):308-14.

23. Guignard S, Gossec L, Salliot C, et al. Efficacy of tumour necrosis factor blockers in reducing uveitis flares in patients with spondylarthropathy: A retrospective study. *Ann Rheum Dis*. 2006 ;65(12):1631-4.

24. Mease PJ. Tumour necrosis factor (TNF) in psoriatic arthritis: pathophysiology and treatment with TNF alpha inhibitors. *Ann. Rheum. Dis.* 2002; 61:298-304.

25. Ken, JB. Biologic therapies in Rheumatoid arthritis. *Curr. Rheu. Rep*. 1999;1:157-163.

26. Sharma, R.; Verma, U. A novel therapeutic approach in rheumatoid arthritis. *Ind. J. Pharmacol*. 2005; 36, 265-266.

27. Vila, A.T, Puig L, Fernandez-Figueras M.T, Laiz A.M, Vidal D, Alomar A. Adverse cutaneous reactions to anakinra in patients with rheumatoid arthritis: Clinicopathological study of patients. *Br. J. Dermatol*. 2005; 153, 417-423.

28. Pascual V, Allantaz F, Arce E, Punaro M, Banchereau J: Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. *J Exp Med.* 2005; 201:1479-1486.

29. Lovell DJ, Giannini EH, Kimura Y, Li S, Hashkes PJ, Reiff AO, Wallace CA, Onel KB, Wei Y, FuryW, Nadler DR, Biedermann S, Osgood G, Papadopoulos JH, Radin AR: Preliminary evidence for sustained bioactivity of IL-1 trap (rilonacept), A long acting IL-1 inhibitor, in systemic onset juvenile idiopathic arthritis (SJIA) [abstract]. *Arthritis Rheum.* 2007; 56:S514.

30. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Pérez N, Silva CA, Abud-Mendoza C, Burgos-Vargas R, Gerloni V, Melo-Gomes JA, Saad-Magalhães C, Chavez-Corrales J,

Huemer C, Kivitz A, Blanco FJ, Foeldvari I, Hofer M, Horneff G, Huppertz HI, Job-Deslandre C, Loy A, Minden K, Punaro M, Nunez AF, Sigal LH, Block AJ, Nys M, Martini A, Giannini EH; Paediatric Rheumatology International Trials Organization and the Pediatric Rheumatology Collaborative Study Group. Long-term safety and efficacy of abatacept in children with juvenile idiopathic arthritis. *Arthritis Rheumatism*. 2010 ;62(6):1792-802.

31. Choy, E.H.S.; Isenberg, DA.; Garrood, T.; Farrow, S.; Ioannou, Y.; Bird, H.; Therapeutic benefit of blocking interleukin-6 activity with an anti-interleukin-6 receptor monoclonal antibody in rheumatoid arthritis. *Arthritis Rheum*. 2002; 46, 3143-3150.
32. 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, doubleblind, placebo-controlled trial. *Arthritis Rheum*. 2004; 50, 1761-1769.
33. Yokota S, Imagawa T, Mori M, Miyamae T, Aihara Y, Takei S, Iwata N, Umebayashi H, Murata T, Miyoshi M, Tomiita M, Nishimoto N, Kishimoto T. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. *Lancet*. 2008; 22;371(9617):998-1006