BIOLOGICAL THERAPY WITH ANTI-TNF AGENTS IN JUVENILE ARTHRITIS CONSIDERATIONS ON A CASE REPORT

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Abstract

The management of juvenile rheumatoid arthritis has advanced dramatically in the last years based on a more effective use of available drugs and on the application of newly discovered ones. More judicious use of corticosteroids and techniques such as intravenous pulse therapy rather than long-term high-dose use of oral corticosteroids, besides the therapy with methotrexate in moderate to severe JRA still represent the gold standard for polyarthritis management. However, the introduction of anti-TNF agents, such as Etanercept or Infliximab could represent a major shift to the use of biological therapy in patients intolerant to or unresponsive to standard disease modifying antirheumatic drugs (DMADs). We present a case of therapy with Etanercept in a boy with refractory JRA and discuss on the perspective of use of the biological agents.

Keywords: etanercept, JRA, children

Background

Juvenile rheumatoid arthritis (JRA) is the most common rheumatic disease in childhood. Unfortunately, less than one third of patients can have their disease controlled by nonsteroidal or steroidal anti-inflammatory drugs, the remainders being candidates for a more aggressive therapy.

Methotrexate was shown to have a therapeutic advantage over placebo, with an acceptable safety profile in randomized controlled trials in children with JRA. However, many patients do not have an adequate response to methotrexate, even at doses of up to 1mg/kg/week. Moreover, the severity and frequency of side effects increase with higher doses of methotrexate and the consequences of long-term use are not known.

Other disease-modifying antirheumatic drugs (DMARDs) such as sulphasalazine, cyclosporine or cyclophosphamide are finding a specific role for resistant disease where they may be used in combination with methotrexate for example.

In some controlled studies the use of intravenous immunoglobulin (IVIG) in patients with systemic-onset JRA suggested that it was of limited benefit, whereas in a controlled phase I/II trial by Giannini et al substantial short-term benefit was demonstrated in about 75% of individuals, particularly if it was used early in the course of disease. Another retrospective study noted benefit for the systemic features and steroid dependency but limited effect on the polyarthritis. Thus, based on their still incompletely understood pathogenic action in blocking the autoimmune phenomena, IVIG may have a role in selected patients with severe disease unresponsive to other approaches.

The introduction of antitumor necrosis factor (anti-TNF) agents represents a real revolution in the treatment of rheumatic disorders. TNF is a proinflammatory cytokine that has a complex role in the pathogenesis of JRA. TNF was found elevated in both the serum and the synovial fluid of children with rheumatoid arthritis. Serum levels of soluble TNF receptor are elevated in patients with all subtypes of JRA and the level is correlated with the activity of the disease. Thus, the rationale for the introduction of anti TNF therapy is based on the understanding that cytokines such as TNF are critical molecules lying at the heart of the chronic autoimmune/inflammatory disease process. This has resulted in the introduction into the clinic of 2 inhibitors of TNF, the soluble TNF receptor (etanercept) and the anti-TNF monoclonal antibody (infliximab).

Etanercept (Enbrel, Immunex, Seatle) is a genetically engineered fusion protein consisting of two identical chains of the recombinant extracellular human P75 TNF-receptor molecules fused with the Fc domain of human IgG1, which effectively binds TNF and lymphotoxin-α and inhibits their activity. It is given 0.4mg/kg twice weekly by subcutaneous injection with onset of effect anticipated within 3-4 weeks. Randomized multicentre double-blind placebo-controlled studies of etanercept for the treatment of active polyarticular JRA in children showed its effectiveness in 74% of pediatric patients with severe polyarticular JRA (regardless of the type of onset) who did not tolerate well or had an inadequate response to methotrexate.

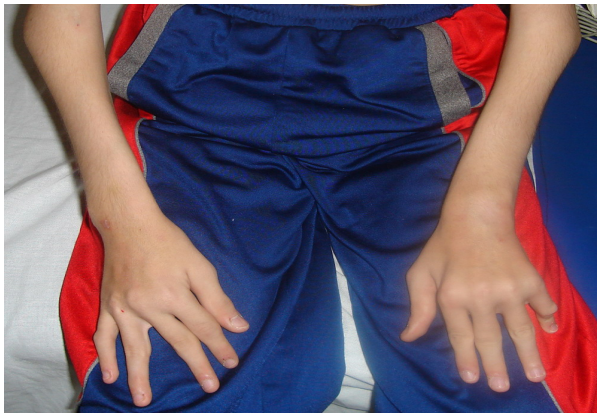
We present a case of polyarticular JRA in a 15y-old boy and his various therapeutic regimes over the time.

Case presentation

The patient was admitted at the hospital for the first time at the age of 10 for swelling, tenderness, pain and limitation of range of motion in small joints (wrists, interphalangeal and metacarpophalangeal joints), but also with knees, ankles and temporomandibular involvement. The onset was approximately 2 months before admittance and the physical examination confirmed the arthritis of the above mentioned joints. Biological findings revealed signs of articular inflammation: elevated ESR (58/95cm) and CRP values, positive rheumatoid factor (RF), whereas antinuclear antibodies (ANA) and anti-double-stranded DNA (anti-dsDNA) were negative. The radiographic changes of hands and knees consisted of soft tissues swelling and discreet periosteal new bone formation. The diagnosis of

polyarticular JRA was established based on the American College of Rheumatology classification criteria.

The initial treatment consisting of nonsteroidal anti-inflammatory therapy was started but within one month no clinical improvement was noted, so the steroid regime was initiated with Prednison 1mg/kg/day. The clinical signs improved, but after 6 months of therapy, MRI examination revealed signs of osteoporosis, so the corticoid therapy was stopped. Further on, the treatment was continued with Na-auro-thiomalate (Tauredon) for a period of 20 months until a total dose of 700mg was reached. The clinical signs did not improve much, moreover, a thoracic cifosis occurred and a certain grade of ankylosis of hands and elbows joints was noticed with limitation of motion. The next approach chosen was methotrexate, hoping it could bring about some improvement, but unfortunately in less than one month a severe cytopenia (leucopenia and thrombocytopenia) was observed which constrained us to stop this last treatment.



The figure presents the limitation of range of motion of the hands and elbows joints after 3 years from the onset.

Having said the above course of the disease, the next recently available choice was to start therapy with anti-TNF agents. The patient received 25mg of Etanercept subcutaneously twice weekly for a period of 24 months. A complete check for infections was performed before the treatment was started. Physical examination, laboratory tests (ESR, CRP, RF, ANA, anti-dsDNA, liver enzymes, renal function, cultures) and evaluation of disease activity measures and response were performed monthly.

The outcome measures used to assess disease response consisted of the following set of 6 response variable (the JRA core criteria): 1) global assessment of disease severity by the physician, 2) global assessment of overall well-being by the patient or the patient's parent or guardian, 3) number of joints with active disease (joints with swelling not due to deformity or joints with limitation of motion and with pain, tenderness or both), 4) number of joints with limitation of motion, 5) functional ability, assessed by Childhood Assessment questionnaire (C-HAQ) and 6) a laboratory marker of inflammation, defined as ESR and CRP.

Response was evaluated according to the JRA definition of improvement (DOI) criteria (the patient had to have 30% of improvement from baseline in at least 3 of the 6 response variable, with no more than 1 variable worsening by more than 30%).

The table bellow presents JRA core criteria at start and after 24 months of therapy showing more than 30% JRA definition of improvement:

Parameter	Month 1	Month 24	% Improvement
JRA core criteria			
Total no. of active joints	26	18	31%
No. of joints with limitation of motion	18	15	17%
Physician's global assessment	2.0	2.0	0
Patient's/parent's global assessment	2.0	1.0	50%
C-HAQ score	0.8	0.5	38%
ESR	66	58	15%

The patient was followed up for adverse effects such as infections, occurrence of other autoimmune disorders, tuberculosis or malignancies. The main incident that occurred was a severe bronchopneumonia after 18 months of therapy which hardly responded to antibiotic treatment.

Discussions

The treatment of JRA continues to evolve, with the introduction of many new pharmacologic interventions. Although methotrexate continues to be the DMARD used most frequently for the treatment of refractory JRA, it is very often not effective or not well-tolerated by some patients. So, the therapy with etanercept (a new anti-TNF agent) becomes the issue of choice in refractory cases. Even if in some adults etanercept is associated with methotrexate, we decided not to add it in this case because the side effects to methotrexate already occurred in our patient. He tolerated well the therapy with etanercept with except an infectious incident (bronchopneumonia) which happened to occur at some point and which was difficult to treat. There was no notice of other adverse events such as tuberculosis, varicella infection, pancitopenia, or new auto antibodies. Unfortunately, when the therapy with etanercept was started a certain grade of ankylosis was already present, so the therapy was effective only on active joint, with an improvement of more than 30% in 3 parameters of core criteria for definition of improvement. Studies coordinated by Daniel Lovell and coworkers have shown that long-term treatment with etanercept can provide significant clinical benefit to pediatric patients with severe polyarticular-course JRA, regardless of disease type of onset and that prolonged use has not been associated with increases in the rates of adverse events or infections. However, the question in

matter is now, for how long can we continue the treatment in our patient or what other alternatives are available (autologous stem cell transplantation, anti IL-1 - Anakira, or B-cell-targeted therapy with anti–CD20 monoclonal antibody- Rituximab).

Conclusions

Early consideration of more aggressive therapy at start should be considered in children with severe arthritis as irreversible joint damage can occur within 1 to 2 years and better predictors of prognosis and responses to therapy are required to identify patients requiring early aggressive treatment. Anti-TNF agents represent a real alternative in children with refractory clinical signs or with severe side effects to methotrexate. National registries of patients treated with anti-TNF agents would be extremely important to support long-term safety profiles, effectiveness and the true risk of potential complications such as severe infections, malignancies or autoimmune disorders.

References:

1. Arthur Kavanaugh, Biologic Agents in Rheumatoid Arthritis, American College of Rheumatology 64th Annual Scientific Meeting, 2005
2. Daniel J. Lovell, Michael L. Miller, James T. Cassidy, Treatment of Rheumatic Diseases in Nelson Textbook of Pediatrics 17th Edition, pp. 795-799, 2004
3. Daniel J. Lovell at all, Long-term Efficacy and Safety of Etanercept in Children with Polyarticular-Course Juvenile Rheumatoid Arthritis, Arthritis&Rheumatism, vol. 48. no.1, January 2003, pp.218-226
4. Michael L. Miller, James Cassidy, Juvenile Rheumatoid Arthritis in Nelson Textbook of Pediatrics 17th Edition, pp. 799-805, 2004
5. John J.Cush, Treatment Advances in the Spondiloarthropathies, American College of Rheumatology 64th Annual Scientific Meeting, 2005
6. Jonathan C.W. Edwards, Efficacy of B-Cell-Targeted Therapy with Rituximab in patients with Rheumatoid Arthritis, N.Engl.J.Med 2004, 350:, pp. 2572-2581
7. Kevin J. Murray, Daniel J. Lovell, Advanced therapy for juvenile arthritis, Best Practice&Research Clinical Rheumatology, vol. 16,no.3, pp 361-378, 2002
8. Lars Klareskog at all, Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomized controlled trial, The Lancet, Saturdau 28February 2004, vol.363, no.9410, pp.675-681

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