Original Research Article

A study on the efficacy, tolerability and safety of biologics in children with juvenile idiopathic arthritis

Ramesh Ramamoorty[1*], Murali R[2], Ragavendra[3], Balameena S[4]

[1]Assistant Professor, Institute of Rheumatology, Madras Medical College, EVR salai, Chennai, Tamil Nadu, India
[2]Associate Professor, Department of Medical Gastroenterology, Madras Medical College, EVR salai, Chennai, Tamil Nadu, India
[3]Post graduate student, Institute of Rheumatology, Madras Medical College, EVR salai, Chennai, Tamil Nadu, India
[4]Associate Professor, Department of Rheumatology, Kilpauk Medical College, Kilpauk, Chennai, Tamil Nadu, India
[*]Corresponding author email: **rameshr27@yahoo.com**

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Abstract

This study was done to assess the efficacy of biologics in patients with various subtypes of Juvenile Idiopathic Arthritis (JIA). All JIA patients with active chronic polyarthritis, who were non responders to methotrexate, were included in this open-label, prospective, study. Systemic arthritis was treated with Tocilizumab and the other JIA subtypes were treated with Etanercept. JADAS-27, Leeds Enthesitis Index (LEI) and ACR Pedi-30 were used to assess improvement. We also assessed the tolerance to treatment of JIA with biologics. 54 patients were enrolled and followed up for a median of 14 months. In Oligoarticular and Polyarticular arthritis, JADAS-scores were improved by ≥30% in 72% of patients after 3 months. There was a statistically significant improvement in JADAS 27 scores. In patients with oligo arthritis, the mean JADAS 27 before treatment was 36± 2.5, which improved to 28.6±1.2 (p=0.008). In polyarticular JIA, the mean JADAS 27 before treatment was 40.2± 2.5, which improved to 31.6±1.2 (p=0.001). In ERA Leeds Enthesitis index improved in 80% of patients and JADAS-27 score improved by ≥ 30% in 80% of patients in 3 months. In Systemic Arthritis, the primary end point was absence of fever and ACR Pedi-30 response at the end of 12 week of treatment achieved in 84% of patients. Tocilizumab and Etanercept were found efficacious in

Systemic arthritis and in other JIA subsets respectively, in methotrexate non-responders. Both tolicizumab and etanercept were well tolerated.

Key words

Efficacy, Tolerability, Safety, Biologics, Children, Juvenile idiopathic arthritis.

Introduction

Juvenile Idiopathic Arthritis (JIA) is the most common chronic rheumatologic disease in children and is one of the most common chronic diseases of childhood. It represents a group of disorders that share the clinical manifestation of chronic joint inflammation.

The ILAR classification of JIA includes the following categories [1]:

- Systemic-onset JIA
- Persistent or extended oligoarthritis
- Rheumatoid factor (RF) – positive polyarthritis
- RF negative polyarthritis
- Psoriatic JIA
- Enthesitis-related arthritis
- Undifferentiated - The disease does not meet criteria for any of the other subgroups, or it meets more than 1 criterion (and therefore could be classified in a number of subgroups).

Arthritis must be present for 6 weeks before the diagnosis of juvenile idiopathic arthritis (JIA) can be made. Disease onset is either insidious or abrupt, with morning stiffness or gelling phenomenon (i.e., stiffness after long periods of sitting or inactivity) being a frequent complaint and arthralgia occurring during the day. A morning limp that improves with time may be noted, and a toddler may no longer stand in the crib in the morning or after naps.

Systemic-onset JIA is characterized by spiking fevers, typically occurring once or twice each day, at about the same time of day, with temperature returning to normal or below normal. Systemic-onset JIA is usually accompanied by an evanescent rash (lasting a few hours), which is typically non-pruritic, macular, and salmon colored on the trunk and extremities. Occasionally, the rash is extremely pruritic and resistant to antihistamine treatment. Children with psoriatic arthritis may have typical psoriasis but dermatological manifestations may be subtle; careful attention should be paid to looking for nail pits. Dactylitis is characteristic of psoriatic arthritis. Enthesitis related arthritis (ERA) frequently presents as evening and post-exercise pain. Attention should be given to buttock pain and back pain that improves with activity (inflammatory back pain). These children cannot lie in bed all morning, but had to get up due to back pain.

In polyarticular JIA, methotrexate (MTX) is the mainstay of treatment and is used as a first line agent, either alone or with initial pulses of methylprednisolone and/or multiple intra-articular steroid injections to achieve rapid disease control [2]. The use of etanercept, either instead of, or in addition to MTX has added another step in improving the condition of the most severely affected patients. However, etanercept deserves the usual cautions for use in children, whereas MTX is safe and effective for use in JIA. Methotrexate has only moderate effect on prevention of disability. Studies have shown etanercept is effective in oligo, poly articular JIA and ERA while Tocilizumab is effective in systemic JIA [3, 4].

Objectives of the study

The primary objective of the study was to assess the efficacy of various biologics in JIA subtypes, who were either methotrexate non responders or intolerant. The secondary objective was to determine the tolerability and safety of biologics in children.

Materials and methods

This study was done in the Institute of Rheumatology, Madras Medical College, Chennai. It was a prospective open labelled interventional study. After obtaining institutional ethical committee approval, written and informed consent were obtained from the parents. The study was conducted for a period of 2 years with a median period of 14 months. JIA patients of the various subcategories in accordance to the established ILAR criteria were admitted to the trial.

Inclusion criteria

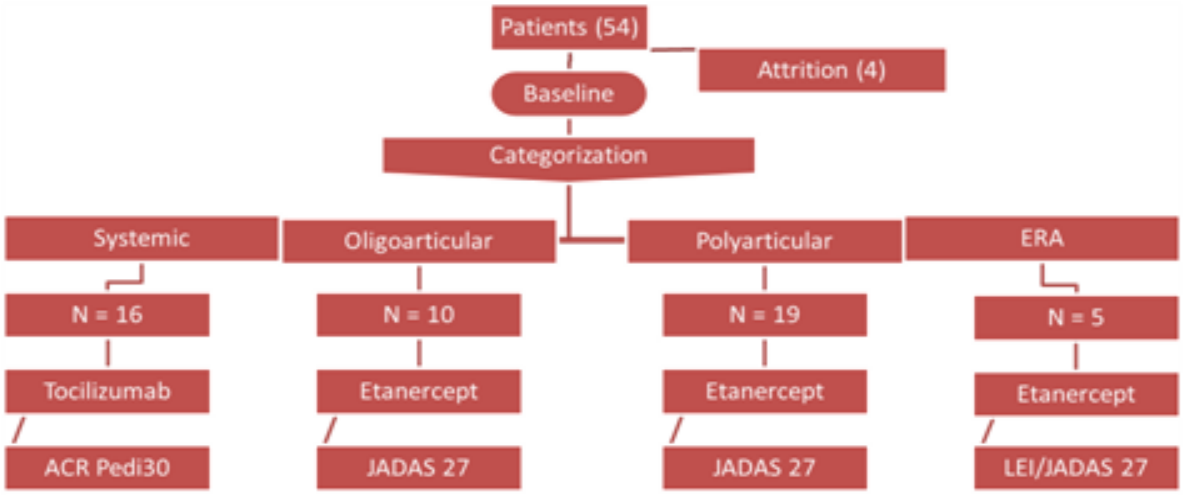
- All patients with JIA, fulfilling the ILAR criteria.
- 'Active' chronic polyarticular disease, as defined by the presence of ≥ 5 swollen joints and ≥ 3 joints with pain and limitation of motion for at least 6 months, regardless of the type of onset of JIA.
- Intolerance to or lack of efficacy of methotrexate at a dosage of at least 0.4 mg/kg of body weight weekly.

Exclusion criteria

- Major concurrent systemic diseases
- Active infection
- Malignancy
- Features of macrophage activation syndrome
- Elevated liver function, with hepatic aminotransferase concentrations more than double the normal value for age
- Low white blood cell, neutrophil, or platelet count
- Radiologic evidence of destructive, nonreversible polyarthritis (Steinbrocker class III or IV)
- Familial and social conditions rendering regular medical assessment impossible.

Initially 54 patients were chosen to participate in the trial (**Figure - 1**). 4 patients withdrew from the trial due to various reasons before the commencement. Among the remaining patients (n=50), 16 had systemic JIA, 10 had oligoarticular JIA, 19 had polyarticular JIA and 5 had ERA. All children were subjected to rigorous clinical examination, scoring based on objective systems and lab investigations to establish the baseline (**Table – 1, 2**). Systemic arthritis was treated with Tocilizumab and the other JIA subtypes were treated with Etanercept.

Figure 1 Study Design



Assessment of efficacy of therapy

JADAS-27, Leeds Enthesitis Index (LEI) and ACR Pedi-30 were used to assess improvement. Systemic arthritis was graded with ACR Pedi-30 and JADAS 27 was used for the rest. LEI was used for ERA.

Table – 1

	Sys	Oligo	Poly	ERA	Tot
Number	16	10	19	5	50
Age (mean years)	12	10	12	13.5	12.2
Sex(M/F)	13/3	6/4	11/8	3/2	33/17
Disease duration (mean years)	6.2	7.7	5.1	4.5	5.9
No of patients using Steroids	16	10	19	2	47
No of patients using MTX	16	10	19	5	50
No of patients using other DMARDs	0	1	4	5	23
No of Joints (mean)	22	11	15	14	16.3
No of joints with limitation of motion (mean)	37	22	28	24	29.3
Physician global assessment (mean)	51	48	49	55	50.04
Parent/patient global assessment (mean)	46	48	42	60	46.28
CHAQ (mean)	2.15	1.64	1.46	2.3	1.80
ESR (mean)	50	39	42	45	44.26
Concomitant MTX use	0	9	15	5	8
Concomitant Prednisone use	16	5	6	2	8.6

Follow up

The patients were seen in the outpatient department every week and assessed for compliance to therapy, improvement or worsening of the condition and titration of dose. All scorings were independently scored by two physicians and their mean values were used to eliminate subjective biases.

Tolerance to therapy

A separate data was maintained for the input of any adverse reactions observed from the patient. All concomitant medications at the time of onset of any adverse event were recorded as well to prevent confabulation by other agents.

Statistics

SPSS 21 software was used for data analysis.

Results

In oligoarticular arthritis, JADAS-27 scores improved by ≥30% from baseline in 72% of patients after 3 months of treatment with Etanercept.

Table 2 Disease severity scoring

Activity	Oligoarticular	Polyarticular	Acute Sacroilitis
LOW	<=1 active joint	<= 4 active joint	Normal back flexion
	Normal ESR/CRP	Normal ESR/CRP	Normal ESR/CRP
	PGA < 3	PGA < 3	PGA < 3
	Parent Global Assessment <2	Parent Global Assessment < 2	Parent Global Assessment < 2
MOD	>= 1 features greater than low disease activity and <3 features of high disease activity	>= 1 features greater than low disease activity and <3 features of high disease activity	>= 1 features greater than low disease activity and <2 features of high disease activity

In ERA, Leeds Enthesitis index improved in 80% of patients and JADAS-27 score improved by ≥ 30% from baseline in 80% of patients, after treatment with Etanercept for 3 months.

In patients with oligoarthritis, the mean JADAS 27 before treatment was 36 ± 2.5, which improved to 28.6 ± 1.2 (p=0.008).

In polyarticular JIA, the mean JADAS 27 before treatment was 40.2 ± 2.5, which improved to 31.6 ± 1.2 (p=0.001).

In polyarticular JIA, it was observed that JADAS-27 scores improved by ≥ 30% from baseline in 72% of patients after 3 months of treatment with Etanercept.

In Systemic Arthritis, ACR Pedi-30 response at the end of 12 week of treatment was achieved in 84% of patients treated with Tocilizumab. No serious adverse events were noted. All children tolerated biologics well.

Discussion

Juvenile idiopathic arthritis (JIA) affects between 1:1000–1:2000 children [5]. This condition is

heterogeneous, divided into several subtypes based upon various clinical, laboratory, and epidemiological features. Untreated, JIA can last well into adulthood, causing significant long-term functional impairment.

Because of the known relevance of IL-6 in juvenile idiopathic arthritis (JIA) pathophysiology, tocilizumab has been investigated and approved for use in the treatment of systemic JIA. Tocilizumab is a humanized monoclonal antibody that inhibits signaling through both membrane bound and soluble IL-6R.Tocilizumab has an important and evolving role in controlling disease activity in patients with JIA [6, 7]. It has been proven useful even in patients whose JIA had previously been refractory to other biologic disease modifying anti-rheumatic drugs (DMARDs) and also appears quite effective as monotherapy. Tocilizumab is relatively well tolerated amongst JIA patients, with systemic JIA patients experiencing more serious adverse events overall. The results of our study reproduce the results obtained by various investigators all over the world.

This study also provides evidence that Etanercept was both effective and well tolerated in subjects with polyarticular, oligoarticular JIA and ERA over a period of 14 months of treatment. Beyond the effectiveness of Etanercept, that was reflected in the arthritis-related variables measured in all three categories, there were substantial improvements in the tender entheseal score, back pain and nocturnal back pain in ERA patients. Etanercept was well tolerated in this pediatric population for up to 14 months. No serious infections were reported. However, the number of patient-years accrued with Etanercept in this study was not sufficient to draw any firm safety conclusions. The immunogenicity profile of Etanercept was favourable and consistent with studies in other paediatric and adult populations [8, 9, 10].

Conclusion

Tocilizumab was effective in systemic JIA and Etanercept was effective in other subtypes. Both the drugs were well tolerated, with acceptable safety. The study was limited methodologically by the open-label design and lack of placebo-control group and the lack of imaging. Additionally, subjects used different and varying concomitant therapies (DMARDs, glucocorticoids and NSAIDs) that might have an effect on the efficacy responses. Larger patient samples followed up for a longer duration are required in the future.

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