

Clinical Remission in Patients with Systemic Juvenile Idiopathic Arthritis Treated with Anti-Tumor Necrosis Factor Agents

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ABSTRACT. *Objective.* To assess the frequency of clinical remission in a cohort of patients with systemic juvenile idiopathic arthritis (JIA) who received continuous anti-tumor necrosis factor (TNF) therapy; and to identify potential predictors of remission.

Methods. Patients with systemic JIA who were treated with anti-TNF agents for > 6 months were studied. Demographic and nosologic variables recorded at the start of anti-TNF therapy were analyzed. Association between early variables and occurrence of remission was evaluated through Cox proportional hazard regression analysis.

Results. Forty-five patients were included (30 girls), median age 9 years (range 2–17 yrs), age at disease onset 5 years (range 0.5–15), disease duration 3 years (range 0.5–13). Twenty-one (47%) children showed systemic symptoms at the start of anti-TNF therapy. Patients received therapy for 24 months (range 6–88): 45 (100%) were given etanercept, 17 (38%) infliximab, and 5 (11%) adalimumab, in combination with methotrexate. Anti-TNF switching was performed in 22 (49%) children. Eleven (24%) met definition criteria for remission while taking etanercept (n = 8), infliximab (2), or adalimumab (1). Remission occurred following 26 (range 9–65) months of therapy. Flares occurred in 5 (45%) patients 2 to 14 months after remission was first recorded. Absence of systemic symptoms at the start of therapy and fulfilment of improvement criteria at Month 3 were associated with remission in univariate analysis; no variable showed any association in multivariate analysis.

Conclusion. Twenty-four percent of patients with systemic JIA experienced remission with anti-TNF therapy, but only 13% experienced sustained benefit. (J Rheumatol First Release April 1 2009; doi:10.3899/jrheum.090952)

Key Indexing Terms:

JUVENILE SYSTEMIC ARTHRITIS
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REMISSION
ETANERCEPT

Systemic juvenile idiopathic arthritis (JIA) is one of the most severe forms of JIA, frequently leading to severe disability and significant mortality¹. Additionally, according to different investigators, patients with systemic JIA frequently show a mediocre response to therapy with methotrexate (MTX) and anti-tumor necrosis factor (TNF) agents²⁻⁵. However, some patients with systemic JIA have been observed to respond to TNF inhibitors as satisfactorily as patients with other forms of JIA, at least in controlled trials, and they may even achieve remission on this therapy⁶. While the American College of Rheumatology Pediatric 30%, 50%, 70%, and 90% improvement criteria (ACR Pedi 30, 50, 70, and 90) have been the most widely reported outcomes in clinical trials and observational studies on efficacy

of biologic agents in JIA, remission — a more robust indicator of efficacy — has seldom been reported.

Definitions for inactive disease and remission in JIA (based on clinical criteria) have recently been elaborated. According to these definitions, remission is the presence of inactive disease for at least 6 consecutive months⁷. Although remission is the ultimate goal of treatment in JIA, the percentage of children with systemic JIA who meet remission criteria on therapy with biologic agents has not been tested in recent controlled trials. However, rates of remission with TNF inhibitors have been reported in some observational, registry-based studies in adults with rheumatoid arthritis and children with JIA⁸⁻¹¹. A recent report from a Dutch registry on etanercept in JIA showed that children with systemic JIA may reach remission rates that are similar to those achieved by patients with other forms of JIA¹¹. To date, no study has focused on inactive disease and remission rates achieved by patients with systemic JIA treated with anti-TNF agents.

We reviewed our experience to assess the frequency of inactive disease and remission observed in a cohort of patients with systemic JIA who have received TNF antagonists, and to identify potential predictors of remission.

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MATERIALS AND METHODS

Patients. All patients diagnosed with systemic JIA using the criteria of the International League of Associations for Rheumatology (ILAR)¹², and who were treated with anti-TNF agents for at least 6 months between December 1999 and August 2008 at the Hospital de Pediatría Prof. Dr. Juan P. Garrahan, were eligible for study. Patients were followed periodically and data were collected prospectively at every clinic or hospital visit, and recorded in the database of the Service of Immunology/Rheumatology. Intervals between visits varied between 1 and 2 months while patients were taking anti-TNF therapy. Clinical and biochemical assessments were performed at baseline (time of the start of anti-TNF therapy) and at each visit. Variables recorded were sex, age at disease onset, disease duration, active joint count (i.e., numbers of swollen/tender joints, or joints having at least 2 of the following features: heat, limited range of movement, and tenderness/pain on movement), number of joints with limited range of motion, presence of systemic symptoms (fever, rash, lymphadenopathy, hepatomegaly, splenomegaly, or serositis), functional ability [measured by Childhood Health Assessment Questionnaire (CHAQ), Argentine-Spanish validation¹³], disease activity according to the physician measured on a visual analog scale (VAS; score range 0–10), patient well-being according to the parents (VAS; range 0–10), and laboratory results [levels of hemoglobin, white blood cell (WBC) count, platelet count, and erythrocyte sedimentation rate (ESR)].

Treatment. Indication for the use of anti-TNF agents was lack of or loss of efficacy of MTX therapy (persistent active polyarthritis despite use of higher-dose MTX (≥ 20 mg/m²/week) for at least 3 months] in all cases. All patients received etanercept as the initial therapy, at 0.4 mg per kilogram of body weight, subcutaneously twice weekly, concomitantly with MTX 5–20 mg/m² weekly. Etanercept dosing was modified (increased up to 1 mg/kg/dose, or 25 mg/dose) if improvement was not achieved. In patients who exhibited lack of or loss of efficacy after 6 months of therapy (failure to achieve or maintain improvement, respectively), etanercept was switched to an anti-TNF- α monoclonal antibody, infliximab (5 to 10 mg/kg/dose, at Weeks 0, 2, and every 4 weeks thereafter) or adalimumab (20 mg in patients weighing < 30 kg, or 40 mg in patients weighing > 30 kg) every other week. There was no specific washout period before the introduction of the second anti-TNF agent (it varied between 1 and 3 weeks). Anti-TNF therapy was discontinued in patients who exhibited moderate or severe toxicity.

Outcome measures. “Improvement” was defined according to the criteria developed by Giannini, *et al*¹⁴. This definition states that there should be at least 30% improvement from baseline in 3 of any 6 variables in the JIA core set, with no more than one of the remaining variables worsening by > 30%. The ACR Pedi American 30, 50, 70, and 90 criteria were used to assess effectiveness.

We used the criteria for inactive disease and remission of Wallace, *et al*⁷. “Inactive disease” was defined as follows: no joints with active arthritis; no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; no active uveitis; normal ESR; and physician’s overall assessment of disease activity that indicated no disease activity (i.e., best score attainable on the scale used). “Clinical remission on medication” was defined as criteria for inactive disease achieved for at least 6 continuous months; while “clinical remission off medication” required fulfilment of criteria for inactive disease for at least 12 continuous months while taking no medications. “Time to remission” was defined as the interval from onset of therapy to the date remission was first recorded. “Disease relapse” was defined as a recurrence of active arthritis or systemic signs/symptoms attributable to JIA following a remission period as defined above.

Analysis. Comparison between groups was performed by chi-square and Mann-Whitney tests. Potential predictors of remission were evaluated by univariate analysis and by proportional hazards model (Cox regression) using 95% confidence intervals for hazard ratios. The following variables were included in the analysis: age at disease onset, age at start of anti-TNF therapy, disease duration, duration of anti-TNF therapy, baseline joint count, presence of systemic symptoms, WBC count, platelet count, hemo-

globin levels, ESR, and achievement of improvement criteria at 3 and 6 months after start of anti-TNF therapy. Kaplan-Meier survival curves were utilized to calculate the probability of remission over time after the onset of anti-TNF therapy and the probability of relapse-free intervals after remission. A *p* level < 0.05 was considered significant. Analysis was performed using Statistix 7 (Analytical Software).

RESULTS

Demographic and baseline data. Fifty patients (34 female, 16 male) with median age at diagnosis of 5 years [interquartile range (IQR) 1.5 to 8 yrs] and disease duration of 3 years (IQR 1.5 to 4) were studied. Five patients were excluded because they had poor compliance or were lost to followup. Thus, data on 45 patients were analyzed in this study. Demographic and clinical data at start of anti-TNF therapy are presented in Table 1. Twenty-one (47%) patients showed systemic symptoms at entry. At treatment baseline, the median number of active joints was 8 in patients who showed systemic symptoms and 16 in patients who did not (*p* = 0.02). All patients had shown an unremitting disease course before receiving anti-TNF treatment. Median duration of anti-TNF therapy was 24 months (IQR 12 to 42 mo). Total followup time was 1454 patient-months (median 24 mo per patient, IQR 12 to 48 mo) and all but 5 patients were followed for more than 1 year. Patients were treated with etanercept for 18 (range 6–82) months. Etanercept dosage was increased up to 0.8 to 1 mg/kg (or 25 mg) in 40 (89%) children. It was switched to infliximab (17 patients) or adalimumab (5 patients) in 22 (49%) patients: 9 had failed to respond upon initial administration of etanercept, and 13 initially responded but efficacy subsequently diminished and they underwent flares. Infliximab was discontinued due to lack of efficacy (4 children) or toxicity (periinfusional wheezing, eyelid edema, and/or urticarial rash in 6 patients). Forty-one patients were receiving corticosteroids (methylprednisone 2–20 mg/day) at the onset of anti-TNF therapy. Corticosteroids were tapered or discontinued in 26 (63%) children while undergoing anti-TNF therapy.

Improvement, inactive disease, and remission. ACR Pedi 30, 50, 70, and 90 were recorded in 35 (78%), 28 (62%), 21 (47%), and 14 (31%) patients, respectively. Fourteen (31%) and 11 (24%) children met criteria for inactive disease and clinical remission on medication, respectively (Table 2). Fifty percent of 22 inactive disease episodes were followed by remission. Remission occurred under etanercept (8 patients), infliximab (2 patients), or adalimumab (1 patient) therapy. Nine patients were receiving MTX, while none was on corticosteroid therapy at the time of remission. Remission occurred following 26 (9–65) continuous months of therapy. It was achieved in 2 (4%) patients at 1 year, in 4 (9%) children at 2 years, and in 9 (20%) patients at 3 years of anti-TNF therapy. Five patients in whom therapy was stopped after remission was achieved met the definition of remission off medications. Flares occurred in 5 (45%) patients 2 to 14 months after remission was first recorded;

Table 1. Clinical and laboratory features at the beginning of anti-TNF therapy. Values represent number of patients (%), or medians* (interquartile range).

Feature	Total, n = 45	Patients Achieved Remission, n = 11	Patients Did Not Achieve Remission, n = 34	p
Age, yrs*	9 (5–13)	9 (6–12)	9.2 (5–14)	NS
Age at disease onset, yrs*	5 (1.5–8)	6 (3–9)	4.3 (1.5–9)	NS
Sex female	30 (67)	6 (55)	24 (71)	NS
No. of active joints*	11 (6–28)	14 (9–28)	10.5 (5.5–28)	NS
No. of joints with limited motion*	10 (5–19)	13 (7–19)	9 (5–20)	NS
Systemic symptoms	21 (47)	2 (18)	19 (56)	0.03
Physician VAS (0–10)*	3.73 (1.7–4.4)	3.73 (3.0–4.06)	3.03 (1.7–4.86)	NS
Parent VAS (0–10)*	4.0 (0.93–6.13)	2.96 (1.93–5.23)	4.28 (0.63–6.4)	NS
CHAQ < 0.5	15 (33)	6 (54)	9 (26)	NS
White blood cell count ($\times 10^9/l$)*	10.8 (8.4–15.7)	10.3 (7.9–17.0)	10.8 (8.8–16.2)	NS
Hemoglobin, g/dl*	11.0 (9.6–11.8)	10.9 (10.2–12.0)	11.0 (9.6–11.9)	NS
Platelet count ($\times 10^9/l$)*	417 (291–565)	419 (352–609)	431 (273–556)	NS
ESR, mm/h	47 (21–68)	45 (36–69)	47 (22–83)	NS

Physician VAS: disease activity according to physician on a visual analog scale. Parent VAS: patient well-being according to the parent, visual analog scale. CHAQ: Childhood Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; NS: nonsignificant.

Table 2. Clinical outcomes during and after anti-TNF therapy. Values represent number of patients (%), or medians* (interquartile range).

Outcome	Total, n = 45	Patients Achieved Remission, n = 11	Patients Did Not Achieve Remission, n = 34	p
Improvement 3 months after onset of therapy	29 (64)	10 (91)	19 (56)	0.03
Improvement 6 months after onset of therapy	33 (73)	10 (91)	23 (68)	NS
Drug toxicity	13 (29)	3 (27)	10 (29)	NS
Duration of anti-TNF therapy, mo*	24 (12–42)	42 (30–57)	18 (11–32)	NS
Discontinuation due to toxicity	7 (16)	0 (0)	7 (21)	NS
Discontinuation due to inefficacy	24 (53)	3 (27)	21 (62)	NS
CHAQ < 0.5 in last visit	31 (69)	11 (100)	19 (56)	0.005

TNF: tumor necrosis factor; CHAQ: Childhood Health Assessment Questionnaire; NS: nonsignificant.

one of them was taking no medications. Indeed, 21 patients of this cohort are still under anti-TNF therapy (4 in remission) and 1 patient is in remission off medications. Median duration of followup was 41 months in patients who achieved clinical remission on medication and 18 months in patients who did not reach remission ($p = 0.001$).

Predictive factors for remission. No demographic or baseline disease variable was predictive of remission in the multivariate analysis. However, absence of systemic symptoms at the start of anti-TNF therapy and achievement of improvement criteria at 3 months were associated with remission in univariate analysis ($p = 0.03$). Probability of continuing in remission was 76% (95% CI 48–92) at 6 months, and 54% (95% CI 30–77) at 1 year after onset of remission (Figure 1).

DISCUSSION

Anti-TNF agents have become standard therapy for JIA that does not respond adequately to MTX, regardless of type of disease onset or ILAR category¹⁵. However, their efficacy in

children with systemic JIA has been largely discredited by numerous publications showing a lower response rate in such patients²⁻⁵. Moreover, since evidence of the efficacy of interleukin 1-inhibiting therapies in children with systemic JIA became available^{16,17}, the role of TNF blockers as the first therapeutic option for patients with refractory systemic JIA has been debatable. Our results show that continuous, longterm treatment with anti-TNF agents may induce remission in a small but significant proportion of patients with systemic JIA. Remission was more frequent in patients who did not show systemic symptoms at the start of anti-TNF therapy and in those who improved after 3 months of therapy.

Comparisons with other studies are difficult due to heterogeneity in the criteria for assessment of remission (consensus on preliminary criteria for remission in selected categories of JIA was reached only recently⁷), patient selection, and disease classification in published clinical trials or “real life” observational studies on the use of anti-TNF agents. Our study is probably the first based on a large cohort of patients with systemic JIA undergoing such

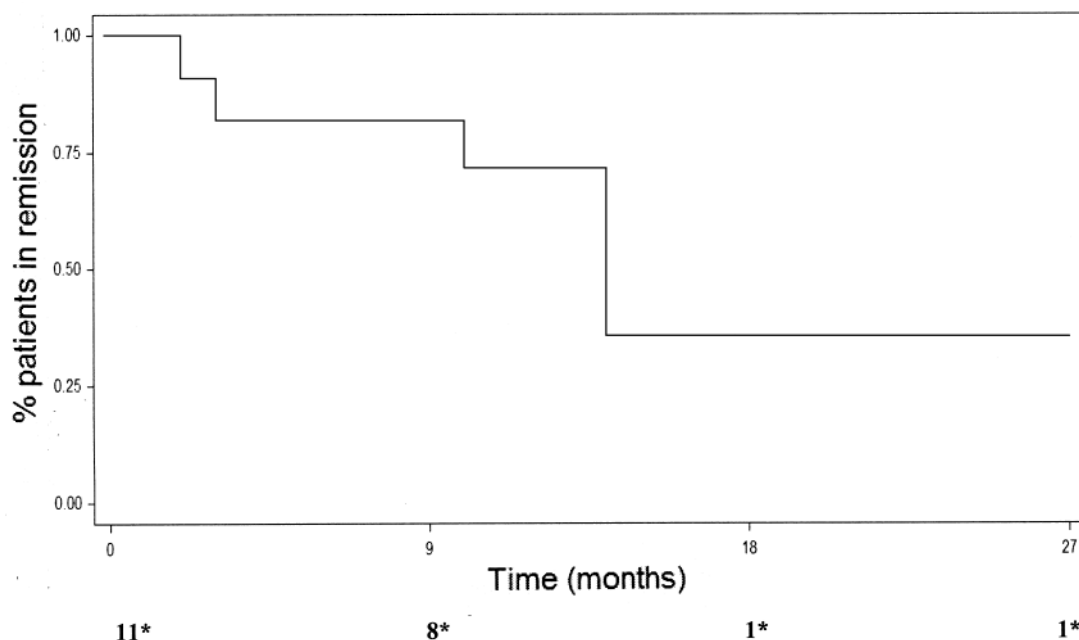


Figure 1. Kaplan-Meier survival analysis of a group of 11 patients with systemic JIA who reached remission under continuous anti-TNF therapy. Time 0 indicates onset of remission. *Number of patients still under observation excluding those who underwent relapse.

therapy that focused on inactive disease and remission as clinical outcomes. Preliminary consensus criteria for remission in JIA include clinical (arthritis, systemic symptoms, and physician's global assessment) and laboratory features (C-reactive protein and ESR) to define clinical remission as having inactive disease for at least 6 consecutive months. As noted by their authors, the selected duration times are arbitrary, there are no biologic markers that can reliably identify active disease, and no radiologic measures are included in these guidelines⁷. However, they are a useful clinical tool that may allow comparisons among studies.

In our observational study of response to anti-TNF therapies, no early features emerged as independent predictors of remission. However, there was an association between absence of systemic symptoms at the beginning of anti-TNF therapy and subsequent achievement of remission, in spite of patients with systemic symptoms at baseline having less active joints. A survey conducted by Kimura, *et al*³ found no differences in terms of baseline systemic symptoms between patients who responded and those who were nonresponsive to etanercept³. In addition, the majority of patients in our cohort who achieved remission had shown an early satisfactory response (improvement after 3 months of treatment) to TNF inhibitors. Thus, early improvement might be a potentially useful marker of effectiveness that may aid in clinical decisions.

The course of systemic JIA has been classified into 3 patterns according to the succession of phases of activity and remission: monocyclic, intermittent, and persistent¹⁸. Using

a different definition of remission, Lomater, *et al*¹⁹ found that a significant proportion of their patients, who had received different therapeutic interventions, entered remission at some point. In our cohort, no patient had achieved remission before anti-TNF therapy was initiated. Although there is a possibility that remission achieved by some of our patients was part of the natural history of the disease, the observational, uncontrolled design of the study did not allow confirmation of this hypothesis. Remission rates in the course of systemic JIA have ranged from 20% to 34% in several studies¹⁹⁻²³. These studies are heterogeneous mainly in sample size, definition of remission, and length of followup. On the other hand, remission has not been used as an outcome measure in most clinical trials that included patients with systemic JIA. Additionally, patients with active systemic symptoms have been included only recently in trials of tocilizumab²⁴, making comparisons difficult.

Our study investigated remission, an outcome not reported in previous studies on the efficacy of anti-TNF agents in patients with systemic JIA. Lovell, *et al*⁶ reported the outcome of a cohort of 58 children with JIA treated with etanercept in a clinical trial. After 4 years of therapy, 28% of patients reached a state of disease inactivity similar to the one required by the definition of remission from Wallace, *et al*⁷ (no active joints, physician overall assessment of disease activity that indicated no disease activity). Patients with systemic JIA represented 33% of the cohort, and none had systemic features at entry to the study. A report from a German registry showed that 13% of 66 patients with systemic JIA

reached remission taking etanercept¹⁰. A recent publication based on a Dutch registry¹¹, which included patients followed for a mean 2.5 years, documented a remission rate of 38% in a cohort of 39 children with systemic JIA receiving etanercept, which is higher than the rate we observed in our sample. Our patient group was a referral-based cohort with probably more severe disease than unselected cohorts from the general population. Interestingly, 3 of our patients achieved remission only after TNF inhibitors were switched (from etanercept to an anti-TNF monoclonal antibody). Although to date there are no controlled studies, anti-TNF switching may prove useful in the treatment of systemic JIA²⁵.

This study should be interpreted in light of its limitations, such as assessment of patients from a single center. The sample size was small and therefore the statistical significance of associations may be different in larger populations. Moreover, since this was an uncontrolled study, changes observed in disease activity might be related to the natural history of systemic JIA (in spite of the unremitting disease course observed prior to the start of anti-TNF therapy). Finally, questions of duration of remission and radiological progression among patients classified as in remission should be addressed in larger studies conducted for longer periods.

Our data demonstrate that remission is attainable in about one-quarter of patients with systemic JIA receiving anti-TNF therapy, but it was sustained in only 13% of our cohort. Patients who do not show fever or other systemic symptoms at the start of therapy and those who achieve criteria after 3 months of therapy may have better chances of benefitting from this outcome. Further studies in larger cohorts are needed to confirm these observations.

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