The rationale for early aggressive treatment in juvenile idiopathic arthritis

Evaluation of: Wallace CA, Giannini EH, Spalding SJ *et al.* Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis. *Arthritis Rheum.* 64, 2012–2021 (2012). The last two decades have brought dramatic changes to the therapy of children and adolescents with rheumatic diseases. A greater understanding of the underlying disease mechanisms and the introduction of biologic agents have resulted in unprecedented treatment outcomes and markedly improved quality of life (QoL). Historically, treatment of juvenile idiopathic arthritis with NSAIDs, corticosteroids and traditional disease-modifying antirheumatic drugs was frequently limited by inadequate efficacy and significant toxicity. Despite the recently published ACR treatment guidelines, which provide directions for clinicians on when and how to effectively manage these aggressive diseases, there still remain some delays in the adaptation of these recommendations owing to fear of an overly aggressive treatment approach and often overstated reports about the toxicity and malignancy risks of biologics. Consequently, the precise timing and method of implementing the most effective therapy remains inconsistent and uncertain. This review attempts to give some insight into the rationale for early aggressive therapy in patients with juvenile idiopathic arthritis.

KEYWORDS: biologics ■ early aggressive treatment ■ juvenile idiopathic arthritis ■ outcomes ■ remission ■ therapy ■ treatment

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Treatment data from adult rheumatoid arthritis (RA) suggest that early aggressive treatment within a window of opportunity is associated with the highest likelihood of achieving remission and avoiding long-term joint damage [1]. A similar view has recently been proposed in pediatric rheumatology, suggesting that early aggressive therapy could lead to better disease control and induction of remission [2–4]. This is of particular significance in juvenile idiopathic arthritis (JIA), where early joint damage can lead to lifelong disability.

Earlier studies in JIA have indicated a possible benefit of early aggressive treatment. Two retrospective studies in methotrexate-treated JIA patients demonstrated that an ACR clinical response score for pediatrics (ACR Pedi) 70 treatment response at 6 months and achieving remission within the first 5 years after disease onset was associated with less cumulative damage and improved radiographic and functional long-term outcomes [4,5]. However, it was not until recently that two studies in JIA specifically focused on early aggressive therapy including biologics, suggesting that this approach would be more advantageous than the traditional therapeutic pyramid approach.

The first study by Tynjälä *et al.*, ACUTE-JIA [6], examined early aggressive therapy with three treatment arms: TNF (methotrexate and infliximab), COMBO (methotrexate, sulfasalazine and hydroxychloroquine) and MTX (methotrexate monotherapy). In this 54-week multicenter, randomized, open-label clinical trial, 60 disease-modifying antirheumatic drug-naive, mainly seronegative, polyarticular JIA patients with a disease duration of ≤6 months (mean: 1.9 months) were evenly randomized into one of the three treatment arms. A total of 37% of the patients were anti-nuclear antibody-positive and 2% were rheumatoid factor (RF)-positive. The mean physician's global assessment was 5.5 (0–10 visual analog scale). The primary end point was an ACR Pedi 75 at 54 weeks. The secondary outcomes included clinically inactive disease (CID) and duration of inactive disease. An ACR Pedi 75 at 54 weeks was achieved by 100, 65 and 50% of the TNF, COMBO and MTX monotherapy arms, respectively ($p < 0.0001$). At 6 months, CID was achieved by 60% in the TNF arm, 30% in the COMBO arm and 5% in the MTX monotherapy arm.

In the second study by Wallace *et al.*, TREAT [7], the goal was to determine whether early aggressive treatment in RF-positive or RF-negative polyarticular JIA (poly-JIA) could induce CID within 6 months. The study's secondary end point was an ACR Pedi 70 at 4 months. This two-phase (a pivotal and exploratory phase), multicenter, prospective, double-blind, randomized, placebo-controlled

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trial compared two treatment arms; arm one included treatment with MTX (0.5 mg/kg/week subcutaneous, 40 mg maximum) in combination with etanercept 0.8 mg/kg/week (50 mg maximum), and prednisolone 0.5 mg/kg/day (60 mg maximum) that was tapered off by 17 weeks. Arm two included the same dose of MTX but etanercept and prednisolone placebo. The pivotal phase evaluated achievement of an ACR Pedi 70 at 4 months and CID at 6 months. The exploratory phase continued up to 12 months and included patients placed on open-label (methotrexate, etanercept and prednisolone taper) treatment.

Eighty five children aged 2–16 years with a disease duration of less than 12 months were enrolled. A total of 68% were anti-nuclear antibody positive and 36% were RF positive.

Although not statistically significant, 17 out of 42 (40%) patients in arm one and ten out of 43 (23%) in arm two achieved CID by 6 months, (χ^2 = 2.91; p = 0.088). After 12 months, nine patients in arm one, but only three in arm two achieved clinical remission (p = 0.0534). No significant differences in adverse events were noted between the two treatment groups. Nevertheless, the study did not meet its primary end point of early aggressive therapy achieving CID within 6 months.

Discussion

Does TREAT, therefore, invalidate the concept of early aggressive therapy or the benefit of early use of biologics? In order to address this question, we first have to examine the rationale for an early aggressive treatment approach. Studies in adult rheumatoid arthritis (RA) have demonstrated improved clinical outcomes including decreased or no radiographic progression with early implementation of aggressive treatment within an early 'window of opportunity' that defines the long-term outcome [1,3,8]. This also appears to be the case in juvenile arthritis. While the outcome of JIA cannot be predicted by baseline features and long-term radiographic studies are lacking, it has been well established that juvenile arthritis can persist into adulthood, causing disability, pain and physical dysfunction [9,10]. There is still a common misconception that children with JIA outgrow their disease. While current management with disease-modifying antirheumatic drugs and biologics results in significant improvement of clinical symptoms, many patients with JIA retain some degree of persistent disease activity and in reality, long-term remission is infrequent, with remission rates (defined as drug-free and asymptomatic for ≥2 years) varying greatly among disease subtypes [11–17]. In their retrospective analysis of 392 patients with juvenile arthritis (≥8 years of age), Oen *et al.* noted that the probabilities of remission was 6, 23, 47 and 37% for RF-positive polyarticular, RF-negative polyarticular, oligoarticular and systemic-onset juvenile arthritis (JA), respectively, 10 years after disease onset. Relapse rates varied from 30 to 100% at 15 years [11]. In addition, Wallace *et al.* noted that only 6% of JIA patients were able to sustain clinical remission off medications at 5 years [18].

A review of seven epidemiologic studies demonstrated the impact of JA into adulthood. Of the 983 patients who had been followed for a mean of 20.5 years (mean age of 30 years), 47% were found to still have active arthritis, 46% had difficulties with daily activities and 22% had arthritis-related surgery [9]. In another study, severe functional limitations were observed in up to one-third of 246 adults with long-standing JIA [10]. Children with JIA experience impairment in health-related quality of life compared to their healthy peers, as measured by decrements in the domains of physical and psychosocial wellbeing [19]. Chronic arthritis also negatively impacts emotional, social and school functioning [11,12,19,20]. Adult patients who had childhood-onset arthritis have been shown to have high rates of anxiety and depressive illness [10], and have a higher mortality rate compared with the general population [21].

Furthermore, some studies have reported radiographic changes in up to 88% of children with JIA at the time of diagnosis that progressed with disease activity over time. While osteopenia was the most common finding, joint space narrowing and erosions were also observed [22,23]. Other studies using MRI demonstrated irregular synovial thickening and low-intensity synovial tissue, not only in recent-onset JIA, but also in joints prior to the onset of clinical symptoms [24,25]. In addition, localized growth disturbances have been reported in 10–48% of children within the first 2–3 years after diagnosis [16,22]. Lastly, severity and duration of disease impact bone mineral density and bone mineral content, which is frequently decreased in JIA [26,27].

As it takes an average of 13 months for a JIA patient to achieve remission [18], earlier and more aggressive treatment strategies for the development of a healthy musculoskeletal system in children need to be pursued. The introduction of the ACR Pedi 30 criteria in 1997 helped further this goal as it standardized the assessment of clinical response and improvement in juvenile arthritis

trials [8]. Following the development of the ACR Pedi criteria, published studies have primarily utilized this validated outcome measure as the benchmark to establish the efficacy of therapies in JA. Furthermore, it has allowed the comparison of treatment therapies across studies.

An ACR Pedi 30 response is defined as an improvement of at least 30% in a minimum of three variables with no worsening by more than 30% in more than one variable:

- Physician global assessment of disease activity;
- Parent/patient assessment of overall wellbeing;
- Functional ability (disability index of the Children's Health Assessment Questionnaire);
- Number of joints with active arthritis;
- Number of joints with limited range of motion;
- CRP or erythrocyte sedimentation rate.

However, achieving only a 30% improvement from baseline should no longer be acceptable as a desirable therapeutic goal. ACR Pedi 50, 70, 90 and 100 responses implying 50, 70, 90 and 100% improvement, respectively, are more meaningful parameters to evaluate true improvement and should become the actual benchmark of a successful clinical outcome. The introduction of biologics has transformed the landscape of clinical trials such that it is no longer unusual for substantial numbers of patients to achieve ACR Pedi 70, 90 and 100 responses [28–34].

While the TREAT study did not meet its primary end point and no statistical difference in CID between the two study arms could be established, there was strong evidence to support a rationale for early aggressive therapy and the role of early initiation of biologic therapy. Shorter disease duration at baseline and achieving an ACR Pedi 70 at 4 months were significant predictors of CID at 6 months. For each month earlier that a patient was treated, their chance of achieving CID was increased by a factor of 1.324. In addition, at 4 months an ACR Pedi 70 was achieved by 71% of patients in arm one and only 44% of patients in arm two ($\chi^2 = 6.46$; $p = 0.011$).

Moreover, when one takes into account the number of patients in each arm who went on to receive open-label medication (MTX, etanercept and prednisolone taper); the role of early combination therapy appears to be even more substantial. Ten patients in arm one and 21 patients in arm two who failed to achieve an ACR Pedi 70 at 4 months, as well as 11 patients in arm one and eight patients in arm two that failed to achieve CID at 6 months were continued on open-label therapy until the completion of the exploratory phase. With this in mind, the role of a biologic in early aggressive therapy appears critical. At 12 months a substantially greater proportion (59%) of patients who began in arm one and had continued to receive the combination therapy were in CID compared to those in arm two (16%) who remained on MTX monotherapy. Additionally, at 12 months, 65% of patients in arm one had achieved an ACR Pedi 70, while only approximately 20% of the patients in arm two were able to achieve this outcome. Moreover, when one includes all patients who received open-label treatment in the 12-month assessment, this proportion increased to nearly 85% and approximately 70% for arm one and two, respectively. This difference not only emphasizes the critical role of biologics, but also the importance of early combination therapy in early aggressive therapy. The results of the ACUTE-JIA trial where treatment was started after an even shorter disease duration support this concept, with 60% of patients achieving CID at 6 months and 100% of patients achieving an ACR Pedi 75 at 54 weeks, respectively, in the TNF treatment arm.

Even though ACUTE-JIA and TREAT were similar in their goal to address the role of early aggressive treatment in JIA, they differed in their patient populations, study design, study drugs and end points (Table 1). The ACUTE-JIA trial had a slightly shorter average disease duration (1.9 vs 5 months) prior to start of treatment and less RF-positive patients than the TREAT study (2 vs 36%), which may have contributed to the seemingly better treatment response. Both studies had treatment arms with an anti-TNF agent; however, infliximab was utilized in ACUTE-JIA and etanercept in TREAT. One could argue that the intravenous administration of the infliximab was a more aggressive therapy although the dose used was only 3–5 mg/kg. In addition, the primary and secondary outcomes were not identical. Patients in TREAT who did not achieve an ACR Pedi 70 at 4 months were placed on open-label treatment and were not included in the end point analysis of each arm. Despite these differences, the results of both investigations provide additional evidence for the benefit of early aggressive therapy.

With the availability of new outcome data, JIA, similar to other childhood rheumatic diseases, can no longer be considered a benign disease. Early, aggressive pharmacologic intervention is a critical component of optimal disease

Table 1. Summary of the ACUTE-JIA and TREAT trials.

Study characteristics	ACUTE-JIA	TREAT
Number of patients	60	85
Diagnosis	JIA (poly-RF positive and RF negative, ERA and PsA)	JIA (poly-RF positive and RF negative)
RF-positive patients	2%	36%
Age (mean)	9.5 years	10.5 years
Disease duration	>6 weeks, but <6 months	<12 months
Average disease duration (months)	1.9	5
Treatment arms	3	2
	TNF: INF[†] + MTX[‡]	Arm one: ETN[§] + MTX[¶] + CS[#]
	COMBO: MTX, SSZ[††] and HCQ[‡‡]	Arm two: MTX + ETN placebo + CS placebo
	MTX	
Previous DMARD	DMARD naive	+/- previous DMARD
Length of study	54 weeks	52 weeks
Primary end point	ACR Pedi 75 at 54 weeks	CID at 6 months
Secondary end point	CID at 54 weeks and duration of inactive disease	ACR Pedi 70 at 4 months
CID at 6 months	60% TNF	40% arm one
	30% COMBO	23% arm two
	5% MTX	
Medication adjustments	Dosage changes allowed	No dosage changes allowed

[†]INF dosing: 3–5 mg/kg at 0, 2 and 6 weeks then every 6 weeks.
[‡]MTX dosing ACUTE: 15 mg/m^2, maximum dose 25 mg/week.
[§]ETN dosing: 0.8 mg/kg/week subcutaneously.
[¶]MTX dosing TREAT: 0.5 mg/kg, maximum dose 40 mg/week.
[#]CS dosing: 0.5 mg/kg, maximum dose 60 mg/day.
[††]SSZ dosing: 40 mg/kg, maximum dose 2 g/day.
[‡‡]HCQ dosing: 5 mg/kg/day, maximum dose 300 mg/day.
ACR Pedi: ACR clinical response score for pediatrics; CID: Clinically inactive disease; COMBO: Methotrexate, sulfasalazine and hydroxychloroquine; CS: Prednisolone; DMARD: Disease-modifying antirheumatic drug; ERA: Enthesitis-related arthritis; ETN: Etanercept; HCQ: Hydroxychloroquine; INF: Infliximab; JIA: Juvenile idiopathic arthritis; MTX: Methotrexate; PsA: Psoriatic arthritis; RF: Rheumatoid factor; SSZ: Sulfasalazine; TNF: Methotrexate and infliximab.

management in order to prevent further disease progression, restore organ function, and promote normal growth and development. The adaptation of a comprehensive management approach with early aggressive treatment in conjunction with physical and occupational therapy and psychosocial support will probably improve the long-term outcome and quality of life of our patients with juvenile arthritis.

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Executive summary

- Over the last two decades, tremendous advancements have been made in the understanding of the pathogenesis and treatment of juvenile idiopathic arthritis.
- Due to the long-term consequences of uncontrolled disease, aggressive treatment, particularly in the early phase, is critical.
- With the introduction of biologics, this goal is now achievable and treatment outcomes have significantly improved.
- The current treatment goal is now remission and no longer just disease control.
- Often overstated reports of toxicity and risks of malignancy may contribute to the hesitation in adopting early aggressive therapy.
- There are now data to show that early aggressive therapy with biologics is efficacious and critical.
- Early aggressive intervention is critical for juvenile idiopathic arthritis patients to have optimal outcomes.

References

Papers of special note have been highlighted as:
▪ of interest
▪▪ of considerable interest

1 O'Dell JR. Treating rheumatoid arthritis early: a window of opportunity. *Arthritis Rheum.* 46, 283–285 (2002).

2 Albers HM, Wessels JAM, Van der Straaten RJHM *et al.* Time to treatment an important factor for the response to methotrexate in juvenile idiopathic arthritis. *Arthritis Rheum.* 61, 46–51 (2009).

3 Woo P. Theoretical and practical basis for early aggressive therapy in paediatric autoimmune disorders. *Curr. Opin. Rheumatol.* 21, 552–557 (2009).

4 Bartoli M, Tarò M, Magni-Manzoni S *et al.* The magnitude of early response to methotrexate predicts long-term outcomes of patients with juvenile idiopathic arthritis. *Ann. Rheum. Dis.* 7, 370–374 (2008).

▪ **Role of early response to treatment in long-term outcome of juvenile idiopathic arthritis (JIA).**

5 Magnani A, Pistori A, Magni-Manzoni S *et al.* Achievement of a state of inactive disease at least once in the first 5 years predicts better outcome of patients with polyarticular juvenile idiopathic arthritis. *J. Rheumatol.* 36, 628–634 (2009).

6 Tynjälä P, Vähäsalo P, Tarkiainen M *et al.* Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomized open-label clinical trial. *Ann. Rheum. Dis.* 70, 1605–1612 (2011).

▪▪ **Role of early aggressive therapy in an open-label study to achieve an ACR Pedi 75.**

7 Wallace CA, Giannini EH, Spalding SJ *et al.* Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis. *Arthritis Rheum.* 64, 2012–2021 (2012).

▪▪ **Double-blind study to determine whether early aggressive therapy could induce clinically inactive disease.**

8 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).

9 Reiff AO. Juvenile arthritis. In: *Making a Difference in Rheumatology: Early and Aggressive Treatment = Better Outcomes for Today's Patients.* Schiff MH (Ed.). The Veritas Institute for Medical Education Inc., NJ, USA, 165–192 (2004).

10 Packham JC, Hall MA. Long-term follow-up of 246 adults with juvenile idiopathic arthritis: functional outcome. *Rheumatology (Oxford).* 41(12), 1428–1436 (2002).

11 Oen K, Malleson PN, Cabral DA, Rosenberg AM, Petty RE, Cheang M. Disease course and outcome of juvenile rheumatoid arthritis in a multicenter cohort. *J. Rheumatol.* 29(9), 1989–1999 (2002).

▪ **Describes remission rates of subtypes of JIA.**

12 Ilowite NT. Current treatment of juvenile rheumatoid arthritis. *Pediatrics* 109(1), 109–115 (2002).

13 Levinson JE, Wallace CA. Dismantling the pyramid. *J. Rheumatol.* 19(Suppl. 330), 6–10 (1992).

14 Minden K. Adult outcomes of patients with juvenile idiopathic arthritis. *Horm. Res.* 72(Suppl. 1), 2–25 (2009).

15 Flato B, Hoffman-Vold AM, Reiff A *et al.* Long-term outcome and prognostic factors in Enthesitis related arthritis: a case control study. *Arthritis Rheum.* 54, 3573–3582 (2006).

16 Minden K, Niewerth M, Listing J *et al.* Long-term outcome in patients with juvenile idiopathic arthritis. *Arthritis Rheum.* 46, 2392–2401 (2002).

17 Oen K, Duffy CM, Tse SML *et al.* Early outcomes and improvement of patients with juvenile idiopathic arthritis enrolled in a Canadian multicenter inception cohort. *Arthritis Care Res.* 62, 527–536 (2010).

18 Wallace CA, Huang B, Bandeira M *et al.* Patterns of clinical remission in select categories of juvenile idiopathic arthritis. *Arthritis Rheum.* 52, 3554–3562 (2005).

▪▪ **Established the rarity of sustained remission in JIA.**

19 Gutierrez-Suarez R, Pistorio A, Cespedes Cruz A *et al.* Health-related quality of life of patients with juvenile idiopathic arthritis coming from 3 different geographic areas. The PRINTO multinational quality of life cohort study. *Rheumatology (Oxford)* 46(2), 314–320 (2007).

20 Denardo BA, Miller LC, Schaller JG, Tucker L. Young children with juvenile rheumatoid arthritis are developmentally delayed in gross and fine motor skills. *Arthritis Rheum.* 39(Suppl. 9), S1715 (1996).

21 French AR, Mason T, Nelson AM, O'Fallon WM, Gabriel SE. Increased mortality in adults with a history of juvenile rheumatoid arthritis: a population-based study. *Arthritis Rheum.* 44(3), 523–527 (2001).

22 Selvaag AM, Flato B, Dale K *et al.* Radiographic and clinical outcome in early juvenile rheumatoid arthritis and juvenile Spondyloarthropathy: a 3-year prospective study. *J. Rheumatol.* 33, 1382–1391 (2006).

23 Mason T, Reed AM, Nelson AM *et al.* Frequency of abnormal hand and wrist radiographs at time of diagnosis of polyarticular juvenile rheumatoid arthritis. *J. Rheumatol.* 29, 2214–2218 (2002).

24 Kirkhus E, Flato B, Riise O *et al.* Differences in MRI findings between subgroups of recent-onset childhood arthritis. *Pediatr. Radiol.* 41, 432–440 (2011).

25 Gardner-Medwin JM, Killeen OG, Ryder CA *et al.* Magnetic resonance imaging identifies features in clinically unaffected knees predicting extension of arthritis in children with monoarthritis. *J. Rheumatol.* 33, 2337–2343 (2006).

26 Lien G, Flato B, Haugen M *et al.* Frequency of osteopenia in adolescents with earl-onset juvenile idiopathic arthritis. A long-term outcome study of one hundred five patients. *Arthritis Rheum.* 48, 2214–2223 (2003).

27 Burnham JM, Shults J, Dubner SE *et al.* Bone density, structure, and strength in juvenile idiopathic arthritis: Importance of disease severity and muscle deficits. *Arthritis Rheum.* 58, 2518–2527 (2008).

28 Lovell DJ, Giannini EH, Reiff A *et al.* Etanercept in children with polyarticular juvenile rheumatoid arthritis. *N. Engl. J. Med.* 342, 763–769 (2000).

▪ **Seminal study demonstrating substantial efficacy of biologic therapy in JIA.**

29 Lovell DJ, Reiff A, Jones OY *et al.* Long-term safety and efficacy of etanercept in children with polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum.* 54(6), 1987–1994 (2006).

30 Horneff G, Ebert A, Fitter S. Safety and efficacy of once weekly etanercept 0.8mg/kg in a multicentre, 12 week trial in active polyarticular course juvenile idiopathic arthritis. *Rheumatology* 48, 916–919 (2009).

31 Ruperto N, Lovell DJ, Quartier P *et al.* Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. *Lancet* 372, 383–391 (2008).

32 Ruperto N, Lovell DJ, Quartier P *et al.* Long-term safety and efficacy of abatacept in children with juvenile idiopathic arthritis. *Arthritis Rheum.* 62, 1792–1802 (2010).

33 De Benedetti F, Brunner H, Allen R *et al.* Tocilizumab is efficacious in patients with systemic juvenile idiopathic arthritis across baseline demographics and disease characteristics and prior/baseline treatments: 52 week data from a phase 3 clinical trial. *Arthritis Rheum.* 63(Suppl. 10), Abstract L111 (2011).

34 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).