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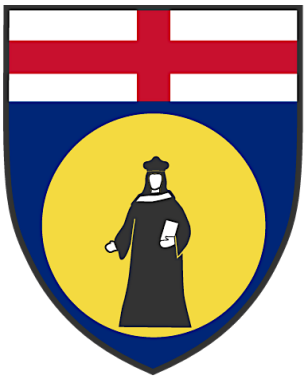

Dottorato di Ricerca in Scienze Pediatriche
Curriculum Reumatologia Pediatrica (XXXVIII ciclo)

# The “Comparison of STep-up and step-down therapeutic strategies in childhood ARthritiS” (STARS) trial: patients’ outcome at six months

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Anno Accademico 2025/2026

*“Genova.*
*Scalinate e vicoli brulicanti,*
*il mare che ti entra negli occhi all’improvviso,*
*le note di De André,*
*sorrisi e mani vere,*
*e tanti colori inaspettati”*

*Fabrizio Caramagna*

## Sommario

# Background

## Introduction

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease of presumed autoimmune etiology that affects ~1 of 1,000 children worldwide [1]. It is the most common chronic rheumatic disease in the pediatric age and an important cause of short-term and long-term disability.

The etiology of JIA is unknown, although it is almost certainly multifactorial, and probably differs from one onset type to another. The pathogenetic process underneath JIA is chronic inflammation, in which both innate and adaptive immune systems play critical roles. In all categories of JIA, an autoimmune synovitis is sustained by cytokines produced by activated T cells and macrophages, leading to the classic signs of inflammation (swelling, pain, heat, loss of function) in the actively inflamed joints [2].

According to the International League of Associations for Rheumatology (ILAR) classification, seven categories of JIA are recognized based on features present in the first 6 months of illness (table 1) [3].

| ILAR category | Frequency* (%) | Onset (age, years) | Sex ratio (F:M) | Inclusion criteria |
|---|---|---|---|---|
| **Systemic arthritis** | 4-17 | Throughout childhood | 1:1 | Arthritis in one or more joints with or preceded by fever of at least 2 weeks' duration that is documented to be daily for at least 3 days and accompanied by one or more of the following: evanescent erythematous rash; generalized lymph node enlargement; hepatomegaly and/or splenomegaly; serositis. |
| **Oligoarthritis** | 27-56 | <6 | 4:1 | Arthritis affecting one to 4 joints during the first 6 months of disease. Two subcategories are recognized: persistent oligoarthritis: affecting not more than 4 joints throughout the disease course; extended oligoarthritis: affecting a total of more than 4 joints after the first 6 months of disease. |
| **RF-positive polyarthitis** | 2-7 | 9-12 | 9:1 | Arthritis affecting 5 or more joints during the first 6 months of disease; 2 or more tests for RF at least 3 months apart during the first 6 months of disease are positive. |
| **RF-negative polyarthritis** | 11-28 | Biphasic distribution (2-4; 6-12) | 3:1 | Arthritis affecting 5 or more joints during the first 6 months of disease; a test for RF is negative. |

| | | | | |
|---|---|---|---|---|
| **Psoriatic arthritis** | 2-11 | Biphasic distribution (2-4; 9-11) | 2:1 | Arthritis and psoriasis, or arthritis and at least 2 of the following: dactylitis, nail pitting or onycholysis, psoriasis in a first-degree relative. |
| **Enthesitis-related arthritis** | 3-11 | 9-12 | 1:7 | Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following: the presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain; the presence of HLA-B27 antigen; onset of arthritis in a male over 6 years of age; acute (symptomatic) anterior uveitis; history of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative. |
| **Undifferentiated arthritis** | 11-21 | | | Arthritis that fulfills criteria in no category or in 2 or more of the above categories. |

**Table 1**: Frequency, age at onset, sex distribution, and inclusion criteria of the International League of Associations for Rheumatology (ILAR) categories of juvenile idiopathic arthritis [1], [3]. *Reported frequencies refer to percentage of all juvenile idiopathic arthritis.

The present study will focus only on two JIA categories: oligoarthritis and rheumatoid factor negative polyarthritis, which are the most common JIA subtype in Italy.

Oligoarticular JIA is defined as an arthritis that affects four or fewer joints during the first 6 months of disease [3]. In the International League of Associations of Rheumatology (ILAR) classification, children who otherwise satisfy these criteria are excluded from the oligoarthritis category if they have psoriasis, a family history of psoriasis, a human leukocyte antigen (HLA) B27-associated disease in a first degree relative, a positive rheumatoid factor (RF) test, or if the disease occurs in a male patient older than 6 years. Although oligoarthritis is probably heterogeneous, most patients have a well defined form of juvenile idiopathic arthritis. This form, which is typical of children and is not seen in adults, is characterized by asymmetric arthritis, early onset (before 6 years of age), female predilection, high frequency of positive anti-nuclear antibodies (ANA), and high risk of iridocyclitis (a chronic, non-granulomatous, anterior uveitis that affects the iris and ciliary body and can cause severe visual impairment). The homogeneity of this subgroup of patients is shown by a strong association with some HLA alleles. Oligoarthritis

is predominantly a disease of the legs, with the knee joint mostly affected, followed by the ankles. In about 30–50% of cases, one joint is affected at presentation. Acute-phase reactants are often normal or moderately increased, although in some instances ESR can be quite high. ANAs are detected in substantial titres in about 70–80% of patients, and they represent a risk factor for iridocyclitis. The ILAR classification distinguishes two categories in the oligoarthritis subtype— persistent oligoarthritis, in which the disease is confined to four or fewer joints, and extended oligoarthritis, in which arthritis extends to more than four joints after the first 6 months of disease. In our opinion, most patients classified as having either persistent or extended oligoarthritis belong to the same clinical entity. Furthermore, ANA-positive patients who belong to these two categories have been reported to be homogeneous for several clinical features, including age at onset, sex ratio, asymmetry of articular involvement, and frequency of iridocyclitis. These features suggest that extended oligoarthritis is the same disease as persistent oligoarthritis, but with a more severe outcome. Involvement of an upper limb joint and high sedimentation rate at onset have been identified as predictors for an evolution to the extended phenotype, which can take place in up to 50% of patients. Iridocyclitis is a characteristic feature of oligoarthritis and affects about 30% of patients. The onset is insidious and often entirely asymptomatic, which contrasts with painful, acute iridocyclitis that can be seen in enthesitis-related arthritis. Since iridocyclitis is asymptomatic at onset, children with this disease should be screened periodically by slit-lamp examination.

Rheumatoid factor negative polyarthritis is defined as an arthritis that affects five or more joints during the first 6 months of disease in the absence of IgM rheumatoid factor (RF) [3]. This disease is less well defined than RF-positive polyarthritis and is probably the most heterogeneous subtype. At least three distinct subsets of RF-negative polyarthritis can be identified. The first is a form that closely resembles early- onset oligoarticular juvenile idiopathic arthritis, except for the number of joints affected in the first 6 months of

disease. Like that illness, RF-negative polyarthritis is characterized by asymmetric arthritis, early age at onset, female predominance, frequent positive ANAs, increased risk of iridocyclitis, and association with HLA-DRB1*0801. These similarities have led to the view that this subset and early-onset oligoarthritis are the same disease, with the former representing a rapid arthritis spread in the latter [4]. The demonstration that ANA-positive oligoarthritis shares homogeneous clinical features with ANA-positive RF-negative polyarthritis, but not with ANA-negative RF negative polyarthritis, lends support to this view. Studies on the frequency of the various disease subsets in different ethnic populations also lend support to this notion. In countries where ANA-positive, early onset, iridocyclitis- associated oligoarthritis is rare, the equivalent RF-negative polyarthritis is also seldom seen. The second subset of RF-negative polyarthritis is similar to adult onset RF-negative rheumatoid arthritis, and is characterized by overt symmetric synovitis of large and small joints, onset in school age, increased ESR, negative ANA, and variable outcome. The third subset is a form known as dry synovitis, which shows negligible joint swelling but stiffness, flexion contractures, and normal or slightly raised ESR. This subset is often poorly responsive to treatment and could follow a destructive course.

In the past two decades, there have been major advances in the management of JIA, which include the widespread use of intra-articular corticosteroids, the tendency toward earlier introduction of methotrexate, and, more recently, the availability of biologic medications. This progress has increased considerably the potential to achieve disease remission or, at least, minimal levels of disease activity, and has consequently moved the therapeutic aims increasingly toward the attainment of an inactive disease status. Complete disease quiescence is regarded as the ideal therapeutic target because its achievement helps prevent further joint damage and disability and may enhance physical function and quality of life. These considerations have led to suggest that future clinical trials incorporate as

endpoints the evaluation of disease activity state, particularly the achievement of inactive disease/clinical remission and minimal disease activity.

Although a satisfactory disease control is nowadays achievable in most patients with JIA, a substantial proportion of them still do not respond adequately or reach long-term drug-free remission.

Several randomized controlled trials have been conducted on synthetic and biologic DMARDs. However most of these trials have included children with polyarthritis and systemic arthritis. In contrast, only little evidence-based information is available to guide the treatment of oligoarthritis, which is the most common JIA subtype in Western countries. In addition, most studies in this disease category have involved nonsteroidal anti-inflammatory drugs (NSAIDs), which may alleviate inflammatory symptoms, but are rarely able to control synovitis. As a result, the management of this condition is largely empiric and likely variable among practitioners. A recent randomized controlled trial in oligoarthritis has shown that oral methotrexate prolongs the efficacy of intra-articular corticosteroids, but may not prevent the new onset of arthritis in non-injected joints [5].

Most registrative trials performed so far in JIA have been based on the so-called “withdrawal design”, which has been successful in assessing the effectiveness of the biologic medications currently used in JIA. However, all trials have only tested a single medications and have used as primary endpoint the percentage of improvement in signs and symptoms according to the American College of Rheumatology (ACR) Pediatric response criteria. To obtain better insights into the therapeutic regimens and protocols that produce optimal outcomes in the real world of standard clinical practice, there is the need to compare strategies based on individual or combined

therapeutic interventions and to scrutinize their ability to induce complete and sustained disease control.

## The “comparison of STep-up and step-down therapeutic strategies in childhood ARthritiS” (STARS) trial

The “comparison of STep-up and step-down therapeutic strategies in childhood ARthritiS” (STARS) trial aims to investigate whether an early aggressive therapeutic intervention, based on the initial start of synthetic and biologic DMARDs (Step-down strategy), is superior to an approach based on treatment escalation conducted following the treat-to-target principle [6] (Step-up strategy), in children with juvenile idiopathic arthritis (JIA).

With a different approach, both interventions aim to obtain a quick and robust disease control and maintain it over time. Historically and according to the ACR recommendation [7], the treatment of JIA is escalated in subsequent steps. In general, treatment begins with NSAIDs or intra-articular joint injections, which, in case of insufficient effectiveness or disease flare, are replaced by or associated with a synthetic DMARD, such as methotrexate (MTX), sulphasalazine or leflunomide. In case of inadequate response and according to the current label indication, a biologic DMARD is usually prescribed in substitution of or in conjunction with the synthetic DMARD.

The treat-to-target strategy was first advocated for the treatment of adult rheumatoid arthritis in 2010, based on its successful use in chronic conditions such as hypertension and diabetes mellitus. This approach is based on the assumption that frequent adjustment of therapy intended to reach minimal levels of disease activity will lead to an improvement in patient outcomes according to quantitative indices [8], [9]. Key components of the treat-to-target include the explicit definition of a therapeutic target (such as clinical remission or low disease activity) at the beginning of the treatment and

the verification of its achievement at each subsequent visit. If the target is reached the treatment is left unchanged, whereas if the target is not reached the treatment is intensified. The 2010 EULAR recommendations [10] for the management of rheumatoid arthritis were centered on the treat-to-target strategy, as were the later joint ACR/ EULAR recommendations. A 2013 update of the EULAR recommendations [11] went even further in highlighting the treat-to-target as a fundamental component of treatment strategies. In 2018, the first recommendations for the application of the treat-to-target study to the care of children with JIA were developed. Although recommendations could not be based on high level of evidence, they reached significant agreement in an international task force of pediatric rheumatologists with a large experience in the field [9]. Evidence supporting the treat-to-target strategy is now increasing. The recent Best for Kids study [12], which aimed to compare three different treatment strategies for JIA (synthetic DMARD monotherapy, synthetic DMARD and bridging prednisone, and a combination of synthetic and biologic DMARDs), showed that regardless of initial specific treatments, after 24months of treatment-to-target aimed at drug-free inactive disease, 71% of recent-onset patients with JIA had inactive disease and 39% were drug free. A non-randomized study showed that patients treated according to a treat-to-target protocol had a higher chance to achieve remission in comparison to a matched cohort [13]. A quality improvement initiative in a tertiary care medical centre showed that intense patient monitoring, target attestation and standardization of clinical decision support lead to better patient outcomes [14].

Early intensive therapy in JIA during the so-called window of opportunity is believed to be able to alter the biology of the disease and improve long-term outcomes, including prevention of cumulative joint damage [9], [15], [16]. In systemic JIA, early anti-IL-1 therapy was found to quickly lead to inactive disease and facilitate sustained disease control. Indeed, in a cohort of steroid-naive patients with new-onset systemic JIA

treated with IL-1 receptor antagonist therapy, 85% of patients had achieved inactive disease or an ACR paediatric 90% response by 3 months of treatment. The benefits of early treatment with other agents and in other JIA categories are less clear but have been increasingly suggested for polyarticular JIA. In the ACUTE-JIA trial [15], initiation of anti-TNF therapy plus MTX in DMARD-naive patients with polyarticular JIA was more effective in achieving minimally active or inactive disease than MTX alone or MTX plus hydroxy-chloroquine and sulfasalazine. The TREAT trial [16] showed a benefit with an early aggressive strategy, even though it failed to reach its primary end-point. More recently, a trajectory analysis of 400 patients in the Start Time Optimization of Biologics in Polyarticular JIA study demonstrated that starting a biologic treatment within 3 months of baseline assessment is associated with a more rapid achievement of inactive disease in subjects with untreated polyarthritis [17].

The approach proposed in the present trial represents a step forward as compared to most previous therapeutic studies in JIA, as it does not involve the exposure of children to a placebo. Furthermore, it does not assess the effectiveness of treatments in terms of mere percentage improvement in disease symptoms or achievement of a particular disease state at a single time point but it evaluates the ability of treatments to induce and maintain the state of clinical remission over time. In addition, the trial includes the administration of systemic corticosteroids only in the most severe disease subsets (i.e., those characterized by involvement of hip or cervical spine joints). Of note, a recent trial of early aggressive therapy in polyarticular JIA [16] has been subjected to major criticism owing to the choice of giving oral prednisone to all children in the more aggressive arms.

The design of the STARS trial is innovative and aims to address the major unmet needs in the current management of JIA in the real world of daily clinical care. For instance, it is still unclear whether progressive treatment intensification based on the magnitude of therapeutic response over time is

more advantageous than initial administration of an aggressive therapy in terms of achievement and maintenance of complete disease control. Furthermore, it is still debated whether intra- articular corticosteroid therapy leads to better results with lower side effects than systemic corticosteroid administration. The Step-up approach will be conducted following the treat-to-target strategy, a novel method of management which has proved effective in the care of adult patients with rheumatoid arthritis and has shown better therapeutic results than conventional regimens in several controlled trials [18]. Note that recommendations for the use of the treat-to-target strategy in adults with rheumatoid arthritis have been recently issued by the European League Against Rheumatism (EULAR) [19]. Although there is an increasing interest among pediatric rheumatologists in the adoption of the treat- to-target strategy, this approach has not been hitherto implemented in the management of children with JIA.

In conclusion, the primary aim of the trial is to scrutinise the ability of the two therapeutic interventions to induce complete disease control early and to maintain it over time. Among other objectives, investigating their capacity to reduce the need for the later introduction of biologic agents, which would lead to a reduction in the costs for the national health-care system and in the exposure of children to the potential (and still unclear) long- term side effects of these medications. The achievement of the main endpoints of the trial might also result in the decreased need of repeated intra-articular corticosteroid joint injections (IACI), which might lessen the child's and parents' related emotional distress and the financial and organizational burden required by these procedures under sedation or general anaesthesia.

# Methods

## Trial design

STARS is a 12-month multicentre randomised single-blinded superiority clinical trial of two different treatment strategies (Step-down versus Step-up) in a treat-to-target setting. After the conclusion of the observation period of the trial, patients will be followed for up to 5 years for the evaluation of the disease course, medication requirements, adverse events and long-term disease-related morbidity. Recruitment started on 21st May 2019 and ended on 10th October 2024.

## Selection of centers

In a first phase, all Italian centres belonging to the Paediatric Rheumatology International Trials Organization (PRINTO) were invited to participate in the study. In January 2022, after a feasibility survey, PRINTO centers outside Italy were also invited to participate, based on the possibility to prescribe MTX in oligoarthritis and etanercept in polyarthritis as a first-line treatment according to local rules.

## Study population

Recent-onset JIA patients with oligoarthritis or rheumatoid factor negative polyarthritis aged between 2 and 17 were included in the study. Participants must be DMARD-naïve (only treatment with one NSAID is allowed for no more than 6weeks from diagnosis) and must not have received corticosteroid joint injections in the 3 months before enrolment.

After obtaining written consents (and assent where appropriate) from the participant, parent or legal guardian, patients' disease severity was assessed based on the clinical phenotype (irrespective of the ILAR classification) and the severity of the disease. Disease severity was defined according to the extension of arthritis and based on the presence/absence of features of poor prognosis according to the 2011 American College of Rheumatology (ACR) recommendations for the treatment of JIA [7] (table 2). Children with oligoarthritis without features of poor

prognosis were considered as “less severe patients”, children with RF-negative arthritis and children with oligoarthritis and features of poor prognosis were considered as “more severe patients”. As stated in the 2011 recommendations, risk stratification is crucial for guiding optimal treatment; features of poor prognosis for oligoarthritis were defined by the recommendations panel based both on literature revision and on the panellists’ clinical experience [7]. In particular, the possible role of erythrocyte sedimentation rate as a predictor of a less favourable outcome for oligoarthritis patients was more recently confirmed by the results of a clinical trial on this subgroup of patients [5].

| **More severe patients** |
| --- |
| • Children with RF negative polyarthritis<br>• Children with oligoarthritis AND features of poor prognosis:<br>  - Arthritis of the hip or cervical spine<br>  - Arthritis of the ankle or wrist and marked (> 40 mm/h) or prolonged (> 20 in at least 3 consecutive assessments within 3 months) erythrocyte sedimentation rate elevation |
| **Less severe patients** |
| • Children with oligoarthritis WITHOUT features of poor prognosis |

**Table 2**: Subjects in both arms are grouped according to the severity of the disease, based on the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis [7].

## Interventions

Randomisation by variable blocks was adopted, stratified per centre and per oligoarticular or polyarticular disease into two strategy arms: “Step-up” and “Step-down”. Patients in the Step-up arm were treated according to a conventional strategy based on treatment escalation and driven by the treat-to-target strategy. Patients in the Step-down arm were treated with an early, combined, aggressive therapy for 6 months.

In the Step-up arm, less severe patients received IACI in all affected joints without systemic therapies. If the juvenile arthritis disease activity score-10 (JADAS10) state of minimal disease activity (MiDA) after 3months or the

JADAS10 inactive disease (ID) state at 6 months was not reached, treatment with MTX was started preferably subcutaneously in a single weekly dose of 15mg/m2 (max 20mg) and IACI could be repeated. Then, if the states of JADAS MiDA after 3 months or JADAS ID at 6 months were not reached, treatment with an anti-TNF agent in a single weekly dose of 0.8 mg/kg (max 50 mg) subcutaneously was started. More severe patients in Step-up arm received IACI(s) and MTX as a first step and then escalate therapy with the same pathway, adding an anti-TNF treatment as a second step and switching to a different biologic medication as a third step (fig. 1).

Patients allocated to the Step-down arm (fig. 2) received an early combined treatment (MTX plus IACI for less severe oligoarthritis, MTX plus etanercept for severe oligoarthritis and polyarthritis). After 6 months, if JADAS10 ID was achieved, less severe patients were discontinued MTX, whereas more severe patients were stopped etanercept and continued MTX. Children in Step- down arm experiencing a worsening from the baseline of the JADAS10 at 3months, not achieving JADAS10 ID at month 6, or losing the state of ID after month 6 were considered as treatment failures and were changed treatment according to the attending physician decision.

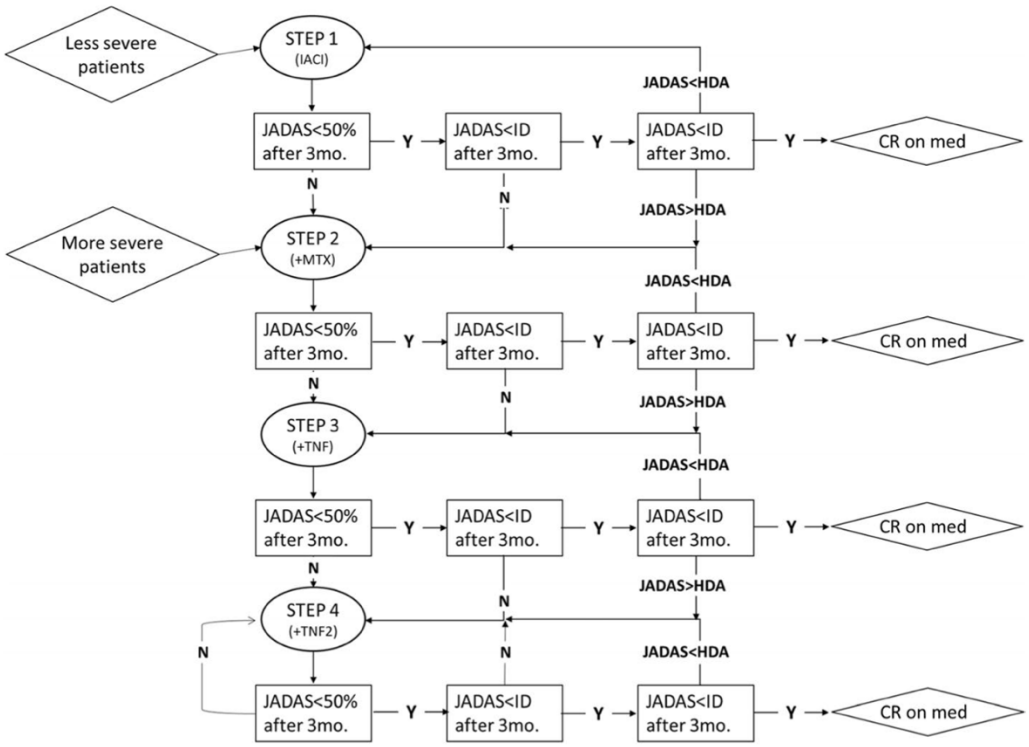

**Fig. 1**: Step-up arm design. T2T Group 1: Subjects with oligoarthritis without features of poor prognosis. T2T Group 2: Subjects with oligoarthritis with features of poor prognosis and subjects with polyarthritis. JADAS: Juvenile Arthritis Disease Activity Score-10. JADAS< 50%: improvement of JADAS10 of at least 50%, JADAS<ID: JADAS10 score below inactive disease cutoff. JADAS<HDA: JADAS10 score under HDA cutoffs. JADAS>HDA: JADAS10 score above HDA cutoffs. If at the visit 3 months after step 1, 2, and 3 the patient is improved by less than 50% in the JADAS score, but he/she reaches the JADAS state of minimal disease activity, treatment is not escalated ID = inactive disease, HDA = high disease activity. CR on med.: clinical remission on medication. IACI: intra-articular corticosteroids injection. +MTX: start methotrexate (repeating IACI or adding a short course of prednisone can be considered). +TNF: add therapy with an anti-TNF agent (repeating IACI or adding a short course of prednisone can be considered). +TNF2: replace anti-TNF agent with another an anti-TNF agent or with an anti IL-6 agent (repeating IACI or adding a short course of prednisone can be considered).

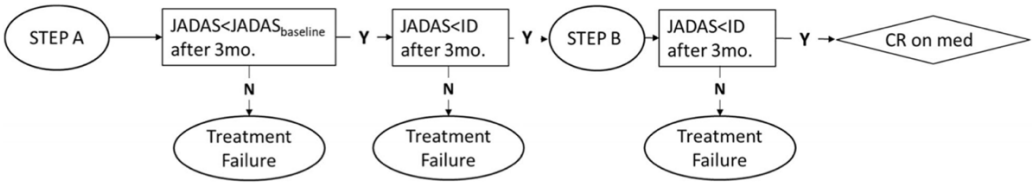


**Fig. 2**: Step-down arm design. Step A is starting methotrexate plus intra-articular joint injections for oligoarthritis without features of poor prognosis, methotrexate plus etanercept and optional intra-articular joint injections for other patients. Step B is withdrawing methotrexate for oligoarthritis without features of poor prognosis, withdraw etanercept and continue methotrexate for other patients. JADAS: Juvenile Arthritis Disease Activity Score-10. JADAS<ID: JADAS10 score below inactive disease cutoff. CR on med.: clinical remission on medication.

For the IACIs, triamcinolone hexacetonide was administered at a dose of 1 mg/kg (max 40 mg) in the hips, knees and shoulders, at the dose of 0.75mg/kg (max 30mg) in the ankles and elbows, at the dose of 0.5 mg/kg (max 20 mg) in the wrists; methylprednisolone acetate was administered at the dose of 1 mg/kg (max 40mg) in the subtalar and inter-tarsal joints and at the dose of 5–10mg, depending on the size of the child, in the small joints of hands and feet. A course of oral prednisone instead of or in addition to joint injection could be prescribed in case hip, temporomandibular joints or cervical spine were involved, or if more than four joints were affected or joint injections could not be performed.

## Patients' assessment and disease activity monitoring

Complete physical examination with joints assessment, main patient/parent reported outcomes collection (including pain level, morning stiffness duration, disease activity self-assessment, physical function, and health- related quality of life), uveitis screening, medication history, treatment adverse events evaluation, and

laboratory tests (haematological and biochemical analysis and urinalysis) was performed at each trial visit.

The level and state of disease activity was measured in all patients at each step of the study by means of the JADAS10. The JADAS10 [20] is a composite disease activity score validate for use in children with JIA and includes the following 4 measures: physician's global assessment of disease activity, measured on a 0–10 21-circle Visual Analogue Scale (VAS) where 0 = no activity and 10 = maximum activity; parent/patient global assessment of well-being, measured on a 0–10 21-circle VAS where 0 = very well and 10 = very poor; the count of joints with active disease cut at 10 joints (i.e. 1 point for each active joint up to a maximum of 10 points); and the erythrocyte sedimentation rate (ESR), normalized to a 0 to 10 scale according to the following formula: (ESR (mm/hour) – 20)/10. Before making the calculation, ESR values < 20 mm/hour are converted to 20 and ESR values > 120 m/hour are converted to 120. The definition of the disease states of ID, MiDA, and high disease activity (HDA) based on the JADAS10 refers to the newest version of JADAS10 cut-off values [21], [22]. New cutoffs for oligoarthritis and polyarthritis are shown in table 3. Data were collected electronically in the PRINTO web-based platform designed for the PharmaChild registry.

| | **JADAS10** | **cJADAS10** |
|---|---|---|
| **Oligoarthritis** | | |
| Inactive disease | ≤ 1.4 | ≤ 1.1 |
| Minimal disease activity | 1.5 - 4 | 1.2 - 4 |
| Moderate disease activity | 4.1 - 13 | 4.1 - 12 |
| High disease activity | > 13 | > 12 |
| **Polyarthritis** | | |
| Inactive disease | ≤ 2.7 | ≤ 2.5 |
| Minimal disease activity | 2.7 - 6 | 2.5 - 5 |
| Moderate disease activity | 6.1 - 17 | 5.1 - 16 |
| High disease activity | > 17 | > 16 |

**Table 3**: New JADAS10 and cJADAS10 cutoffs for disease activity states [21], [22].

## Endpoints

The effectiveness of the two therapeutic strategies will be compared by assessing the frequency of clinical remission (CR) at 12 months [23]. CR is defined

as the persistence of the JADAS10 state of ID for at least 6 months. Patients will be considered to be in ID from the day of the first visit with JADAS10 ID until the day before the first subsequent visit in which the patient is found to have lost the state of JADAS10 ID.

Then, a number of secondary endpoints will be assessed in order to better understand the efficacy of the two treatment strategies (table 4). The rate of patients achieving the JADAS-defined and the ACR-defined state of ID, the time to achieve ID and clinical remission, the time spent in inactive disease, the cumulative level of disease activity and the rate of uveitis will be compared between the two arms.

| |
|---|
| **Primary endpoint** |
| Clinical remission on or off medication at 12 months. |
| The effectiveness of the two therapeutic strategies will be compared by assessing the frequency of clinical remission (CR) at 12 months. CR is defined as the persistence of the JADAS state of ID for at least 6 months |
| **Secondary endpoints** |
| Inactive disease |
| The rate of patients who achieve the JADAS/JIA ACR state of ID at any single point in time throughout the study period will be compared between the 2 arms. |
| Time to inactive disease as per JADAS/JIA ACR criteria |
| Time to achieve the JADAS/JIA ACR state of ID will be calculated as the time difference (in days) between the date of randomization and the date of the visit on which the patient will be observed to be in ID. |
| Time to JADAS/JIA ACR clinical remission |
| Time to achieve the JADAS/JIA ACR state of clinical remission will be calculated as the time difference (in days) between the date of randomization and the date of the visit on which the patient will be observed to be in clinical remission (i.e. persistent inactive disease for at least 6 months). |
| Time spent in JADAS/JIA ACR inactive disease |
| The cumulative time spent in the JADAS/JIA ACR state of ID will be calculated as the time difference (in days) between the date of the first visit on which the patient will be observed to be in ID and the date on which he/she will be observed to be no longer in ID, that is when the disease will flare (see later for definitions), or database closure for analysis purposes. We will assume that if a patient is found to be in ID at 2 consecutive visits, the patient had ID on all days between these visits. If a patient will be found to have ID at a particular visit, but lost the ID status at the subsequent visit, the patient will be considered to have been in ID until the recurrence of active disease. Patients found to be in ID only at the time of database closure will contribute a single day of ID. The time in inactive disease per patient will be recorded and compared between the 2 arms. |
| Cumulative level of disease activity throughout the study period |
| The area under the curve of the JADAS10 score assessed at every study visit and the AUC of the parent version of the JADAS (parJADAS) assessed monthly will be recorded and compared between the 2 arms. |
| Time spent on therapy |
| The cumulative time on therapy will be calculated as the time difference (in days) between the date of the visit on which the patient will start a systemic medication (synthetic or biologic DMARDs or steroids) and the date on which he/she will be observed to no longer be in treatment with a systemic medication or completed the study. We assume that if a patient does not receive medications at 2 consecutive visits, the patient had not received medications everyday between these visits. Patients initiating a systemic treatment at the final visit of the study will contribute a single day of time in therapy. The mean percentage of time spent on therapy per patient will be recorded and compared between the 2 arms. |
| Rate of flares |
| The rate of patients who develop flare, defined as the recurrence of active disease after attaining inactive disease at last visit according to JADAS or JIA ACR definition, and the number of flares and the time to flare per patient will be recorded and compared. Notably, all patients prescribed intra-articular injections, synthetic or biologic DMARDs or systemic steroids will be considered as flare independently from JADAS or ACR criteria. |
| Rate of uveitis onset |
| The rate of patients who develop uveitis according to the Standardized Uveitis Nomenclature (SUN) will be recorded and compared between the 2 arms. The rate of patients requiring systemic medications for treatment of uveitis will be also recorded and compared between the 2 arms. However, these patients will be excluded from the study and followed for safety only. |

**Table 4**: STARS trial endpoints.

## Preliminary endpoints at 6 months

After completing data collection of all visits of study children from baseline to the primary endpoint assessment, a preliminary analysis of endpoints at six

months will be performed. The frequency of inactive disease and the JADAS-based disease status will be compared at six months between the two arms in the whole cohort and after stratifying by disease severity group.

We chose to use the 6-month endpoint as preliminary data in order to include data from all enrolled patients. Complete 12-month data for all patients are not yet available, and this would have resulted in missing data.

## Safety

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

A Serious Adverse Event (SAE) is any untoward medical occurrence that:

• results in death;

• is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);

• requires inpatient hospitalization or causes prolongation of existing hospitalization;

• results in persistent or significant disability/incapacity;

• is a congenital anomaly/birth defect;

• is an important medical event (defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above. Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization).

A non-serious adverse event is any AE that is not classified as serious.

Adverse events were collected and reported according to the PharmaChild registry.

## Statistics

For proportional data the chi-square test or, where appropriate, the Fisher's exact test was applied. For continuous variables the t-test procedure or the ANOVA were applied as appropriate. Non-parametric ANOVA was applied in case of ordinal data or not-normally distributed variables; the Bonferroni correction was applied for all a posterior test, in order to avoid multiple comparisons'error. Treatment effect size was calculated by dividing the difference between the baseline and the final visit value by the standard deviation of the first visit value. Survival analysis with censored data will be used in order to evaluate time to remission and time to flare. Emphasis was placed on the intention-to-treat approach rather than on the analysis of the completers of the trial only. All analysis was done in a blinded manner. Missing data were not imputed; analyses were conducted using only available observations.

Safety events were recorded by a medical monitor; all visit data were checked by the PRINTO coordinating centre and by a medical monitor. All moderate/severe AEs (including those leading to MTX or biologic treatment discontinuation) were summarized per patient year of follow-up, describing the relationship to the treatment. The AE incidence rate by drug was estimated after partitioning the follow-up periods of each patient into subintervals corresponding to the administration of the drug, with any event being attributed to the drug itself. This implicitly assumes the independence of the outcome in different subintervals pertaining to the same patient.

Trial data were entered online by the participating centres on a secure web system managed by the coordinating calculated to compare the primary AE rates with the remaining comparator groups. As possible covariate for the analysis JIA category, gender, age and drug use history were considered.

## Sample size

Sample size calculations were extrapolated from a recent study of early aggressive therapy on JIA patients [16]. Using the sample size calculation for superiority trials with a delta of at least 20% (being the expected proportion of favorable outcome in the first arm p1=0.45 and in the second arm p2 = 0.25) and considering a drop out rate of 10%, a sample size of 109 patients in each group for a total of 218 patients has been required. Since an interim analysis has also been planned at enrolment of half of the sample, the total sample size was increased to 240 subjects. The trial has 0.8 power for comparisons of the treatment arms, 0.05 type I error.

# Aim of the study

This randomised clinical trial aims to compare the effectiveness of a conventional therapeutic regimen, based on treatment escalation and driven by the treat-to-target approach, with that of an early aggressive intervention based on the initial start of a combination of conventional and biological DMARDs.

The aim of this study is to compare:

- the demographic data of patients enrolled in the STARS trial;
- the frequency of inactive disease and the JADAS-based disease status between the two arms at 6 months;
- the AE incidence rate by drug.

# Results

## Patient characteristics

A total of 337 participants were assessed for eligibility, and 240 were enrolled. Nine patients were excluded from the analysis: 6 of them did not receive allocated intervention, 2 patients were found to have an exclusion criterion during the study, and 1 patient's severity was wrongly assessed. Of the 231 analyzable patients, 116 patients (50.2%) were started on the Step-up arm and 115 (49.8%) on the Step-down group (fig. 3). Eight patients (3.4%) were lost to follow-up before the 6-month visit. That left 223 patients who continued with follow-up at the registry site for at least 6 months (112 Step-up, 111 Step-down).

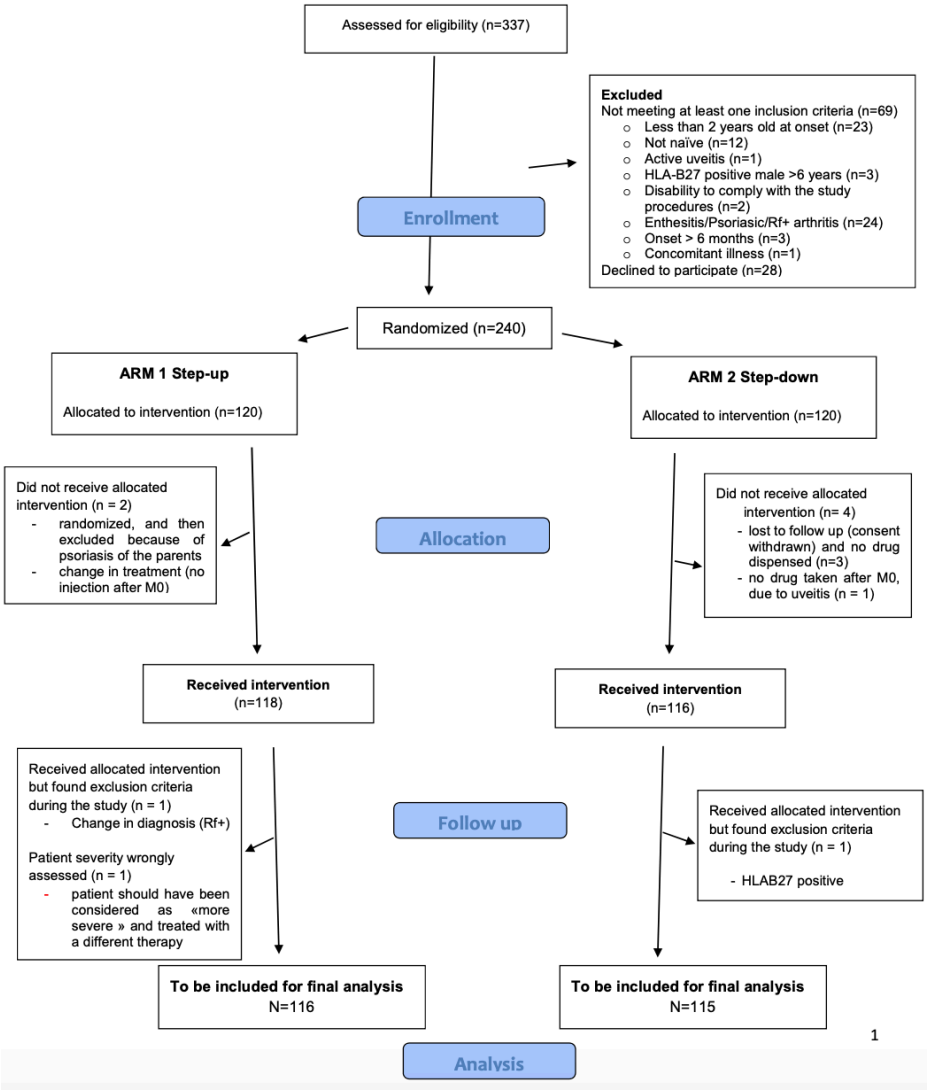


**Fig. 3**: Participant Flow Diagram.

The baseline characteristics of all participants are shown in table 5. There are not difference in some baseline disease characteristics, including number of active joints, limited joints, physician global assessment of disease activity, JADAS score, disease course (JIA category), and ESR. In general, the two groups are balanced with equal disease activity levels in both arms.

| Features | Arm 1 | Arm 2 | P | Overall |
|---|---|---|---|---|
| Number of patients | 120 | 120 | | 240 |
| Gender = | | | 0.053 | |
| Male, n. (%) | 46 (38.3) | 31 (25.8) | | 77 (32.1) |
| Female, n. (%) | 74 (61.7) | 89 (74.2) | | 163 (67.9) |
| Age at onset (median [IQR]) | 6.0 [3.5, 9.9] | 5.4 [3.0, 9.7] | 0.402 | 5.6 [3.2, 9.8] |
| Age at diagnosis (median [IQR]) | 6.1 [3.8, 10.2] | 5.4 [3.2, 10.0] | 0.434 | 5.8 [3.3, 10.2] |
| Diagnosis: | | | 0.604 | |
| Oligoarthritis, n. (%) | 73 (60.8) | 74 (61.7) | | 147 (61.3) |
| Polyarthritis (FR negative), n. (%) | 47 (39.1) | 46 (38.3) | | 93 (38.7) |
| More severe Group, n. (%) | 53 (44.2) | 57 (47.5) | 0.698 | 110 (45.8) |
| Physician global assessment VAS (median [IQR]) | 5.5 [4.0, 7.0] | 5.2 [3.9, 7.5] | 0.915 | 5.5 [4.0, 7.1] |
| N. swollen joints (median [IQR]) | 2.0 [1.0, 5.0] | 2.0 [1.0, 6.0] | 0.998 | 2.0 [1.0, 5.0] |
| N. tender joints (median [IQR]) (painful) | 2.0 [1.0, 4.0] | 2.0 [1.0, 5.0] | 0.687 | 2.0 [1.0, 4.0] |
| N. limited joints (median [IQR]) | 2.0 [1.0, 4.0] | 2.0 [1.0, 5.0] | 0.785 | 2.0 [1.0, 4.0] |
| N. active joints (median [IQR]) | 2.5 [1.0, 5.0] | 3.0 [1.0, 6.2] | 0.974 | 3.0 [1.0, 5.0] |
| Erythrocyte sedimentation rate (median [IQR]) | 28.0 [10.0, 54.0] | 33.5 [17.0, 49.0] | 0.824 | 30.0 [12.0, 51.0] |
| JADAS10 (median [IQR]) | 13.5 [9.9, 17.0] | 14.8 [8.5, 20.0] | 0.367 | 14.0 [9.4, 18.1] |

**Table 5:** Baseline characteristics of the patients with juvenile idiopathic arthritis in each arm.

## Inactive disease and disease status at 6 months

Complete data for the assessment of the primary preliminary endpoint at 6 months were available for 223 participants.

JADAS-10 and clinical JADAS-10 scores improved over time in all participants and the majority (66.8%) achieving inactive disease at 6 months (median 0.5). ID according to the JADAS-10 was achieved at 6 months by an estimated 55.4% of participants on the Step-up arm, and 78.4% of participants on the Step-down arm (table 6). The percentage with ID according to the JADAS-10 was significantly higher in the Step-down group compared to the Step-up group.

JADAS-based disease status showed moderate to high disease activity in 32.1% of participants on the Step-up arm, and 11.7% of participants on the Step-down arm (table 6).

Physician's global assessment of disease activity, number of active joints and patient reported outcomes also improves in both groups, especially in the Step-down arm (table 6).

| | Arm 1 | Arm 2 | p | Overall |
|---|---|---|---|---|
| n | 112 | 111 | | 223 |
| group = 2 (%) | 51 (45.5) | 56 (50.5) | 0.548 | 107 (48.0) |
| Physician global assessment (median [IQR]) | 0.0 [0.0, 2.8] | 0.0 [0.0, 0.0] | <0.001 | 0.0 [0.0, 1.0] |
| Limited joints count (median [IQR]) | 0.0 [0.0, 1.0] | 0.0 [0.0, 0.0] | 0.01 | 0.0 [0.0, 1.0] |
| Active joints count (median [IQR]) | 0.0 [0.0, 1.0] | 0.0 [0.0, 0.0] | <0.001 | 0.0 [0.0, 1.0] |
| esr (median [IQR]) | 9.0 [5.0, 15.8] | 8.0 [5.0, 10.5] | 0.295 | 8.0 [5.0, 14.0] |
| JADAS10 (median [IQR]) | 1.5 [0.0, 7.1] | 0.0 [0.0, 1.5] | <0.001 | 0.5 [0.0, 3.8] |
| cJADAS10 (median [IQR]) | 1.5 [0.0, 7.0] | 0.0 [0.0, 1.5] | <0.001 | 0.5 [0.0, 3.5] |
| Disease Status (%) | | | 0.001 | |
| ID | 62 (55.4) | 87 (78.4) | | 149 (66.8) |
| MiDA | 14 (12.5) | 11 (9.9) | | 25 (11.2) |
| MoDA | 25 (22.3) | 11 (9.9) | | 36 (16.1) |
| HDA | 11 (9.8) | 2 (1.8) | | 13 (5.8) |
| Functional ability score (median [IQR]) | 0.0 [0.0, 2.0] | 0.0 [0.0, 0.0] | 0.007 | 0.0 [0.0, 1.0] |
| HRQoL (median [IQR]) | 2.0 [0.0, 4.1] | 1.0 [0.0, 3.0] | 0.028 | 1.0 [0.0, 4.0] |
| Well Being VAS 0-10 (median [IQR]) | 0.5 [0.0, 2.0] | 0.0 [0.0, 1.0] | 0.001 | 0.0 [0.0, 1.5] |
| VAS_pain (median [IQR]) | 0.5 [0.0, 2.5] | 0.0 [0.0, 0.0] | <0.001 | 0.0 [0.0, 1.0] |

**Table 6:** Analysis of the primary end point at 6 months in each arm

Similar results are observed when evaluated according to different disease groups: less severe disease (table 7) and more severe disease (table 8).

| | Arm 1 | Arm 2 | p |
|---|---|---|---|
| n | 61 | 55 | |
| Physician global assessment (median [IQR]) | 0.0 [0.0, 3.0] | 0.0 [0.0, 0.0] | 0.12 |
| Limited joints count (median [IQR]) | | 0.0 [0.0, 0.0] | 0.153 |
| Active joints count (median [IQR]) | 0.0 [0.0, 1.0] | 0.0 [0.0, 0.0] | 0.005 |
| esr (median [IQR]) | 9.0 [5.8, 15.2] | 8.0 [5.0, 13.2] | 0.741 |
| JADAS10 (median [IQR]) | 1.0 [0.0, 7.0] | 0.0 [0.0, 1.8] | 0.002 |
| cJADAS10 (median [IQR]) | 1.0 [0.0, 7.0] | 0.0 [0.0, 1.8] | 0.003 |
| Disease status (%) | | | 0.039 |
| ID | 31 (50.8) | 38 (69.1) | |
| MiDA | 10 (16.4) | 9 (16.4) | |
| MoDA | 10 (16.4) | 7 (12.7) | |
| HDA | 10 (16.4) | 1 (1.8) | |
| Functional ability score (median [IQR]) | 0.0 [0.0, 1.0] | 0.0 [0.0, 0.0] | 0.021 |
| HRQoL (median [IQR]) | 2.0 [0.0, 6.0] | 0.0 [0.0, 2.5] | 0.005 |
| Well Being VAS 0-10 (median [IQR]) | 0.5 [0.0, 2.0] | 0.0 [0.0, 0.8] | 0.005 |
| VAS_pain (median [IQR]) | 0.5 [0.0, 3.0] | 0.0 [0.0, 0.5] | 0.002 |

**Table 7**: Analysis of the primary end point at 6 months in less severe disease (oligoarthritis with absence of ACR features of poor prognosis)

| | Arm 1 | Arm 2 | p |
|---|---|---|---|
| n | 51 | 56 | |
| Physician global assessment (median [IQR]) | 0.0 [0.0, 2.6] | 0.0 [0.0, 0.0] | 0.005 |
| Limited joints count (median [IQR]) | 0.0 [0.0, 1.0] | 0.0 [0.0, 0.0] | 0.027 |
| Active joints count (median [IQR]) | 0.0 [0.0, 1.0] | 0.0 [0.0, 0.0] | 0.004 |
| esr (median [IQR]) | 9.0 [5.0, 15.8] | 7.0 [5.0, 9.5] | 0.287 |
| JADAS10 (median [IQR]) | 2.0 [0.0, 7.2] | 0.0 [0.0, 1.0] | 0.004 |
| cJADAS10 (median [IQR]) | 1.5 [0.0, 7.2] | 0.0 [0.0, 1.0] | 0.003 |
| Disease status (%) | | | 0.012 |
| ID | 31 (60.8) | 49 (87.5) | |
| MiDA | 4 (7.8) | 2 (3.6) | |
| MoDA | 15 (29.4) | 4 (7.1) | |
| HDA | 1 (2.0) | 1 (1.8) | |
| Functional ability score (median [IQR]) | 0.0 [0.0, 2.8] | 0.0 [0.0, 0.8] | 0.153 |
| HRQoL (median [IQR]) | 1.3 [0.0, 4.0] | 1.0 [0.0, 3.0] | 0.9 |
| Well Being VAS 0-10 (median [IQR]) | 0.5 [0.0, 2.0] | 0.0 [0.0, 0.9] | 0.059 |
| VAS_pain (median [IQR]) | 0.0 [0.0, 2.0] | 0.0 [0.0, 0.0] | 0.016 |

**Table 8**: Analysis of the primary end point at 6 months in more severe disease (polyarthritis and those with oligoarthritis with presence of ACR features of poor prognosis)

## Adverse events

Seventy-seven and six participants experienced 137 adverse events (AEs) and 6 serious AE (SAEs), respectively. No deaths were reported (table 9).

| | Arm 1 | Arm 2 | p | Overall |
|---|---|---|---|---|
| Number of patients with at least 1 adverse event, n. (%) | 30 (26.5%) | 47 (41.6%) | 0.020 | 77 (33.9%) |
| Total number of adverse events, n. | 55 | 82 | | 137 |
| Number of patients with at least 1 Serious AE, n. (%) | 4 (3.5%) | 2 (1.8%) | 0.45 | 6 (2.6%) |
| Total number of Serious AE, n. | 4 | 2 | | 6 |

**Table 9:** Adverse event and serious adverse event in each arm

The most reported AEs were infections (35.7%), gastrointestinal (30.1%), hepatobiliary (11.1%) and general disorders (9.5%) (table 10). Regarding SAEs five patients developed infections requiring hospitalization, including gastroenteritis (n = 2), bronchitis (n = 1), pyrexia (n = 1) and lymphadenitis bacterial (n = 1).

| | Arm 1 | Arm 2 | Overall |
|---|---|---|---|
| Infections | 16 | 29 | 45 |
| Gastrointestinal disorders | 15 | 23 | 38 |
| Hepatobiliary disorders | 6 | 8 | 14 |
| General disorders and administration site conditions | 5 | 7 | 12 |
| Injury, poisoning and procedural complications | 3 | 1 | 4 |
| Psychiatric disorders | 1 | 2 | 3 |
| Musculoskeletal and connective tissue disorders | 1 | 1 | 2 |
| Nervous system disorders | 1 | 1 | 2 |
| Respiratory, thoracic and mediastinal disorders | 2 | 0 | 2 |
| Skin and subcutaneous tissue disorders | 1 | 1 | 2 |
| Renal and urinary disorders | 0 | 1 | 1 |
| Surgical and medical procedures | 1 | 0 | 1 |

**Table 10**: Description of adverse events in each arm

Eleven patients developed eyes disorders including new-onset uveitis (n = 9), cataract (n = 1) and vitritis (n = 1) (table 11).

| | Arm 1 | Arm 2 | Overall |
|---|---|---|---|
| Uveitis | 3 | 6 | 9 |
| Vitritis | 0 | 1 | 1 |
| Cataract | 1 | 0 | 1 |

**Table 11**: Eyes disorders in each arm

# Discussion

This innovative trial compares the effectiveness of a conventional therapeutic regimen, based on treatment escalation and driven by the treat-to-target approach with that of an early aggressive combined intervention, including the first-line treatment with an anti-TNF agent in polyarthritis and more severe oligoarthritis.

The STARS trial is the first Italian multicenter randomized study to evaluate two different treatment strategies (Step-down vs. Step-up) in patients with JIA in a treat-to-target setting. More than 200 patients were enrolled in this study, one of the largest cohorts of children with JIA in Europe, followed prospectively at the start of treatment.

As expected, nearly 70% of enrolling subjects were females. The median age at disease onset was 5 years and seven months; this figure is higher than that in published Italian case series. This may be partly due to the exclusion of children younger than 2 years of age. Approximately 60% of enrolled children had oligoarthritis; however, nearly half of the subjects belonged to the more severe groups, i.e, they had polyarthritis or oligoarthritis with features of poor prognosis according to ACR treatment recommendations for JIA. At enrollment, children had moderate to high disease activity, with a PhGA above 5 out of 10 and a JADAS10 of 14. The median number of active joints was 4. Randomization resulted in well-balanced arms, with a very similar level of disease activity in the two arms.

For the purposes of this study, we chose to adopt a shorter primary endpoint by comparing the frequency of patients achieving inactive disease at 6 months after the first therapeutic intervention between the two arms. Subsequently we will evaluate the more robust primary endpoint by comparing the frequency of clinical remission at the end of the study, defined as maintaining inactive disease status for at least 6 consecutive months.

At six months, the median number of active joints and the median PhGA were both 0, showing that in general the two treatment intervention were effective in the short time. Two-thirds of children achieved inactive disease; however, approximately 20% still had moderate to high disease activity at month 6.

Regarding patient reported outcomes, functional ability, pain, and wellbeing dropped to 0.

Comparison between the two arms showed remarkable differences: children in the Step-down arm, treated with early aggressive treatment, demonstrated greater improvement across all outcomes. The frequency of ID was 55% in arm 1 and 78% in arm 2. The distribution of children across JADAS-based disease states was significantly different between the two groups. These results clearly demonstrate greater improvement at six months in children treated with early aggressive therapy.

We compared our results with those of recent studies with a similar design. In the randomized, single-blind BeSt for Kids study [24], which also included oligoarticular patients compared the efficacy and safety of three treatment strategies and showed that, after 24 months, inactive disease (ID) was achieved in over 70% of patients, regardless of the initial treatment strategy, including tapering and discontinuation approaches. Differently, the three-year analysis of the STOP-JIA trial demonstrated that patients who initiated early combination therapy spent significantly more time in inactive disease states than those treated with a step-up approach [25]. The TREAT trial [16] demonstrated that early, aggressive, treat-to-target therapy in polyarticular JIA improves clinical outcomes, increases rates of inactive disease, and accelerates achievement of remission compared with standard care.

If confirmed in the primary endpoint analysis, our results, together with those of the TREAT study, the BeSt for Kids study and the STOP-JIA trial, suggest that a strategy combining early initiation of bDMARDs with a treat-to-target approach may be even more effective and could provide important evidence supporting the concept of the so-called “window of opportunity”.

We selected clinical remission (on medication), defined as six continuous months of inactive disease, as the primary endpoint outcome instead of ACR inactive disease criteria because the latter reflects disease inactivity at a single time point time and may represent a transient, clinically less meaningful state. The clinical significance of inactive disease at 6 months, and whether it predicts longer-term outcomes remains unclear. An analysis conducted in the UK showed that achieving inactive disease according to the clinical JADAS-10 was associated with

better functional ability, improved psychosocial health, and fewer joints with limited range of motion in the short-term and long-term (5 years) compared with achieving clinically inactive disease according to the ACR criteria [23] at 1 year [26]. In the STOP-JIA cohort, analysis of both the ACR Pedi 70 and the clinical JADAS-10 scores indicated that participants in the early combination CTP group had significantly higher rates of achieving both outcomes than those in the step-up CTP group after PS weighting and multiple imputation.

Adverse events (AEs and serious adverse events) and new-onset uveitis were reported among STARS trial participants; however, event numbers were too low to detect group differences. A higher number of AEs occurred in arm 2, likely related to the greater use of MTX, alone or in combination with the biologic. AEs were mild in general and involved mostly gastrointestinal complaints, upper respiratory tract and other infections and general malaise. In arm 1, a higher number of adverse events requiring hospitalization occurred; no patients had permanent sequelae. The percentage of children experiencing an AE was comparable to that reported in other large observational safety registries of JIA patients.

We acknowledge that the exclusive focus on short-term outcomes, particularly the assessment of inactive disease at six months, represents the main limitation of the present work. While the six-month analysis provides useful preliminary information on early treatment response, this time frame is relatively short for a chronic disease such as juvenile idiopathic arthritis, in which the key clinical question concerns the ability of therapeutic strategies to induce sustained disease control and long-term remission.

Another potential limitation of the STARS trial is the choice, for sake of uniformity, of etanercept as a first-line biologic medication in both arms. Etanercept is still the most widely adopted choice for non-systemic JIA, and it is the biologic drug for which we have the longest experience on the field. However, we acknowledge that other drugs could also be the optimal choice in this population at higher risk for uveitis. Children requiring systemic medications due to uveitis will discontinue the trial and the comparison of the rate of uveitis between the two arms will be a secondary endpoint of the study.

In conclusion, the results of the STARS study, if confirmed, will help guide shared decision-making discussions between families and physicians as they weigh the risks and benefits of initial treatment approaches. The STARS dataset represents a unique and rich resource of highly curated data on a large cohort of patients with newly diagnosed JIA, which will answer additional questions through further data analysis and long-term follow-up.

# References


[1] A. Ravelli e A. Martini, «Juvenile idiopathic arthritis», *The Lancet*, vol. 369, fasc. 9563, pp. 767–778, mar. 2007, doi: 10.1016/S0140-6736(07)60363-8.

[2] Petty RE, Laxer R, Wedderburn L. Juvenile idiopathic arthritis. In: Petty RE, Laxer R, Lindsley C, Wedderburn L., «Textbook of pediatric rheumatology, 7th Edition. Philadelphia: Elsevier2015».

[3] Petty RE, Southwood TR, Manners P et al., «International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001», vol. J Rheumatol 2004;31:3902.

[4] A. Ravelli *et al.*, «Antinuclear antibody–positive patients should be grouped as a separate category in the classification of juvenile idiopathic arthritis», *Arthritis Rheum.*, vol. 63, fasc. 1, pp. 267–275, gen. 2011, doi: 10.1002/art.30076.

[5] A. Ravelli *et al.*, «Intra-articular corticosteroids versus intra-articular corticosteroids plus methotrexate in oligoarticular juvenile idiopathic arthritis: a multicentre, prospective, randomised, open-label trial», *The Lancet*, vol. 389, fasc. 10072, pp. 909–916, mar. 2017, doi: 10.1016/S0140-6736(17)30065-X.

[6] C. Hinze, F. Gohar, e D. Foell, «Management of juvenile idiopathic arthritis: hitting the target», *Nat. Rev. Rheumatol.*, vol. 11, fasc. 5, pp. 290–300, mag. 2015, doi: 10.1038/nrrheum.2014.212.

[7] T. Beukelman *et al.*, «2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: Initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features», *Arthritis Care Res.*, vol. 63, fasc. 4, pp. 465–482, apr. 2011, doi: 10.1002/acr.20460.

[8] Smolen JS., «Treat-to-target: rationale and strategies. Clin Exp Rheumatol. 2012 Jul-Aug;30(4 Suppl 73):S2-6. Epub 2012 Oct 18. PMID: 23073266.».

[9] A. Ravelli *et al.*, «Treating juvenile idiopathic arthritis to target: recommendations of an international task force», *Ann. Rheum. Dis.*, vol. 77, fasc. 6, pp. 819–828, giu. 2018, doi: 10.1136/annrheumdis-2018-213030.

[10] J. S. Smolen *et al.*, «EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs», *Ann. Rheum. Dis.*, vol. 69, fasc. 6, pp. 964–975, giu. 2010, doi: 10.1136/ard.2009.126532.

[11] J. S. Smolen *et al.*, «EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update», *Ann. Rheum. Dis.*, vol. 73, fasc. 3, pp. 492–509, mar. 2014, doi: 10.1136/annrheumdis-2013-204573.

[12] P. C. E. Hissink Muller *et al.*, «A comparison of three treatment strategies in recent onset non-systemic Juvenile Idiopathic Arthritis: initial 3-months results of the BeSt for Kids-study», *Pediatr. Rheumatol.*, vol. 15, fasc. 1, p. 11, dic. 2017, doi: 10.1186/s12969-017-0138-4.

[13] A. Klein *et al.*, «Treat-to-target study for improved outcome in polyarticular juvenile idiopathic arthritis», *Ann. Rheum. Dis.*, vol. 79, fasc. 7, pp. 969–974, lug. 2020, doi: 10.1136/annrheumdis-2019-216843.

[14] L. Buckley, E. Ware, G. Kreher, L. Wiater, J. Mehta, e J. M. Burnham,

«Outcome Monitoring and Clinical Decision Support in Polyarticular Juvenile Idiopathic Arthritis», *J. Rheumatol.*, vol. 47, fasc. 2, pp. 273–281, feb. 2020, doi: 10.3899/jrheum.190268.
[15] P. Tynjälä *et al.*, «Aggressive Combination Drug Therapy in Very Early Polyarticular Juvenile Idiopathic Arthritis (ACUTE–JIA): a multicentre randomised open-label clinical trial», *Ann. Rheum. Dis.*, vol. 70, fasc. 9, pp. 1605–1612, set. 2011, doi: 10.1136/ard.2010.143347.
[16] C. A. Wallace *et al.*, «Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis», *Arthritis Rheum.*, vol. 64, fasc. 6, pp. 2012–2021, giu. 2012, doi: 10.1002/art.34343.
[17] M. S. Ong *et al.*, «Improved Disease Course Associated With Early Initiation of Biologics in Polyarticular Juvenile Idiopathic Arthritis: Trajectory Analysis of a Childhood Arthritis and Rheumatology Research Alliance Consensus Treatment Plans Study», *Arthritis Rheumatol.*, vol. 73, fasc. 10, pp. 1910–1920, ott. 2021, doi: 10.1002/art.41892.
[18] Consolaro A, Negro G, Lanni S, Solari N, Martini A, Ravelli A., «Toward a treat-to-target approach in the management of juvenile idiopathic arthritis. Clin Exp Rheumatol. 2012 Jul-Aug;30(4 Suppl 73):S157-62. Epub 2012 Oct 16. PMID: 23072725.».
[19] J. S. Smolen *et al.*, «EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update», *Ann. Rheum. Dis.*, vol. 76, fasc. 6, pp. 960–977, giu. 2017, doi: 10.1136/annrheumdis-2016-210715.
[20] A. Consolaro *et al.*, «Development and validation of a composite disease activity score for juvenile idiopathic arthritis», *Arthritis Care Res.*, vol. 61, fasc. 5, pp. 658–666, mag. 2009, doi: 10.1002/art.24516.
[21] C. Trincianti *et al.*, «Definition and Validation of the American College of Rheumatology 2021 Juvenile Arthritis Disease Activity Score Cutoffs for Disease Activity States in Juvenile Idiopathic Arthritis», *Arthritis Rheumatol.*, vol. 73, fasc. 11, pp. 1966–1975, nov. 2021, doi: 10.1002/art.41879.
[22] Consolaro A, Trincianti C, van Dijkhuizen P, Januskeviciute G, Giancane G, Alongi A, et al., «New JADAS10- and cJADAS10-based cutoffs for juvenile idi- opathic arthritis disease activity states: validation in a multinational dataset of 4830 patients [abstract] Arthritis Rheumatol. 2018;70 (suppl 10). https:// acrabstracts.org/abstract/new-jadas10-and-cjadas10-based-cutoffs-for- juvenile-idiopathic-arthritis-disease-activity-states-validation-in-a-multinatio nal-dataset-of-4830-patients/. Accessed 6 Sept 2022.».
[23] C. A. Wallace *et al.*, «American College of Rheumatology provisional criteria for defining clinical inactive disease in select categories of juvenile idiopathic arthritis», *Arthritis Care Res.*, vol. 63, fasc. 7, pp. 929–936, lug. 2011, doi: 10.1002/acr.20497.
[24] P. Hissink Muller *et al.*, «Treat to target (drug-free) inactive disease in DMARD-naive juvenile idiopathic arthritis: 24-month clinical outcomes of a three-armed randomised trial», *Ann. Rheum. Dis.*, vol. 78, fasc. 1, pp. 51–59, gen. 2019, doi: 10.1136/annrheumdis-2018-213902.
[25] S. Ringold *et al.*, «Three-Year Outcomes and Latent Class Trajectory Analysis of the Childhood Arthritis and Rheumatology Research Alliance Polyarticular JIA Consensus Treatment Plans Study», *Arthritis Rheumatol.*, vol.

77, fasc. 10, pp. 1433–1441, ott. 2025, doi: 10.1002/art.43216.
[26] S. J. W. Shoop-Worrall *et al.*, «Long-Term Outcomes Following Achievement of Clinically Inactive Disease in Juvenile Idiopathic Arthritis: The Importance of Definition», *Arthritis Rheumatol.*, vol. 70, fasc. 9, pp. 1519–1529, set. 2018, doi: 10.1002/art.40519.

# Ringraziamenti

Desidero innanzitutto ringraziare Alessandro Consolaro, per aver creduto in me sempre, sostenendomi e trasmettendomi la passione per la reumatologia pediatrica. GRAZIE!

Ringrazio il Professor Angelo Ravelli, per i preziosi consigli ed insegnamenti, nonché per le tante chiacchierate sull'unica squadra di Milano, il Milan!

Ci tengo a ringraziare il Dr. Marco Gattorno e tutti i medici con cui ho condiviso questa bellissima esperienza (Roberta, Silvia, Clara, Stefania, Riccardo, Stefano e Caterina) a cui mando un grande abbraccio!

Grazie al Team Centro Trial e Alessandra per le "marmelle" all'ora del caffè e le indimenticabili partite di beach-volley al tramonto;

Ringrazio tutti gli specializzandi, infermiere, suore e OSS che ho conosciuto in questi anni e che si sono sempre resi disponibili;

Grazie al Dottor Pasetti e i suoi "belin", con la speranza di rivederci in un Centro privato in Brianza;

Ringrazio ovviamente la mia famiglia, recentemente allargata (benvenuto Leone!), per esserci sempre;

Infine ringrazio Anna, Caterina, Paola, Saverio, Simona e Valentina, amici ancor prima che colleghi, per le "lotte" continue senza mai mollare. Swapno Swap!