Oral or Parenteral Methotrexate for treatment of Non- Systemic Juvenile Idiopathic Arthritis

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List of abbreviations

ACR	American Academy of Rheumatology
AE	Adverse Event
AcDA	Acceptable disease activity
ANA	Antinuclear Antibody
BSA	Body surface area
CCP	Cyclic citrulinated peptide
CHAQ	Childhood Health Assessment Questionnaire
CRP	C-reactive protein
DMARD	Disease Modifying Antirheumartic Drugs
ERA	Enthesitis related arthritis
ESR	Erythrocyte sedimentation rate
HLA	Human Leukocyte Antigen
Ig	Immunoglobulin
ITT	Intention to treat
IL	Interleukin
ILAR	International League of Association for Rheumatology
JADAS	Juvenile Disease Activity Score
JIA	Juvenile Idiopathic Arthritis
JPsA	Juvenile Psoriatic Arthritis
LOM	Limited range of motion
MDA	Minimal disease activity
MS	Morning stiffness
MTX	Methotrexate
RF	Rheumatoid Factor

SAE	Serious adverse event
Sc	Subcutaneous
SD	Standard Deviation
SoJIA	Systemic onset Juvenile Idiopathic Arthritis
TNF	Tissue Necrosis Factor

1. Introduction

1.1 Introduction

Juvenile idiopathic arthritis is an umbrella term used to describe a heterogeneous group of disorders of unknown etiology, characterized by chronic arthritis affecting children below 16 years (Pettet al, 2004). Juvenile idiopathic arthritis is the most chronic rheumatic illness in children and it is responsible for short and long-term disability (Weis and Ilowite, 2007). In the recent years, an increased number of disease-modifying anti-rheumatic drugs (DMARDs) have been developed for treatment of juvenile idiopathic arthritis, but methotrexate is still the most common second line therapeutic agent used in treatment of juvenile idiopathic arthritis worldwide (Miller and Cassidy, 2007). However, there is variation in the clinical response to methotrexate among the patients. Prediction of response can prevent further exposing of patients to side effects of methotrexate and saving the time by progressing to the treatment with biologics as soon as possible to prevent irreversible complications.

This is a retrospective study on 794 patients with Juvenile Idiopathic Arthritis. The Cohort of patients was collected from the German Biker Registry Data Base. The data bank was screened for patients treated with MTX orally vs. s.c. as first disease modifying treatment and for the first time. The JIA-ACR criteria and the JADAS10 definition of remission were used as outcome parameters.

1.2 Juvenile Idiopathic Arthritis

Traditionally, this term was used to describe chronic arthritis persisting for at least 6 weeks in an individual 16 years of age or younger after exclusion of other reasons of arthritis (Miller and Cassidy, 2007) Juvenile idiopathic arthritis is the most common chronic rheumatic illness in children and is a significant cause of short and long term disability (Weis and Ilowite, 2007).

1.2.1 Epidemiology

There are differences in estimates for the prevalence and incidence of JIA. These differences occurred due to many factors, which include development of new diagnostic criteria, in addition to the differing of definitions of clinical cases and to the factors occurring with the passage of time, for examples; standards of living, health care resources and increasing knowledge. In one study by Manners and Bower in 2002 a review of 34 epidemiological studies of JIA since 1966 was undertaken, the results show that the prevalence of JIA is reported as 7-401 per 100.000 children, and the annual incidence is reported as 0.8-22.6 per 100.000 children (Manners and Bower, 2002).

1.2.2 Classification of JIA

The classification of juvenile idiopathic arthritis according specific criteria in the JIA categories allows better understanding of their pathogenesis and clinical course. Many of the recent studies on pathogenesis have simply divided patients in three main categories: oligoarthritis, polyarthritis and systemic arthritis. In the fact, there are different classifications for juvenile idiopathic arthritis, but in our study, we used the most recent classification according ILAR (International League of Association for Rheumatology) congress 2001, in which juvenile idiopathic arthritis divided in seven categories which were not comparable to former ACR classification as outlined in table 1:

Type 1 systemic onset juvenile arthritis (formerly called Still's disease)

Type 2 seronegative polyarthritis (at least 5 joints affected during first 6 months and rheumatoid factor (RF) is repeatedly negative)

Type 3 seropositive polyarthritis (at least 5 joints affected during first 6 months and RF is positive)

Type 4a persistent oligoarthritis (less than 5 joints affected during the first six months of disease who do not develop arthritis in other joints over time)

Type 4b extended oligoarthritis (5 or more joints become affected after 6 months)

Type 5 Enthesitis related arthritis (ERA)

Type 6 Juvenile psoriatic arthritis (JPsA)

Type 7 unclassified arthritis (matching no or more than 2 categories)

According the frequency of each subtype, the oligoarticular JIA is the most common (50-60 %), followed by polyarticular JIA (30-35 %), SoJIA (10-20 %), JPsA (2-15 %), and ERA (1-7 %)

The categories are recognized based on the clinical features during the first 6 months of the disease (Tab. 1). Important clinical features that assist in classifying patients include the presence of enthesitis (inflammation at the sites of attachment of ligament, tendon, or fascia to bone), dactylitis, inflammatory lumbosacral pain, nail pitting, sacroiliitis, fever, rash, and serositis.

Tab. 1: Comparison of the ILAR and ACR, the criteria and the associated systemic manifestation

ACR classification	ILAR classification	Extraarticular feature
Systemic	Systemic arthritis	Fever, rash,pleuritis, pericarditis, lymphadenopathy, hemophagocytic syndrome
Pauciarticular early onset	Oligoarthritis (persistent)	Uveitis
	Oligoarthritis (extended)	Uveitis
Polyarticular, seronegative	Polyarthritis, RF-ve	Low grade fever, uveitis
Polyarticular, seropositive	Polyarthritis, RF+ve	Nodules, Felty syndrome, Sjögren syndrome, Vasculitis.
Pauciarticular, late onset	Enthesitis related	Spondylitis, acute iritis
Psoriatic arthritis	Psoriatic arthritis	Psoriasis and uveitis

*Separate diagnostic disease, ACR= American College of Rheumatology, ILAR= International League of Associations for Rheumatology, RF= Rheumatoid Factor (Passo and Rosen, 2005)

Systemic arthritis

Systemic arthritis is a less common subtype, and usually begins with high, spiking fevers to greater than 39.4°C, the fever frequently is accompanied by rash that comes and goes with temperature elevations. Joint involvement may occur either at onset or later during the disease.

Oligoarthritis

Oligoarthritis category of JIA affects four or fewer joints in the first six months of disease. If more than four joints become involved after six months, it is defined as extended oligoarthritis, otherwise it is classified as persisting oligoarthritis. Oligoarthritis is the most common form of JIA, and preferentially afflicts 1 to 3 years old Caucasian girls.

Although all races can be affected, the prevalence is much reduced in non-Caucasians. Girls outnumber boys 4:1, clinically about half of oligoarticular JIA patient will have a single joint involved at onset, mainly the knee. The next most commonly affected joints are the ankle, and the small joints of the hand are the third most commonly affected. Wrist involvement is rare and may indicate the progression to extended oligoarthritis. Up to 20
% of patients can develop uveitis, which usually is asymptomatic and it is more prevalent in the children, who are ANA positive. (Woo et al., 2007).

Polyarthritis

In both polyarthritis categories, there are five or more joints involved in the first six months, girls outnumber boys in both categories, seronegative subtype is more common than seropositive. Polyarthritis subtypes characteristically involves the small joints of the hands and feet, but large joints involvement is also common. Approximately one fourth of the seronegative polyarthritis patients have positive test results for ANA, and few of the

patients have associated chronic uveitis. The onset of illness usually occurs when the child is 10 years old or younger.

In general, seronegative JIA patients respond better to treatment with NSAIDs than do seropositive patients. Only about 5-8 % of all children with chronic arthritis are seropositive for rheumatoid factor. The onset of this illness usually occurs when the child is 9-16 years of age (Miller and Cassidy, 2007).

Enthesitis Related Arthritis (ERA)

Enthesitis related arthritis is defined as arthritis and/or enthesitis (inflammation of tendons or ligaments where they attach to bone) with at least two of the following features: (1) sacroiliac joint tenderness, or inflammatory lumbosacral pain (2) HLA-B27 positive (3) first degree relative with medically confirmed HLA-B27 associated disease
(4) uveitis (5) onset of arthritis in a boy six years or older. Enthesitis related arthritis is more frequent in boys (Burgos-Vargas et al., 1997). The onset typically occurs in children over six and there is a familial predilection.

Juvenile Psoriasis related Arthritis (JPsA)

Juvenile psoriatic arthritis is chronic inflammatory arthritis with a peak age of onset in mid childhood. JPsA is difficult to be diagnosed, because the arthritis may develop many years before the skin manifestation. JPsA is an asymmetric arthritis that often affects the knees, and the ankles, and the small joints of the hands and feet. Proximal interphalangeal joints, and tendon sheath are often inflamed, resulting in the diffuse swelling of the digit known as sausage digit (Shore, 1982). Extra-articular manifestations include rash, nail changes (including pitting, onycholysis, oil drop sign), and uveitis. One third of patients with JPsA develop the psoriasis by 15 years of age (Petty and Malleson, 1986).

All children with JPsA should have a slit-lamp examination at least every 6 months, because asymptomatic anterior uveitis may be found in up 17 % of patients. Laboratory data show elevated acute phase reactants, anemia of chronic disease, and thrombocytosis. Also, ANA may be positive (Southwood and Petty, 1989).

1.2.3 Etiology and Pathology

The causes of juvenile idiopathic arthritis remain unclear, but it seems to be a complex genetic trait involving the effects of multiple genes related to immunity and inflammation. Some hypothesize that arthritis may be triggered in a genetically predisposed individual by psychologic stress, abnormal hormone levels, trauma to a joint, or bacterial or viral infection.

Several studies have implicated rubella and parvovirus B19 as possible causes of JIA because rubella virus persists in lymphocytes and establishes a focus of persistent infection in the synovium resulting in chronic inflammation (Lang and Shore, 1990).

Certain HLA class 1 and class 2 alleles are associated with an increased risk of JIA. The class 1 antigen HLA-A2 is associated with early onset oligoarthritis in girls (Murray KJ, et al, 1998). The class 2 antigens HLA-DRB1*08 and *11, DQA1*04 and *05, and DQB1*04 are associated with persistent oligoarticular and extended oligoarticular JIA. HLA-DRB1*08 confers an increased risk of rheumatoid factor (RF) negative polyarthritis, and HLA-DRB1*11 confers an increased risk of systemic onset JIA (SOJIA). HLAB1*04, associated with adult rheumatoid arthritis, is associated with an increased risk of RF positive polyarticular arthritis. The class 1 antigen HLA-B27 and class 2 antigens HLA-DRB1*01 and DQA1*0101 are associated with enthesitis related arthritis (ERA) and JsA. Other genes conferring risk include cytokine production regulating genes. Anti-nuclear antibodies (ANA) are found in approximately 40 % of patients with JIA, especially in young girls with oligoarticular disease (Petty RE, Cassidy JT, Sullivan DB, 1973). Approximately 5 % to 8 % of patients with JIA are rheumatoid factor positive (Lang BA, Shore A, 1990). The T-lymphocytes mediated immune response is involved in chronic inflammation, and T cells are the predominant mononuclear cells in synovial fluid.

Patients with JIA have elevated serum levels of interleukin (IL) -1, -2, -6, and IL-2 receptor (R), and elevated synovial fluid levels of IL-1B, IL-6 and IL-2R, suggesting a Th1 profile. Elevated serum levels of IL-6, IL-2R, and soluble tumor necrosis factor (TNF) receptor correlate with inflammatory parameters, such as C-reactive protein, in JIA patients indicate active disease. Serum levels of IL- 6 are increased in SJIA and rise before each

fever spike, correlating with active disease and elevation of acute phase reactants (Weis and Ilowite, 2007).

1.2.4 Prognosis of JIA

The prognosis of JIA in an individual child is so far unpredictable. Studies from United States indicate that despite the current management, approximately 45 % of JIA patients have active disease persisting into early adulthood, often with severe limitation of physical function (Miller and Cassidy, 2007)

Most children with oligoarthritis do well, in about 20-30 % of these children oligoarthritis becomes extended and the outcome is poor until methotrexate is introduced as the treatment of choice. Remission is induced in 60-70 % while on methotrexate. Anti-TNF agents are effective if patients fail to respond to methotrexate, especially if given in combination with methotrexate (Woo P et al., 2007). The child with oligoarticular disease, particularly a girl with early onset of arthritis at < 6 years of age is at risk to develop chronic uveitis. There is usually no association in the course of the arthritis and chronic uveitis. Uveitis can result in posterior synechiae, untreated or refractory disease can result in blindness, which can be decreased by frequent monitoring with slit-lamp examination to exclude asymptomatic uveitis (Miller and Cassidy, 2007).

Other sequelae include leg length discrepancy, especially in those with knee arthritis. Muscle atrophy can occur due to persistent swelling and pain. The child with polyarticular disease often has a more prolonged course. Poor prognosis associated with older age of onset, the presence of rheumatoid factor seropositive or rheumatoid nodules, or the early involvement of cervical spine or hips (Miller and Cassidy, 2007)

The child with systemic JIA onset is often the most difficult to manage in terms of both articular and systemic manifestations. However systemic manifestations are usually present only during the first few years after onset. The prognosis after that time dependent on the number of the joints involved and severity of arthritis (Miller and Cassidy, 2007).

The long-term outcome of enthesitis related arthritis is poorly described, enthesitis is more symptomatic in teens and young adults, and it improves with age. Boys with HLA-B27 and

hip arthritis, or tarsitis are at high risk of developing progressive spinal involvement. Children with psoriatic arthritis tend to have longer lasting disease, and small but significant percentage (up to 10 %) may be disabled (Woo et al., 2007).

1.2.5 Treatment of JIA

The objectives of treatment include controlling pain and inflammation, preserving function, and promoting normal growth, overall development, and wellbeing as well as to achieve these goals with minimal risk of side effects. The long-term treatment of children with JIA is initiated and subsequently modified according to disease subtype, severity of the disease, specific manifestation of the illness and the response to therapy (Miller and Cassidy, 2007).

Therapy is directed toward the underlying inflammation of JIA (e.g. joint damage). Medication include first line NSAIDs and second line drugs that include immunomodulators, biologic agents, corticosteroids and gold. Initial drug therapy for children with polyarticular juvenile idiopathic arthritis should be aggressive to control the inflammatory process and relieve symptoms as quickly as possible while minimizing drug side effects (Lachman, 2007). Treatment usually started with the least toxic medication usually NSAID, and proceeding through methotrexate to modulatory biologics. Medications that place the child 's present and future health most at risk, such as azathioprine, and cyclophosphamide, are reserved for the very few children who do not respond to less aggressive therapy.

NSAIDs traditionally have been the preferred first line drugs, these medications reach full efficacy within two to three months, but usually start to relieve symptoms within a few days. The improvement will be clear in most of the patients within the first three months (Ruperto et al., 2005).

Systemic corticosteroids are very powerful anti-inflammatory medications, but their use is limited, because the risk of side effects, which include Cushing’s syndrome, hyperglycemia, immunosuppression, cataract, glaucoma, peptic ulcer, osteopenia, and growth retardation. Although glucocorticoids are the mainstay of treatment for controlling

serious systemic manifestations of systemic JIA, use in polyarthritis patients should be limited as bridging agent to patients with extreme pain, disabling morning stiffness and functional limitation while waiting for a second – line agent to show some effect (Klein and Horneff, 2009) However short term use of low dose corticosteroids (less than o.25 mg /kg per day of prednisolone or its equivalent) may provide substantial benefits without complication, so that the use of glucocorticosteroids bridges between the NSAIDs and other DMARDs.

Intraarticular injections of corticosteroid is an effective therapy for patients with JIA, and majority of patients having complete and long lasting response (Srinivasan et al., 2012) . Triamcinolone hexacetonide (10-40 mg/joint or 1-2 mg/ kg/ joint) is commonly used and has been shown to result in improvement of signs and symptoms of arthritis (18). The side effects may include infection, atrophic skin changes at the site of injection, and asymptomatic calcifications on radiographs.

Disease modifying antirheumatic agents

DMARDs are a group of drugs which effective in treatment of JIA e.g. sulfasalazine, methotrexate and leflunomide.

Methotrexate

MTX is the most common used as a second line treatment of JIA and it will be discussed in details in section 1.3.

Leflunomide

Leflunomide is an immunomodulator that inhibits pyrimidine synthesis, it has been shown to be safe and effective in adults with rheumatoid arthritis, and has also been studied for use in JIA. Preliminary results show efficacy similar to that of methotrexate, but has not been shown to be superior to methotrexate (Silverman et al., 2005a, 2005b) .Side effects

of leflunomide include diarrhea, elevated liver enzymes, mucocutaneous abnormalities and teratogenicity (Weiss and Ilowite, 2007).

Sulfasalazine

Sulfasalazine has been shown to be beneficial for many children with enthesitis related arthritis, families must be warned of the possible development of rare severe reactions seen with sulfa drugs e.g Stevens-Johnson syndrome. Sulfasalazine does not prevent chronic changes and therefore should not be relied upon in erosive disease (Lachman, 2007). Other immunomodulators like azathioprine and cyclosporine have been used with varying success in the past. Currently they are not preferred for treatment because of their significant potential toxicity, and they are less effective than the newer biologic agents (Klein and Horneff, 2009).

Biologic agents

They are group of agents, including the TNF inhibitors etanercept, infliximab, adalimumab, golimumab and certolizumab, the IL-1 inhibitor anakinra, rilonacept and canacinumab, the IL-6 receptor blocker tocilizumab and the B- cell depleter rituximab, they are currently being used in patients with RA and JIA resistant to methotrexate.

All biologic agents carry a risk of immunosuppression, infection, and possibly malignancies. Live virus vaccines are relatively contraindicated. Cases of reactivated tuberculosis have been reported in JIA patients using the TNF inhibitors (Weiss and Ilowite, 2007).

Etanercept

Etanercept is a fusion protein containing tumor necrosis factor (TNF) receptor and FC fragment from human IgG. It is effective in many children with resistant polyarthritis disease (Horneff et al., 2004; Lovell et al., 2000).

Patients treated with etanercept show dramatic improvements within weeks of starting therapy, with benefits persisting for years. Etanercept was proven effective in controlling pain and swelling and in improving laboratory parameters (Lovell et al., 2003,2006, 2008).

Approximately three fourths of patients who do not respond adequately to methotrexate will have a good response to etanercept. Etanercept 0.4 mg /kg (maximum 25 mg) given subcutaneously twice weekly has a dramatic response, and is highly recommended for patients with extended oligoarthritis or polyarthritis who have not responded to NSAIDs and methotrexate.

In addition, there is increasing evidence from the studies that the combination of etanercept and methotrexate in synergistic was well tolerated and highly effective especially in treatment of juvenile polyarthritis but not in patients with systemic arthritis (Schmeling et al., 2001).

Infliximab

Infliximab is a chimeric mouse-human monoclonal anti-TNF-alpha antibody. Infliximab may have similar efficacy to that seen with the use of etanercept, but the incidence of adverse effects was higher and more serious in the infliximab group than in etanercept group. A short-term head to head placebo controlled study in juvenile idiopathic arthritis patients has shown that infliximab failed to reach the primary endpoint (Ruperto et al., 2007).

Adalimumab

Adalimumab is a fully humanized monoclonal anti-TNF antibody, which is administered either weekly or every other week as a single s.c. injection. Preliminary experience has shown that adalimumab has been effective in many children who had not responded adequately to etanercept (Lovell et al., 2004).

Rituximab

Rituximab is a chimeric anti-CD20 monoclonal antibody, which has been approved for treatment of adult onset rheumatoid arthritis only and not for JIA (Lachman, 2007).

Anakinra

Is an interleukin 1 (IL1) receptor antagonist. Used for treatment of cryopyrin-associated periodic syndrome (CAPS), approved in pediatric patients and adults.it is also used for treatment of moderately to sever active rheumatoid arthritis in patients who have failed on one or more disease-modifying antirheumatic drugs (DMARDS); maybe used alone or in combination with DMARDS that are not tumor necrosis factor blocking agent (eg, etanercept, adalimumab). Anakinra has also been used as the first line therapy for systemic JIA, it was associated with rapid solution of systemic symptoms and prevention of refractory arthritis, it shows superiority in short term placebo controlled study (Quartier et al., 2011).

Tocilizumab (Humanized anti-interleukin 6 receptor antibody)

There is evidence that systemic onset JIA is in part an IL-6 mediated disease, and the use of humanized anti-interleukin 6 receptors such as tocilizumab had significant improvement in the ACR improvement criteria and disease activity indices, an addition to decrease in acute-phase reactant. It is effective in treatment of systemic onset JIA and in polyarthritis JIA and may be useful in patients with intractable disease (Yokota et al., 2008).

Autologous Stem Cell Transplantation

Autologous Stem cell transplantation has been considered in recalcitrant cases of SoJIA, and because the procedure carries a significant mortality risk (usually from macrophage activation syndrome). Stem transplantation should be performed only in experienced centers after all other treatment options have failed (Weiss and Ilowite, 2007).

1.2.6 Treatment of complications

The treatment of JIA should be directed towards not only the inflammation of JIA but also for specific complications of JIA flexion contractures, weakness and difficulty with ambulation are not rare. The children with later complications should be referred for physical therapy. In rare cases, joint replacement is indicated. In patients with temporomandibular joint involvement especially with significant micrognathia, surgical correction may be required, but this operation should not be done until the facial bones are fully developed.

Uveitis is initially treated with topical corticosteroids, if there are no improvement systemic corticosteroids and/ or MTX may be helpful, and in especially severe disease cyclosporine, adalimumab or infliximab have been used successfully.

Osteoporosis and growth retardation are associated with severe systemic or polyarthritis subtypes of JIA. Preliminary studies of growth hormone therapy have shown some improvement in bone mineral contents and accelerated linear growth (Bechtold et al., 2004; Rooney et al., 2000; Simon et al., 2003) (31-32). However, the use of growth hormone therapy also has been associated with an increase incidence of deformities, such as scoliosis (Lachman, 2007).

1.3 Methotrexate

Methotrexate which formerly known as a methopterin, is an immunomodulator, by acting as antimetabolite and antifolate drug. It is used for in treatment of cancer, autoimmune disease, ectopic pregnancy, and for induction of medical abortion.

When it used at dose of 10-15 mg/m body surface area (BSA) per week, it acts as an inflammatory agent rather than as a cytotoxic drug. MTX has been the standard therapy for children with JIA especially with polyarticular course, and considered as the drug of choice in the second line treatment for patients with JIA who did not respond to NSAIDs (Ruperto et al., 2004; Ravalli and Martini, 2000; Wallace, 1998).

The short and long term data suggest that MTX is a safe drug in the pediatric population with rheumatic disease. And not surprisingly MTX is the DMARD of choice in JIA either as monotherapeutic drug or in combination with biologic agents (Gutierrez-Suarez and Burgos-Vargas, 2010).

Usually, the starting dose of MTX in children with JIA is 10-15 mg/m^2 and is administered weekly, either orally or parenterally (subcutaneously or intramuscular), at these standard doses, the oral route is preferred by most pediatric rheumatologists because of it 's easer administration and greater child comfort, furthermore there does not appear to be any advantages related to efficacy or safety with either the oral or parenteral method of administration (Klein et al., 2012).

Some food such as milk-rich food may decrease MTX absorption, so it is better when drug is given without food. Although MTX is effective for many patients, it does not work quickly, usually taking four to eight weeks before demonstrating its benefits. Some physicians will initiate therapy with a low dose (0.2-0.35 mg/kg per day) of prednisone, to be taken until MTX has begun to take effect. The maximum therapeutic effect usually becomes apparent 4 to 6 months after the beginning of treatment and sometimes even after 12 months. A higher dose up to 25-30 mg/ m^2/week may be considered in children who had only a partial response to the drug or have a more severe disease. Doses greater than 15-20 mg/m^2 administered parenterally because of the decreased oral bioavailability of the drug at higher dose (Ravelli and Martini, 2000).

Interactions and contraindications

Salicylates may delay MTX 's clearance. Sulfonamides, salicylates, phenytoin displace MTX from protein binding sites. Live virus vaccines may result in vaccine infection. Pyrimethamine, fluorouracil, NSAIDs increase toxicity of MTX by elevating serum MTX concentration (do not use NSAIDs with high dose MTX therapy), penicillin may decrease renal clearance of MTX, probenecid decreases the renal elimination of MTX. Also, MTX may decrease theophylline clearance. Contraindication for MTX use are hypersensitivity to MTX, severe renal or hepatic impairment, lung fibrosis and pre-existing profound bone marrow suppression.

1.4 Health assessment in patients with JIA

Assessment for children with JIA should be regularly done. The historical focus in assessment of children has been on hard outcomes such as persistent disease activity, disease remission, joint damage, and organ system damage. Number of the measures of these outcomes have been grouped as a core set and used to define improvement (Giannini et al., 1997) (38). Juvenile idiopathic arthritis like most other chronic diseases of childhood, influences all aspects of the child ‘s life, including physical, social, emotional, intellectual and economic aspects, and affects the entire family with ultimate effects on the child’s overall outcome (Allaire et al., 1992; Miller, 1993).

1.4.1 Instrument used to assess juvenile idiopathic arthritis

A- Measures of physical function

- Childhood Arthritis Impact Measurement Scales (CHAIMS)

- Juvenile Arthritis Assessment Scale (JAFAS) and Report (JAFAR)

- Childhood Health Assessment Questionnaire (CHAQ)

- Juvenile Arthritis Self-Report Index (JASI)

B- Measures of quality of life

Disease specific

- Juvenile Arthritis Quality of life Questionnaire (JAQQ) -Childhood Arthritis Health Profile (CHAP)

Generic

- Childhood Health Questionnaire (CHQ)

- Pediatric Quality of Life Inventory Scales (Peds QL) -Quality of My LifeQuestionnaire (QOMLQ)

1.4.2 Instrument to measure function: Childhood Health Assessment Questionnaire

CHAQ is a disease- specific measure of functional status that comprises two indices focus on physical function. The disability index assesses function in eight areas that include dressing, grooming, eating and general physical activities distributed among a total of 30 items. Each question is rated on difficulty in performance and is scored from 0 to 3. The disability index is calculated as the mean of eight functional areas. Discomfort is determined by the presence of pain measured by a 100-mm visual analogue scale. The CHAQ has been shown to be a useful instrument for evaluating outcome in longitudinal studies (Minden et al., 2000; Oen, et al, 2003)), it has been shown to have reasonable responsiveness in clinical drug trials (Lovell et al., 2000) (20) and in the evaluation of rehabilitative interventions.

The CHAQ has excellent reliability and validity, and responsiveness, it also has good discriminative properties and can be administered to children of all ages and in several languages, and because it is short and easy to use, it is used with increasing frequency in the clinical settings (Duffy CM, 2007).

1.5 Definition of improvement

1.5.1 Measurement of response

Until the mid-1990's, the assessment of clinical response in JIA was not standardized, there had been no single uniform definition of improvement for use in the clinical trials of JIA and multiple outcome measures were utilized and various trials used different endpoints.

Previous response criteria focused on single outcome measures, including the percentage improvement in number of active joints, physician preference, and overall improvement in physician global assessment, which led to difficulty in comparing study outcomes.

In 1997 the pediatric core set and the American college of Rheumatology (ACR) Pediatric 30 response criteria has been developed. The ACR Pediatric 30 was initially designed to

distinguish between active treatment and placebo, it is well studied and validated but more commonly used in research versus practice.

ACR Pediatric 30 is now used as the primary outcome measure for trials of biologic agents and second line therapies and remains the only prospective validated measure of disease activity in JIA (Ringold and Wallace, 2007). The components of ACR Pediatric criteria include the following:

- Physician ‘s global assessment of overall disease activity (measured on a 10-cm visual analogue scale {VAS}).

- Parents (or, if appropriate in age, patient) global assessment of overall wellbeing measured on a 10-cm VAS.

- Functional ability (usually assessed with CHAQ).

- Number of joints with active arthritis.

- Number of joints with limited range of motion.

- Erythrocyte Sedimentation Rate (ESR).

ACR Pediatric 30 means a minimum of 30 % improvement from baseline in a minimum of 3 out the above 6 components with no more than one component worsening more than 30 %. Also, PedACR 50, PedACR 70 and PedACR90 defined as 50, 70 and 90 percent improvement in a minimum of 3 out the above 6 components with no more than one component worsening more than 30 %.

1.5.2 Definition of remission

The primary goal in management of JIA is the achievement and maintenance remission. Until recently, reaching remission has been difficult to achieve in most forms of JIA, but with the development of new therapeutic agents and combination treatment strategies, more children with arthritis can experience protracted periods of low levels of disease activity and in limited number of cases, a complete clinical remission, but it is difficult to define precisely with a single disease activity measure, although many definitions for

remission has been developed, until recently no uniform and widely accepted criteria for defining remission in JIA.

According to the preliminary criteria of clinical remission the patients divided in three groups: - patients with inactive disease, clinical remission with medication and clinical remission without medication (Tab. 2).

Tab. 2: Preliminary criteria for inactive disease and clinical remission of JIA

Inactive Disease 1. No joints with active arthritis. 2. No fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA 3. No active uveitis (to be defined) 4 normal ESR or CRP (if both are tested, both must be normal) 4. Physicians global assessment of disease activity indicates no disease activity (i.e.,best score attainable on the scale use)
Clinical remission Two types of clinical remission are proposed 1. Clinical remission on medication. The criteria for inactive disease must be met for a minimum of 6 consecutive months while the patient is taking medication. 2. Clinical remission without medication. The criteria for inactive disease must be met for a minimum of 12 consecutive months while the patient is off all anti-arthritis and anti-uveitis medication

1.5.2.1 ACR definition of remission

The modified criteria for defining clinical inactive disease in oligoarticular (persistent and extended), polyarticular (RF + and RF -), and systemic JIA include:

- No joints with active arthritis
- No fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA
- No active uvitis as defined by the SUN Working Group
- ESR or CRP level within normal limits
- Physician's global assessment of disease activity score of best possible on scale used
- Duration of morning stiffness of ≤ 15 minutes

All criteria must be met. Although this table contains criteria that refer to extraarticular manifestations of disease and uveitis, these were not part of this exercise because patients with systemic manifestations or uveitis were ineligible for enrollment into the randomized controlled trial. The uveitis and systemic criteria are shown here in order to present the entire set as it currently exists. RF rheumatoid factor; JIA juvenile idiopathic arthritis; ESR erythrocyte sedimentation rate; CRP C-reactive protein.

The American College of Rheumatology defines a joint with active arthritis as a joint with swelling not due to bony enlargement or, if no swelling is present, limitation of motion accompanied by either pain on motion and/or tenderness. An isolated finding of pain on motion, tenderness, or limitation of motion on joint examination may be present only if explained by either prior damage attributable to arthritis that is now considered inactive or non-rheumatologic reasons, such as trauma.

The Standardization of Uveitis Nomenclature (SUN) Working Group defines inactive anterior uveitis as "grade zero cells," indicating 1 cell in field sizes of 1 mm by a 1-mm slit beam. (Wallace and group 2011).

1.5.2.2 JADAS definition of remission

The Juvenile Disease Activity Score (JADAS), represent an important tool for the assessment of clinically relevant changes in disease activity, leading more and more to a treat-to-target strategy, based on a tight and thorough control of the patient condition.

JADAS is a composite disease activity index that is made up by pooling four individual measures: physician's global assessment of disease activity (PGA), parent's/patient's assessment of child's well-being (PPGA), count of joints with active arthritis (assessed in 71, 27 or 10 joints, depending on the version) and ESR. Recent studies have shown that the ESR can be replaced by the CRP value without altering the performance of the instrument

The composite scores are perfectly designed to follow over time the disease course of a child with JIA. However, the utility of these tools is greatly enhanced by the availability of criteria for identifying high and low levels of activity.

The cut-offs obtained by Backström et al. are slightly different from those previously found by Consolaro et al. of Italian patients with JIA (Tab. 3), particularly in the oligoarthritis subgroup. These discrepancies can be partially explained by differences in the study samples and in the methodology used to calculate the cut-offs.

Tab. 3: Comparison between the JADAS cut offs between the studies of Backstörm et al. and Consolaro et al.

JADAS		
	Backstör et al	Consolaro et al.
Oligoarthritis		
Inactive disease	<< 0.5	<< 1
Low disease activity	0.6-2.7	1.1-2.0
Moderate disease activity	>> 2.8	2.1-4.2
High disease activity	-	> 4.2
Polyarthritis		
Inactive disease	<< 0.7	<< 1.0
Low disease activity	0.8-3.0	1.1-3.8
Moderate disease activity	>> 4.0	3.9-10.5
High disease activity	-	> 10.5

1.6 Objectives

Methotrexate is the most common second line therapeutic agent used in treatment of JIA worldwide, however, there is variation in the clinical response and toxicity observable between the patients who used MTX. Although serious toxicity in patients using MTX is uncommon, a prevalence of adverse effects as high as 42 % has been reported (Ravelli et al, 1998).

The main goal of JIA treatment is the achievement of wellbeing with minimal risk of side effects. Identification of predictors of response is helpful to develop recommendations for MTX use, especially starting of MTX as well as further continuation or early discontinuation and starting use of biological drugs.

Sc Methotrexate is thought to be more effective or act more rapidly than oral Methotrexate. Thus, we wanted in this study to

- Analyze the kinetic of response in JIA patients treated with oral vs sc MTX.
- Check the superiority of sc over oral application in childhood.
- Analyze tolerance with sc compared to oral Methotrexate.

2. Materials and methods

2.1 Patients selection

Patient's data were taken from the German BIKER Registry founded in 2001. The registry is a non-interventional long term study and has been approved by the ethics committee of the Aerztekammer Nordrhein, Duesseldorf, Germany. Since 2005 patients newly started with methotrexate were included into the registry. Data of patients admitted to the registry until December 31, 2010 were used for this analysis and followed up thereafter.

The inclusion criteria used were:

* Patients documented in the German BIKER Registry

* Diagnosis of JIA according to the ILAR definition

* JIA category for which MTX is recommended:

- Polyarthritis (Rf positive and RF negative)

- Extended oligoarthriitis

- Psoriatic arthritis

Exclusion criteria used were:

* Systemic JIA

* ERA

* Persistent oligoarthritis

* Previous or concomitant treatment with a biologic agent

* Concomitant treatment with a second DMARD (other than MTX)

* previous treatment with MTX

Endpoints were defined as:

* Discontinuation of treatment (reasons for discontinuation were inefficacy,intolerance, remission)

* Change from oral to parenteral MTX

* Change of parenteral to oral MTX

* Start of a biologic

* Occurrence of uveitis

Until September 2016, the total number of patients included in the MTX registry was 1517.

The total number of patients included in our study who are fulfilling all inclusion and exclusion criteria were 794 patients. 410 patients received MTX orally and 384 received it parenterally. The final analysis cohorts exist of 216 patients receiving MTX orally and who were compared to 246 patients receiving MTX parenterally.

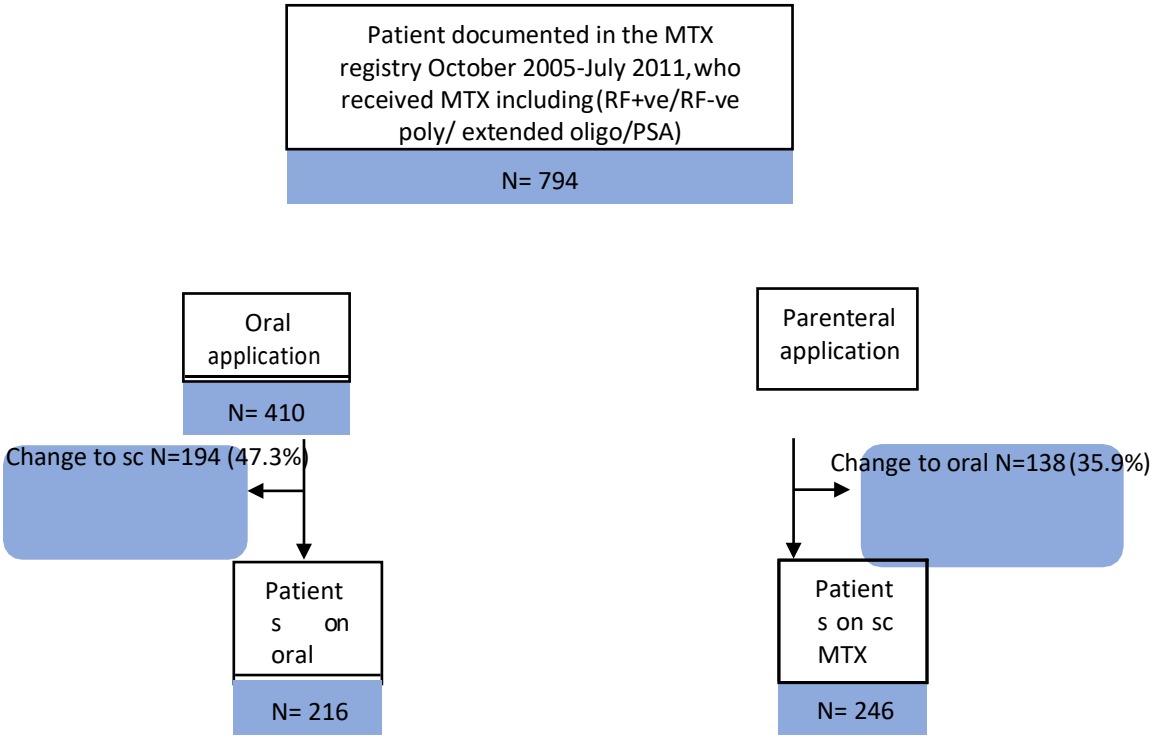

Fig. 1: Flow chart showing the number of patient included in the study. MTX= methotrexate, RF+ve poly= Rheumatoid factor positive polyarthritis, RF-ve poly= Rheumatoid factor negative polyarthritis, PSA= Psoriatic Arthritis, sc=subcutaneous

2.2 Evaluation of response to treatment

2.2.1 Ped ACR Score (30\50\70\90)

In this study the response to treatment was analyzed at 3 months, 6 months, 12 months, 18 months, and at 24 months. At each time the patients were divided into responders and non-responders according to the American College of Rheumatology Pediatric (PedACR) 30, 50, 70 or 90 improvement criteria, this means 30 %, 50 %, 70 % or 90 % improvement from baseline in at least three of the following six variables.

2.2.2 JADAS Response

The Juvenile Disease Activity Score (JADAS), represent an important tool for the assessment of clinically relevant changes in disease activity, leading more and more to a treat-to-target strategy, based on a tight and thorough control of the patient condition.

The composite scores are perfectly designed to follow over time the disease course of a child with JIA. However, the utility of these tools is greatly enhanced by the availability of criteria for identifying high and low levels of activity. Tab. 4 shows cutoff values in the JADAS that correspond to the states of inactive disease, low disease activity, moderate disease activity and high disease activity. Tab. 3 shows cut-off for improvement and goodness-of-fit parameters. Higher ΔJADAS10indicatesbettertreatmentefficacy.JADAS10 indicates better treatment efficacy. Only integer cut-offs were considered. sensitivity (specificity) here is defined as the probability of higher (lower) ΔJADAS10indicatesbettertreatmentefficacy.JADAS, conditioned on improvement (yes or no) (Yokota S.,2008).

Tab. 4: Interquartile ranges (IQRs) of variable ΔJADAS10indicatesbettertreatmentefficacy.JADAS10 by improvement and baseline class absolute and relative values

JADAS10 baseline class (score)			
	Low (5-15)	Moderate (15-25)	High (25-40)
Improvement JADAS10 absolute values, IQR (n)			
Yes	4.1-9.5	10.4-17.1	17.6-27.1
No	-3.3-3.0	1.5-10.2	5.3-15.5
Cut-off for improvement, %	4	10	17
Accuracy, %	76.8	75.6	79.2
Sensitivity, %	76.1	76.0	77.1
Specificity, %	81.6	73.6	87.9
Improvement, JADAS10 relative values,			
Yes	45-86	55-88	65-94
No	-33 to 35	9-50	20-50
Cut-off improvement, %	41	53	57
Accuracy, %	78.1	78.5	85.5
Specificity, %	77.8	77.9	84.3
Sensitivity, %	80.3	81.6	90.9

2.3 Adverse events response and analysis

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

An SAE is defined as any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Life-threatening
- Death
- Hospitalization/prolongation of hospitalization
- Congenital anomaly
- Persistent or significant disability/incapacity
- Required intervention to prevent permanent impairment/damage

All side effects that has occurred during drug administration, were identified and registered. Data of adverse event and serious adverse event were collected from Biker registry then analyzed using comparative statistics.

2.4 Statistics

Population for analysis in our study are two groups of patients; first group received MTX orally and the other received it parenterally.

Two set of analysis were performed. “The as observed analysis” was performed on patient’s number actually reported.” The intention to treat” analysis was performed on all patients and included patients who discontinued treatment, changed the mode of application or added a biologic treatment. Those patients were labeled as non- responders in the ITT data set.

The descriptive statics as median with first and third quartile or mean ± standard deviation (SD) for quantitative variables and as absolute frequencies and percentage for qualitative variables.

Comparative statistics as t-test, Chi-square and Wald test are used to compare between the two mode of application of MTX according to sort and long term of improvement.

The velocity of improvement was described statistically using Kaplan Mayer analysis.

Endpoint of analysis was reached if patients discontinued MTX, switched mode of application or started a biologic treatment.

3. Results

3.1 Character of the study sample

3.1.1 Gender

The patient population consisted of 794 patients in whom the diagnosis of juvenile idiopathic arthritis has been given according to the ILAR criteria. In our study the female represents 71 % (299 patients) in oral cohort and 78 % (301 patients) in the sc cohort, while the male sample was 27 % (109 patients) in oral group and 22 % (83 patients) in the sc group. (Fig. 2).

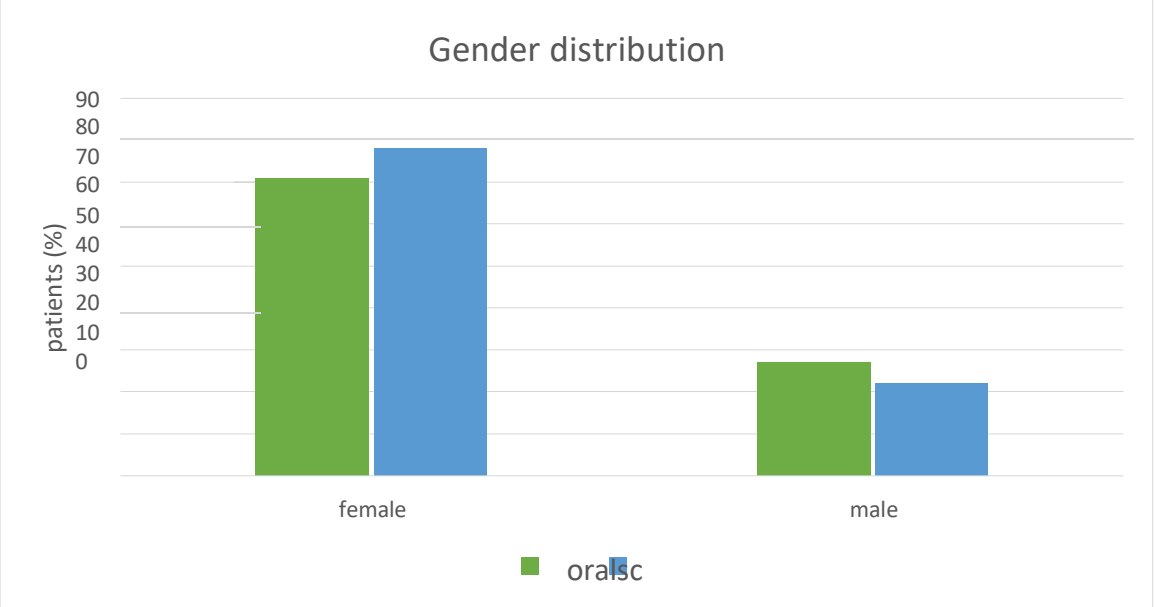

Fig. 2: Distribution of patients according to gender in oral and sc cohort. sc=subcutaneous

3.1.2 JIA category

As seen in Tab. 5 and fig. 3 below, seronegative polyarthritis is the most common category involved in the study sample with 203 patients in the oral group and 195 patients in sc group, almost 50 % in both groups. While, the least patients involved were the RF+ve polyarthritis. Only for the RF+ve JIA category, there was a preference of the sc application, which was statistically significant.

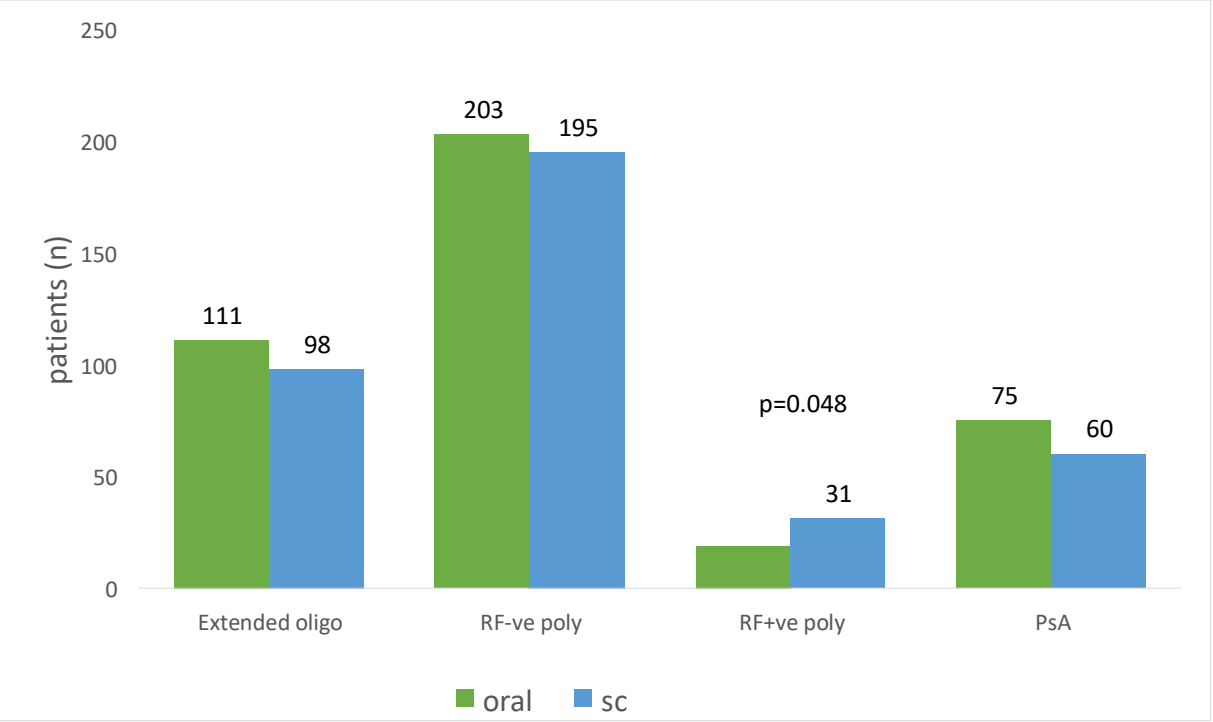

Fig. 3: Category of JIA patients involved in the study

ExOligo= extended oligoarthritis, RF-ve poly= rheumatoid factor negative polyarthritis, RF+ve poly=rheumatoid factor positive polyarthritis and PsA= psoriasis related arthritis, sc= subcutaneous.

Tab. 5: Clinical and disease characteristics of patients at baseline

	Oral n=410	SC n=384	χ^2-test, odd's ratio [95%CI]
Female (%)	299 (71%)	301(78%)	n.s
Age, Median (IQR); mean +/- SD, Years	7(3.3-11.8) 7.6+/-4.6	7(2.8-11) 7.3+/-4.6	n.s
MTX dosage, Median (IQR); Mean +/- SD, mg/kg/week	12.5(10-16.2) 13.5+/-5.3	13.1+/- 4.5 13.3 +/- 4.5	n.s
Disease duration, Median (IQR); Mean +/- SD, years	1 (0.4-2.1) 2.3+/-3	0.7(0.31-2.1) 1.8+/-2,7	n.s
JIA category			
RF-negative polyarthritis	203(49.7%)	159(50.5%)	n.s
RF-positive polyarthritis	19(4.6%)	31(8%)	P=0.048
Extended oligoarthritis	111(27%)	98(12.3%)	n.s
Psoriatic arthritis	28(22%)	9(12.3%)	n.s
Disease characteristic			
Number of active joints Median(IQR); Mean +/-SD	5(2-10) 6.1+/-7.2	5(3-11) 9+/-10	P=0.012
Number of tender joints Median (IQR); Mean+/-SD	5(2-8) 7.1+/-8.1	4(2-10) 8.7+/-10	P=0.009
Number of swollen Joints Median (IQR); Mean +/-SD	4(1.5-8) 6.1+/-7.2	4(2-9) 7.6+/-9.1	P=0.006
Number of joints with LROM, Median (IQR) Mean+/-SD	4(2-8) 6.7+/-7.2	5(2-10) 9.1+/-10.8	P=0.0004
Baseline JADAS, 2-10)Median(IQR) Mean +/-SD	14(9.5-19.7) 14.6+/-8.1	15.75(11.3-21) 16+/-7.2	P <0.001
Baseline ESR Median (IQR) Mean +/_SD	15(8-31) 21.4+/-19.3	18(10-36) 26+/-24	P=0.0003
Baseline CRP Median (IQR) Mean +/-SD	3.99(1-14) 12.1+/-22.8	5(2-14.3) 15.3+/-26.9	P=0.036
Baseline CHAQ Median (IQR) Mean +/-SD	0.5(0-1) 0.6+/-0.62	0.5(0.125-1.125) 0.7+/-0.64	P=0.0008

Continuous values were analyzed by t-test; categorical values were analyzed by □2-test. P values < 0.1 were outlined in the table.

3.1.3 Age at onset of disease

The age of onset of both cohorts was statistically not significant. The mean age (+/-SD) in the oral group was 7.6+/-4.6 years. The median age was 7 years with IQR of (3.3- 11.7) years, compared with mean age (+/-SD) of 7.3+/- 4.6 years and the median of 6.9 with IQR of (2.8-11.1) years in the sc group. (Tab. 5).

3.1.4 Age at start of treatment with methotrexate

Methotrexate treatment was started at a mean age (+/-SD) of 9.9+/-4.6 years in the oral group with median age of 10 years with range of (10-13.8 years) and at the age (+/-SD) of 9.4+/- 4.9 years in the SC patients with median of 9.9 years (IQR: 4.8-13.7 years). (Tab. 5).

3.1.5 Disease duration

The mean (+/-SD) disease duration in the oral patient's group was 2.3 +/- 3 years with median of 0.98 years (range of 0.38-2.9years). In the sc patient's group, the mean disease duration was 1.8 +/- 2.7 years with median of 0.68 years (IQR: 0.33- 2.1 years). It was statistically not significant. (Tab. 5).

3.1.6 Medical treatment before MTX

Most of the patients in the study sample of both groups received NSAIR with 95 % and 89 % in oral and sc patients respectively. Intraarticular steroid injections were done for 5.6 % of the oral population and 7.5 % in the sc population (Tab. 6).

Tab. 6: pretreatment medication

Medications	oral N=410	sc N=384	χ^2-test, odd's ratio [95%CI]
NSAIDs	391 (95.4%)	342 (89%)	P=0.0008
Oral Steroids	98 (23.9%)	96 (25%)	n.s
Intra articular steroids	23 (5.6%)	29 (7.5%)	n.s
Pulse steroids, n (%)	14 (3.4%)	24 (6.2%)	n.s.
Sulphasalazine	7 (1.7%)	2 (0.5%)	n.s.
Azathioprine	2 (0.5%)	1 (0.26%)	n.s

3.1.7 Articular character of the patients

As seen in Tab. 4, analysis showed significant statistical difference regarding the articular character of oral and sc cohorts. The number of active joints in the sc study population was significantly higher at base line compared to the oral group (p value= 0.012). Swollen joint count was also significantly higher in the sc cohort compared to the oral cohort (p=0.006). Tender joint count at baseline was more in the sc population then the oral population (p=0.009). 146 patients had no morning stiffness in those who received MTX orally and the remaining had morning stiffness in a mean of 35.9 minutes. while, 119 patients out of 384 who received MTX parenterally had no morning stiffness at baseline and the rest of the patients had it in a mean of 36.8 +/-53.7 minutes. So, the analysis of the articular character of patients, showed higher disease activity in the sc group at baseline.

3.1.8 Laboratory characteristic at baseline

About 50 % of our patients were ANA positive in both groups. HLA B27 counted positive in 9.5 % of oral cohort compared to 11.7 % in sc cohort. More than 90 % of involved patients were lack of information of CCP, since it's not routinely done in RF negative JIA. (Tab. 7). On the other hand, baseline ESR and CRP were statistically significant difference

with p value of (0.0003 and 0.036) respectively, indicating a probably higher inflammatory activity of sc group.

Tab. 7: Biomarker of the disease

		oral N=410	sc N=384	χ^2-test, odd's ratio [95%CI]
ANA	positive	205 (50 %)	219 (57 %)	n.s
	negative	190(46.3 %)	157 (40.9 %)	n.s
	lack of info	15 (3.7 %)	8 (2.08 %)	n.s
HLA B27	positive	39 (9.5 %)	45 (11.72 %)	n.s
	negative	303 (73.4 %)	287 (74.7 %)	n.s
	lack of info	68 (16.6 %)	52 (13.5 %)	n.s
CCP	positive	4(1%)	6 (1.5 %)	n.s
	negative	23 (5.6 %)	23 (5.9 %)	n.s
	Lack of info	383 (93.4 %)	355 (92.4 %)	n.s

3.2 Treatment efficacy

321 PedACR 30

According to PedACR 30 criteria, there was no significant difference between the response of treatment between oral and sc cohort at 3, 6 and 12 month of treatment in the observed as well as in the intention to treat population. At the 18th and 24th month of treatment, the response rate was higher in the sc cohort in the intention to treat population ($p<0.0001$: 2.6[1.8-3.7]) (Fig. 4, Tab. 8 & 9).

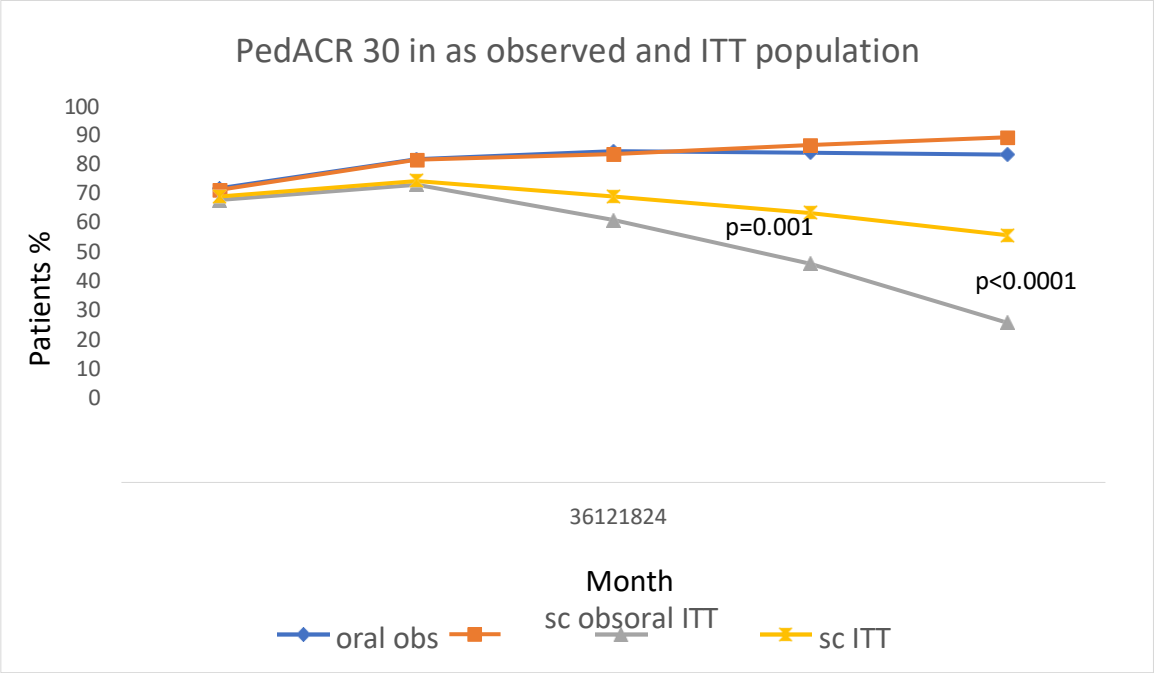

Fig. 4: PedACR 30 response among oral and sc cohort in the observed population and in the intention to treat population. obs=observed, ITT= intention to treat, sc= subcutaneous

Tab. 8: PedACR 30 response in oral and sc cohort as observed population

As observed analysis- ACR JIA 30					
		oral MTX N=410		sc MTX N=384	χ^2-test
month	Total pts no.	Responders (%)	Total pts no.	Responders (%)	P, odd's ratio [95%CI]
3	244	190 (77.9%)	320	248 (77.5%)	n.s
6	243	208 (85.6%)	282	241 (85.5%)	n.s
12	203	178 (87.7%)	276	240 (87%)	n.s
18	158	138 (87.3%)	245	219 (89.4%)	n.s
24	114	99 (86.8%)	210	192 (91.4%)	n.s

Tab. 9: PedACR 30 response among oral and sc cohort in Intention to treat (ITT) population

Intention to treat population –ACR JIA 30					
	oral MTX N=410		sc MTX N=384		χ^2-test
month	Total Pts no.	Responder (%)	Total Pts no.	Responder (%)	P, odd's ratio [95%CI]
3	254	190 (74.8%)	327	248 (75.8%)	n.s
6	264	208 (78.8%)	302	241 (79.8%)	n.s
12	256	178 (69.5%)	317	240 (75.7%)	n.s
18	238	138 (58%)	307	219 (71.3%)	P=0.001; 1.8 [1.26-2.6]
24	234	99 (42.3%)	293	192 (65.5%)	P<0.0001; 2.6 [1.8-3.7]

3.2.2 PedACR 50

As shown in Fig. 5, there is no difference between the percentage of patients who reached PedACR 50 through 24 month of treatment in the observed population. However, the response rate was statistically significant higher in the sc cohort at 18th month (p=0.02;1.5[1.07-2.15]) and 24th month (p<0.0001;2.4[1.65-3.34]) in the intention to treat population. (Fig. 5, Tab. 10 & 11).

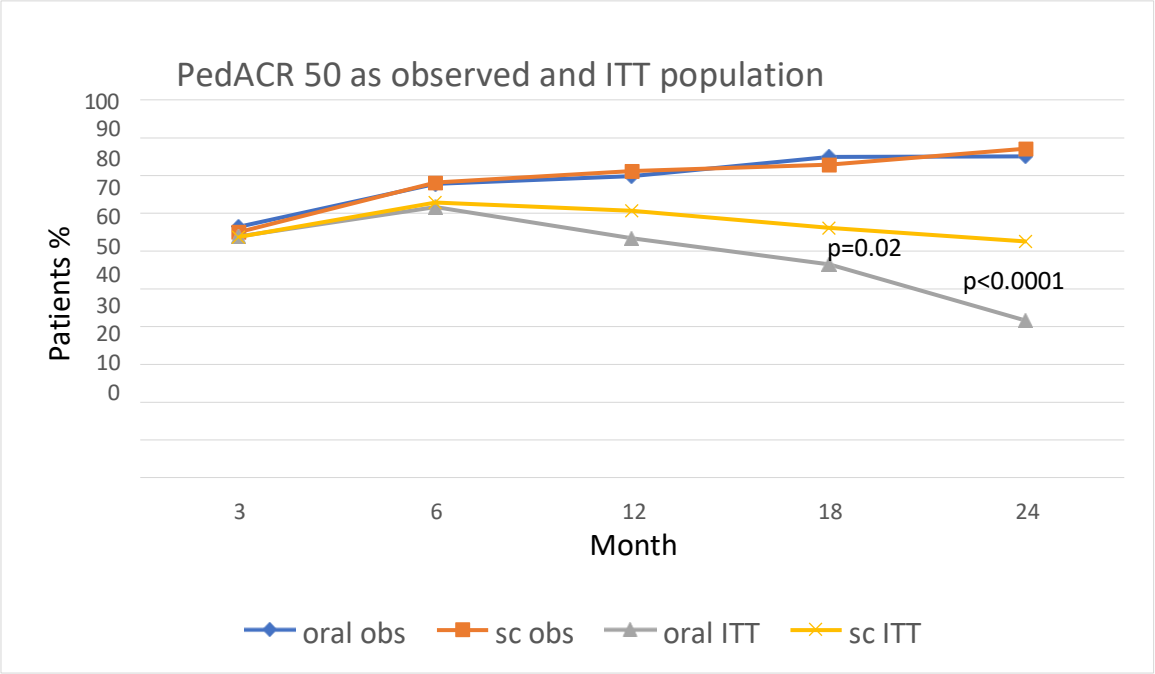

Fig. 5: PedACR 50 response among oral and sc cohort as observed and intention to treat. obs= observed, ITT= intention to treat, sc=subcutaneous. In the intention to treat population The response rate was statistically significant higher in the sc cohort at month 18 (p=0.02;1.5 [1.07-2.15]) and at month 24 (p<0.0001;2.4 [1.65-3.34])

Tab. 10: PedACR 50 Response among oral and sc cohort as observed and intention to treat (ITT) population

As observed analysis-ACR JIA 50					
		oral MTX N=410		sc MTX N=384	χ^2-test
month	Total pts no.	Responders (%)	`total pts no.	Responders (%)	P, odd's ratio [95%CI]
3	244	162 (66.4%)	320	208 (65.0%)	n.s
6	243	189 (77.8%)	282	220 (78.0%)	n.s
12	203	162 (79.8%)	276	224 (81.2%)	n.s
18	158	134 (84.8%)	245	203 (82.9%)	n.s
24	114	97 (85.1%)	210	183 (87.1%)	n.s

*Patients who discontinued due to inefficacy or intolerance were defined as non-responders

Tab. 11: PedACR 50 response among oral and sc cohort in intention to treat (ITT) population

Intention to treat population-ACR JIA 50					
	oral MTX N=410		sc MTX N=384		χ^2-test
month	Total Pts no.	Responder (%)	Total Pts no.	Responder (%)	P, odd's ratio [95%CI]
3	254	162 (63.8%)	327	208 (63.6%)	n.s
6	264	208 (71.6%)	302	220(72.8%)	n.s
12	256	162 (69.5%)	317	224 (75.7%)	n.s
18	238	134 (56.3%)	307	203 (66.1%)	P= 0.02; 1.5 [1.07-2.15]
24	234	97 (41.5%)	293	183 (62.5%)	P<0.0001; 2.4 [1.65-3.34]

323 PedACR 70

Statistical analysis according to pedACR 70 response, showed no statistical significant in response rate over 24-month observation in the observed population. There was a statistical significance at 18th and 24th month in favor of the sc cohort in the intention to treat population (p<0.0001; 2.3[1.64-3.32]) (Fig. 6, Tab.12 & 13).

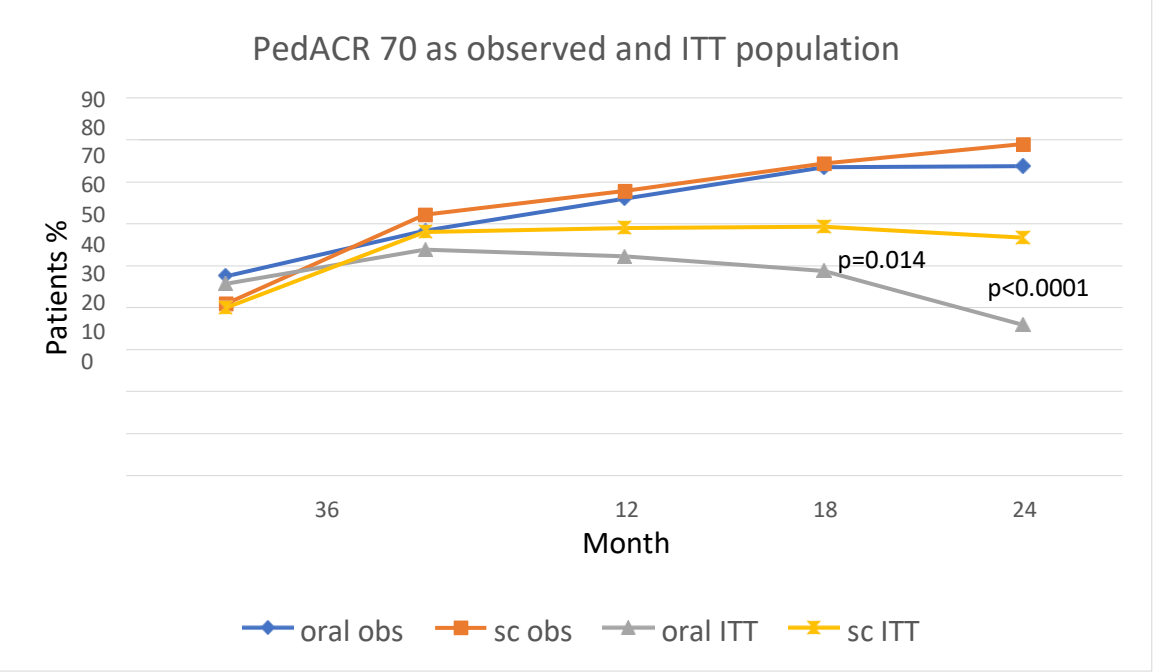

Fig. 6: PedACR 70 response among oral and sc cohort as observed and intention to treat. obs=observed, ITT= intention to treat, sc=subcutaneous. In the intention to treat population there was a statistical significance at month 18 (p=0.014; .5 [1.09-2.1]) and 24 (p<0.0001; 2.3 [1.64-3.32]) in favor of the sc cohort

Tab. 12: PedACR 70 response among oral and sc cohort as observed population

As observed analysis – ACR JIA 70					
		oral MTX N=410		sc MTX N=384	χ^2-test
month	Total pts no.	Responders (%)	Total pts no.	Responders (%)	P, odd's ratio [95%CI]
3	244	116 (47.5%)	320	131 (40.9%)	n.s
6	243	142 (58.4%)	282	175 (62.1%)	n.s
12	203	134 (66%)	276	187 (67.8)	n.s
18	158	116 (73.4%)	245	182 (74.3%)	n.s
24	114	84 (73.7%)	210	166 (79%)	n.s

Tab. 13: PedACR 70 response among oral and sc cohort in intention to treat (ITT) population

Intention to treat population – ACR JIA 70					
	oral MTX N=410		sc MTX N=384		χ^2-test
month	Total Pts no.	Responder (%)	Total Pts no.	Responder (%)	P, odd's ratio [95%CI]
3	254	116 (45.7%)	327	131 (40.1%)	n.s
6	264	142 (53.8%)	302	175 (57.9%)	n.s
12	256	134 (52.3%)	317	187 (59.0%)	n.s
18	238	116 (48.7%)	307	182 (59.3%)	P=0.014; 1.5 [1.09-2.1]
24	234	84 (35.9%)	293	166 (56.7%)	P<0.0001; 2.3 [1.64-3.32]

324 PedACR 90

As shown in Fig.7 and Tab. 14 & 15, analysis of PedACR 90 response rate showed statistical significant response to treatment for the sc MTX then oral MTX at 6th month (P=0.004;1.8[1.35-2.9]) in the observed population. Also, statistical significant different response rate in the intention to treat population at 6th month (P=0.0003;1.9[1.4-2.8]), 18th month (P=0.050;1.41[1.0-2.0]), and 24th month (P<0.0001; 2.02[1.4-2.3]) were observed.

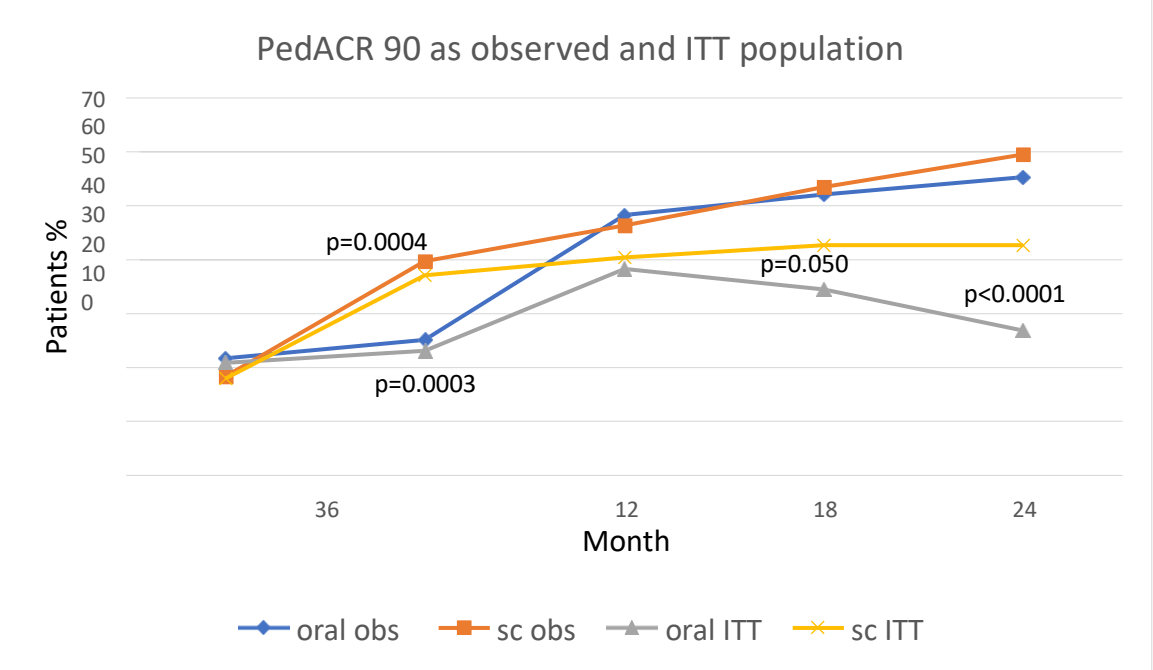

Fig. 7: PedACR 90 response among oral and sc cohort as observed and intention to treat

obs= observed, ITT =intention to treat, sc=subcutaneous. In the as observed population, the response rate was statistically significant higher in the sc cohort at month 6 (p=0.0004; 1.79{1.35-2.9]. In the intention to treat population the response rate was statistically significant higher in the sc cohort at month 6 (p=0.0003; 1.9[1.4-2.8]), month 18 (p=0.05; 1.41 [1.0-2.0]) and at month 24 (p<0.0001; 2.02 [1.4-2.3])

Tab. 14: PedACR 90 response among oral and sc cohort as observed population

As observed analysis – ACR 90					
	oral MTX N=410		sc MTX N=384		χ_2-test
month	Total pts	Responders no.(%)	Total pts	no. Responders (%)	P, odd's ratio [95%CI]
3	244	53(21.7 %)	320	59(18.4 %)	n.s
6	243	61(25.1 %)	282	112(39.7 %)	P=0.0004; 1.79{1.35-2.9]
12	203	98(48.3 %)	276	128(46.4 %)	n.s
18	158	82(51.9 %)	245	131(53.5 %)	n.s
24	114	63(55.3 %)	210	125(59.5 %)	n.s

Tab. 15: PedACR 90 response among oral and sc cohort in intention to treat (ITT*)* population

Intention to treat population – ACR 90					
	oral MTX N=410		sc MTX N=384		χ^2-test
month	Total Pts no.	Responder (%)	Total Pts no.	Responder (%)	P,odd's ratio [95%CI]
3	254	53(20.9 %)	327	59(18.0 %)	n.s
6	264	61(23.1 %)	302	112(37.1 %)	P=0.0003;1.9[1.4-2.8]
12	256	98(38.3 %)	317	128(40.4 %)	n.s
18	238	82(34.5 %)	307	131(42.7 %)	P=0.050;1.41 [1.0-2.0]
24	234	63(26.9 %)	293	125(42.7 %)	P<0.0001;2.02 [1.4-2.3]

325 JADAS10 Acceptable disease activity (JADAS acDA)

At baseline the rate of patients, who already had a JADAS ≤5.6 was significantly higher in the oral cohort.

Almost 80 % of observed patients have met the criteria to reach acceptable disease activity at 24th month of therapy in the as observed population. While, the response rate was much lower in the intention to treat population (Fig. 8).

The analysis also showed no statistical difference in response among oral and sc cohorts in the intention to treat and the observed population data. (Tab 16 & 17).

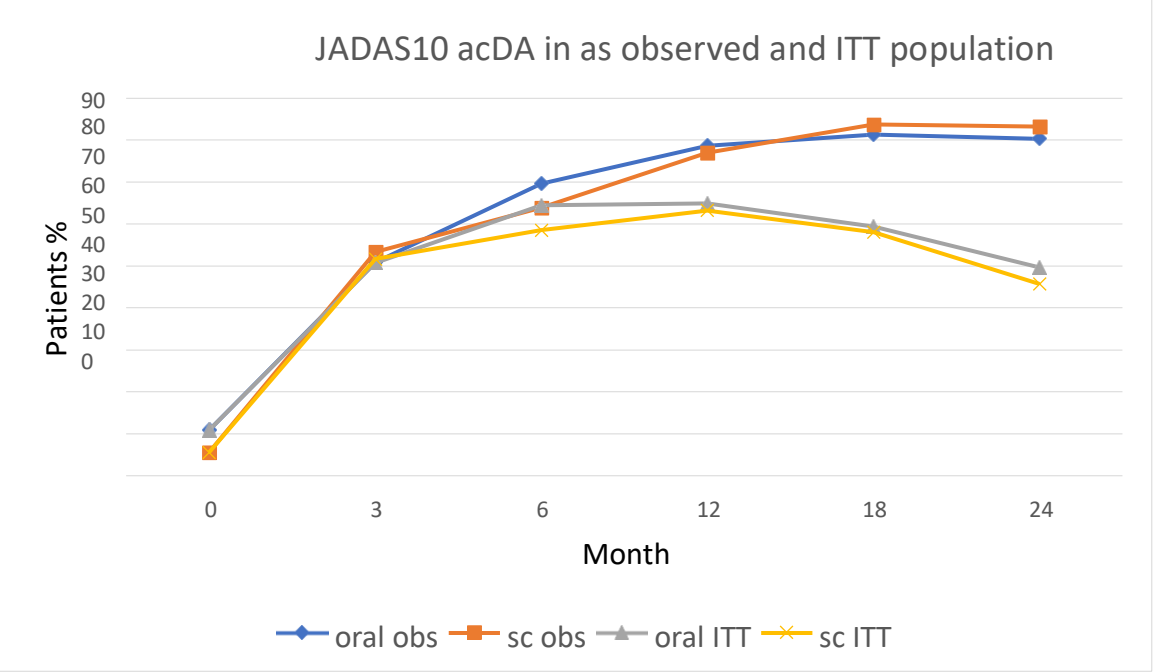

Fig. 8: JADAS10 Acceptable disease activity response among oral and SC Cohort as observed and intention to treat

obs=observed, ITT= intention to treat, JADAS acDA= JADAS acceptable disease activity, sc=subcutaneous.

Tab. 16: JADAS 10 Acceptable disease Activity (acDA) response among oral and sc cohort as observed population

As observed analysis-JADAS acDA					
		oral MTX N=410		sc MTX N=384	χ^2-test
month	Total pts no.	Responders (%)	Total pts no.	Responders (%)	P, odd's ratio [95%CI]
0	357	39(10.9%)	339	19(5.6%)	P=0.01;2.06 [1.1-3.6]
3	293	149(50.9%)	214	114(53.3%)	n.s
6	261	182(69.7%)	216	138(63.9%)	n.s
12	252	198(78.6%)	187	144(77%)	n.s
18	219	178(81.3%)	141	118(83.7%)	n.s
24	194	156(80.4%)	101	84(83.2)	n.s

Tab. 17: JADAS 10 Acceptable disease activity (acDA) response among oral and sc cohort in intention to treat (ITT) population

Intention to treat population –JADAS acDA					
	oral MTX N=410		sc MTX N=384		χ^2-test
month	Total pts no.	Responder (%)	Total pts no.	Responder (%)	P, odd's ratio [95%CI]
0	357	39(10.9%)	339	19(5.6%)	P=0.011;2.0 [1.7-3.6]
3	303	149(50.8%)	221	114(51.6%)	n.s
6	282	182(64.5)	236	138(58.5%)	n.s
12	305	198(64.9%)	228	144(63.2%)	n.s
18	299	178(59.5%)	203	118(58.1%)	n.s
24	314	156(49.7%)	184	84(45.7%)	n.s

3.2.6 JADAS 10 Minimal disease activity MDA

According to Fig. 9 and Tab 18 & 19, analysis of the data in our study showed no significant difference of response between oral and sc cohorts. In the intention to treat population at 6 months, response rate was higher in the oral cohort in the ITT analysis (p=0.05, OR 1.4[1.0-2.0]). Afterwards, results didn't show any statistical difference among the two groups. For the interpretation of these data, it has to be considered that the mean baseline JADAS10 was significantly higher in the sc cohort (16+/-7.2) than in the oral cohort (14.6 +/-8.1; p<0.001).

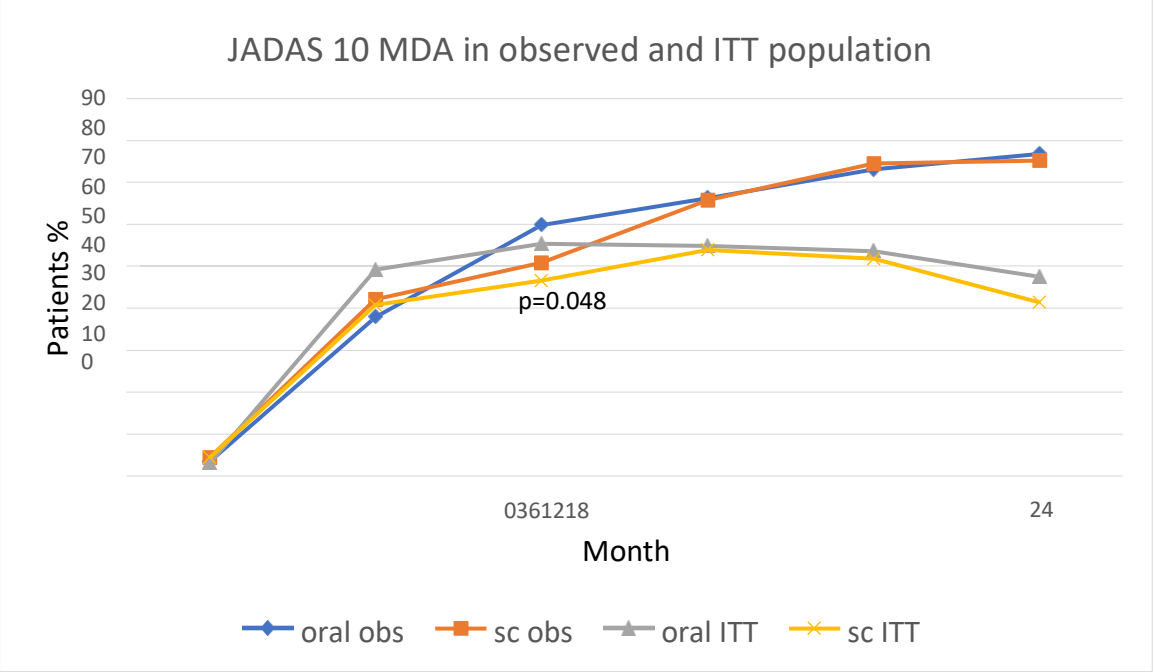

Fig. 9: JADAS10 response among oral and sc cohort as observed and intention to treat

obs= observed, ITT= intention to treat, MDA= minimal disease activity, sc=subcutaneous. In the intention to treat population statistically significant more patients showed a JADAS10 MDA in the oral cohort at month 6 (p=0.048; 1.4[1.0-2.0]).

Tab. 18: JADAS 10 minimal disease activity (MDA) response among oral and sc cohort as observed population

As observed analysis-JADAS MDA					
		oral MTX N=410		sc MTX N=384	χ^2-test
month	Total pts no.	Responders (%)	Total pts no.	Responders (%)	P, odd's ratio [95%CI]
0	357	12(3.4%)	339	15(4.4%)	n.s
3	293	111(37.9%)	214	90(42.1%)	n.s
6	261	156(59.8%)	216	110(50.9%)	n.s
12	252	167(66.3%)	187	123(65.8%)	n.s
18	219	160(73.1%)	141	105(74.5%)	n.s
24	194	149(76.8%)	101	76(75.2%)	n.s

Tab. 19: JADAS 10 minimal disease activity (MDA) response among oral and sc cohort in intention to treat (ITT) population

Intention to treat population –JADAS MDA					
	oral MTX N=410		sc MTX N=384		χ^2-test
month	Total Pts no.	Responder (%)	Total Pts no.	Responder (%)	P,odd's ratio [95%CI]
0	357	12(3%)	339	15(4.4%)	n.s
3	303	111(49.2%)	221	90(40.7%)	n.s
6	282	156(55.3%)	236	110(46.6%)	P=0.048;1.4[1.0-2.0]
12	305	167(54.8%)	228	123(53.9%)	n.s
18	299	160(53.5%)	203	105(51.7%)	n.s
24	194	149(47.5%)	184	76(41.3%)	n.s

327 JADAS10 Remission

At 6 months of, data showed statistically significant more patients reached JADAS remission upon oral MTX than upon subcutaneous MTX for both as observed and in the intention to treat population (P=0.013,1.7[1.1-2.8]) and (P=0.012,1.78[1.1-2.3]) respectively (Fig. 10, Tab 20 & 21). For the interpretation of these data, it has to be considered that the mean baseline JADAS10 was significantly higher in the sc cohort (16+/-7.2) than in the oral cohort (14.6 +/-8.1; p<0.001).

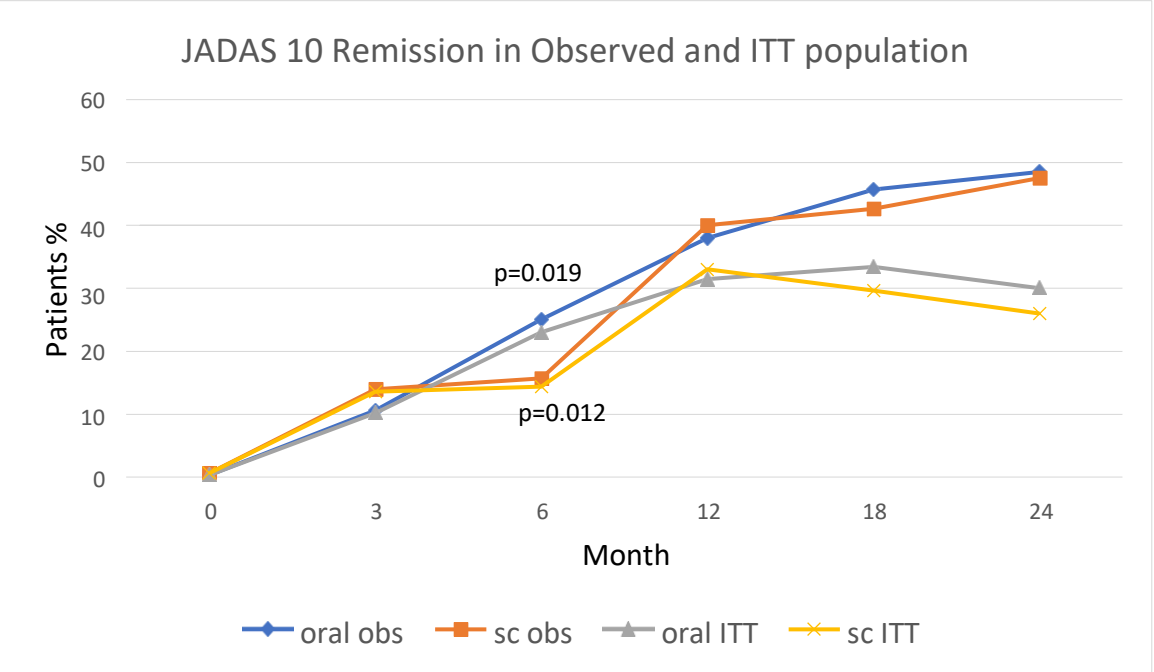

Fig. 10: JADAS10 Remission response among oral and sc cohort as observed and intention to treat. In the as observed and in the intention to treat population statistically significant more patients showed a JADAS10 Remission in the oral cohort at month 6 (p=0.019;1.77[1.12-2.8]) and (p=0.012;1.78[1.1-2.3]).

obs= observed, ITT= intention to treat, sc=subcutaneous.

Tab. 20: JADAS 10 remission response among oral and sc cohort as observed population

As observed analysis-JADAS remission					
		oral MTX N=410		sc MTX N=384	χ^2-test
month	Total pts no.	Responders (%)	Total pts.no	Responders (%)	P, odd's ratio [95%CI]
0	357	1(0.3 %)	339	2(0.6 %)	n.s
3	293	31(10.6 %)	214	30(14 %)	n.s
6	261	65(24.9 %)	216	34(15.7 %)	P=0.019;1.77[1.12-2.8]
12	252	96(38.1 %)	187	75(40.1 %)	n.s
18	219	100(45.7 %)	141	60(42.6 %)	n.s
24	194	94(48.5 %)	101	48(47.5 %)	n.s

Tab. 21: JADAS 10 remission response among oral and sc cohort in intension to treat (ITT) population

Intention to treat population –JADAS remission					
	oral MTX N=410		sc MTX N=384		χ^2-test
month	Total pts no.	Responder (%)	Total pts no.	Responder (%)	P, odd's ratio [95%CI]
0	357	1(0%)	339	2(0.6%)	n.s
3	303	31(10.2%)	221	30(13.6%)	n.s
6	282	65(23%)	236	34(14.4%)	P=0.012;1.78[1.1-2.3]
12	305	96(31.5%)	228	75(32.9%)	n.s
18	299	100(33.4%)	203	60(29.6%)	n.s
24	314	94(29.9%)	184	48(26.1%)	n.s

3.3 Kinetic of response

Kaplan Meyer analysis were performed to analyze the kinetic of reaching the response to MTX.

In our study, the survival time of Kaplan-Meier analysis was defined as reaching JIA- ACR 30, 50,70 and 90, JADAS-minimal disease activity or JADAS-remission. Patients who discontinued MTX due to inefficacy or intolerance, who switched route of administration or started a biologic were censored.

3.3.1 ACR 30 response

As shown in Fig. 11, there was no statistical significant difference between oral and sc cohort in the observed and intention to treat population after 1 year of treatment in term of kinetic of response (61.9 % orally vs 59.75 parenterally, p=0.633).

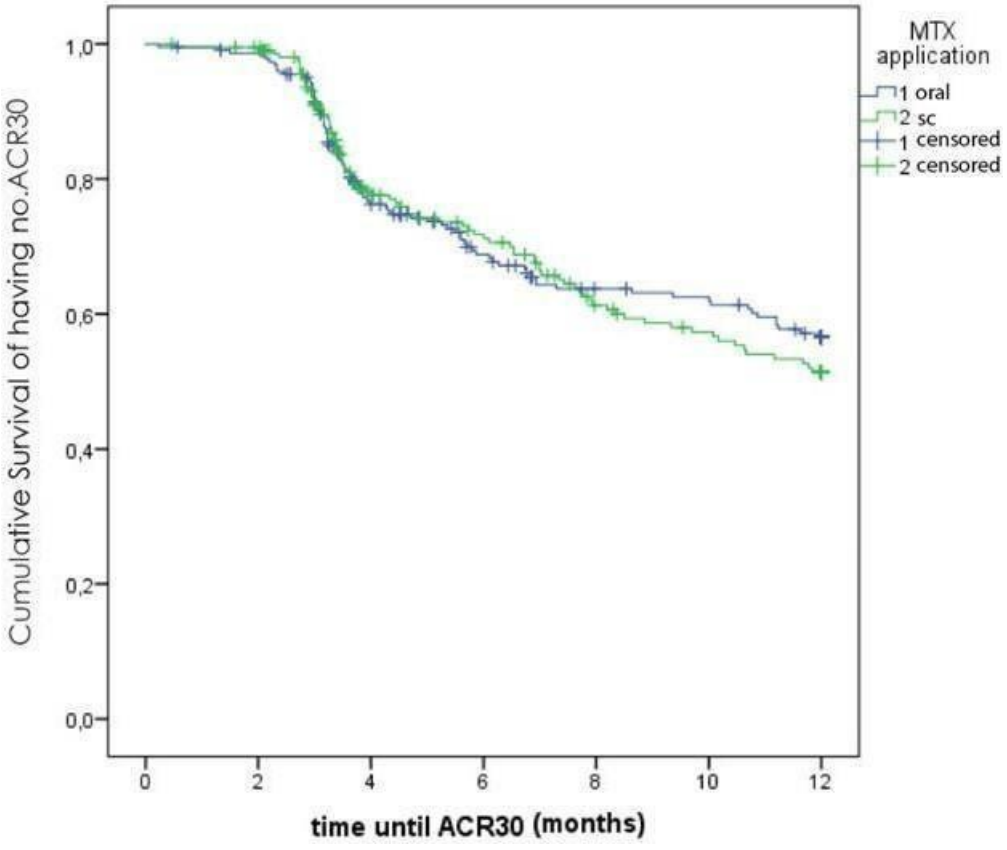

Fig. 11: Kaplan-Meyer until first year of definition of ACR 30

3.3.2 ACR 50 response

After the first year of treatment, neither the rate of patients who reached the definition of ACR 50 nor the velocity of response in both oral and sc cohort in the as observed analysis and in the intention to treat populations were statistically significant (48.2 % orally vs 44.5 % sc, p=0.440) (Fig. 12).

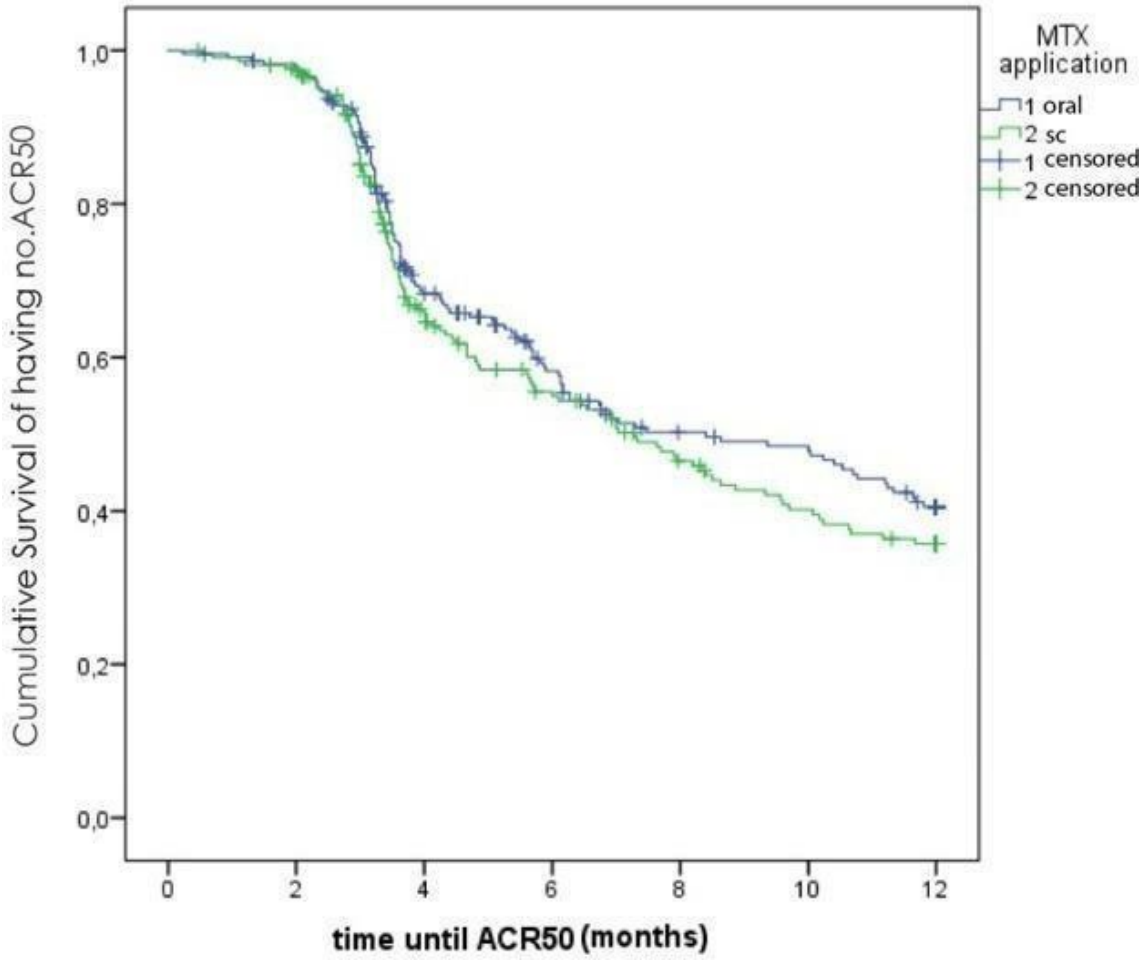

Fig. 12: Kaplan-Meyer until definition of ACR 50 during the first year of treatment

3.3.3 ACR 70 response

As shown in Fig.13, Kaplan-Meier analysis showed no statistical difference between the oral and sc cohort in both as observed and in the intention to treat population in reaching definition of ACR 70 after first year of treatment (51.8 % orally vs 52.6 % sc, p=0.861).

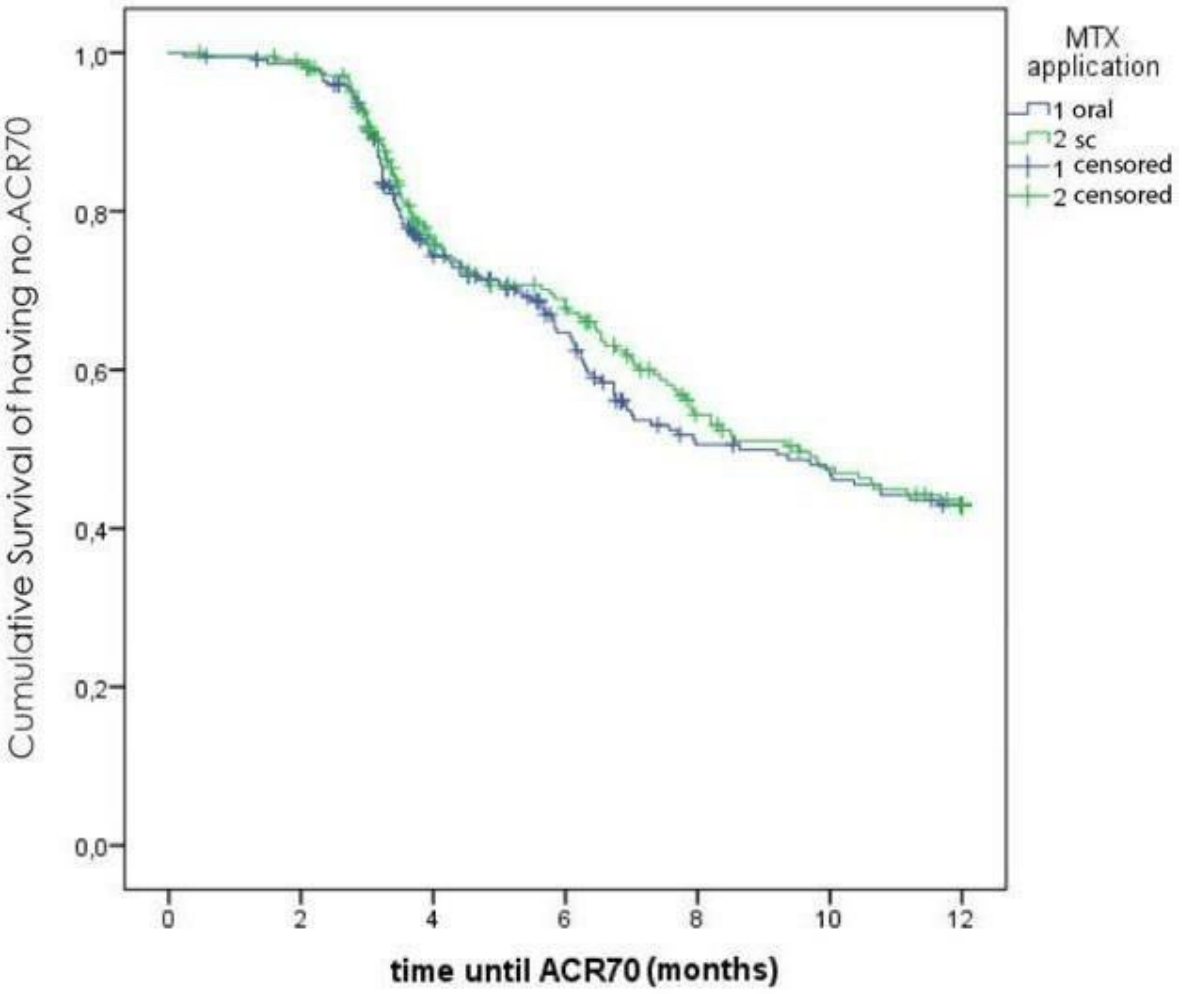

Fig. 13: Kaplan-Meyer until definition of ACR 70 during the first year of treatment

3.3.4 ACR 90 response

By definition of ACR 90, A tendency of earlier response in the sc cohort was visible which did not reach statistical significance in both populations (62.8 % orally vs 69.7 % sc, p=0.130). This effect seems to set in at about 3 months of treatment but was balanced until the end of first year.

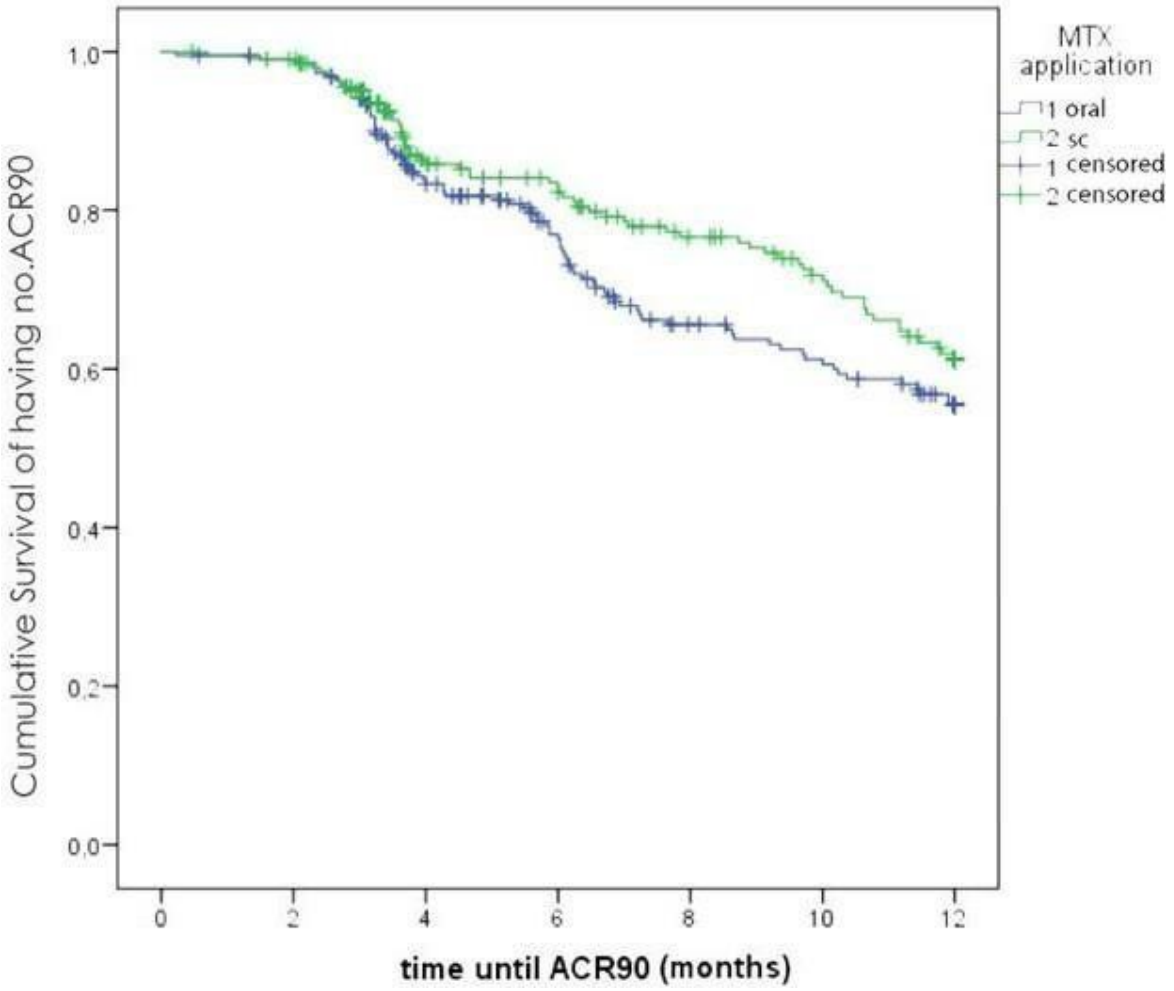

Fig. 14: Kaplan-Meyer until definition of ACR 90 during the first year of treatment

3.3.5 JADAS10 Acceptable disease activity response (acDA)

There was no statistical difference in survival time between oral and sc cohort in as observed and intention to treat population in reaching definition of acceptable disease after the first year of treatment (35.4 % orally vs 38.2 % sc p=0.210).

Again, in the sc cohort JADAS-acDA seems to reach earlier significance at month 5 to 6 but the effect was balanced at month 12.

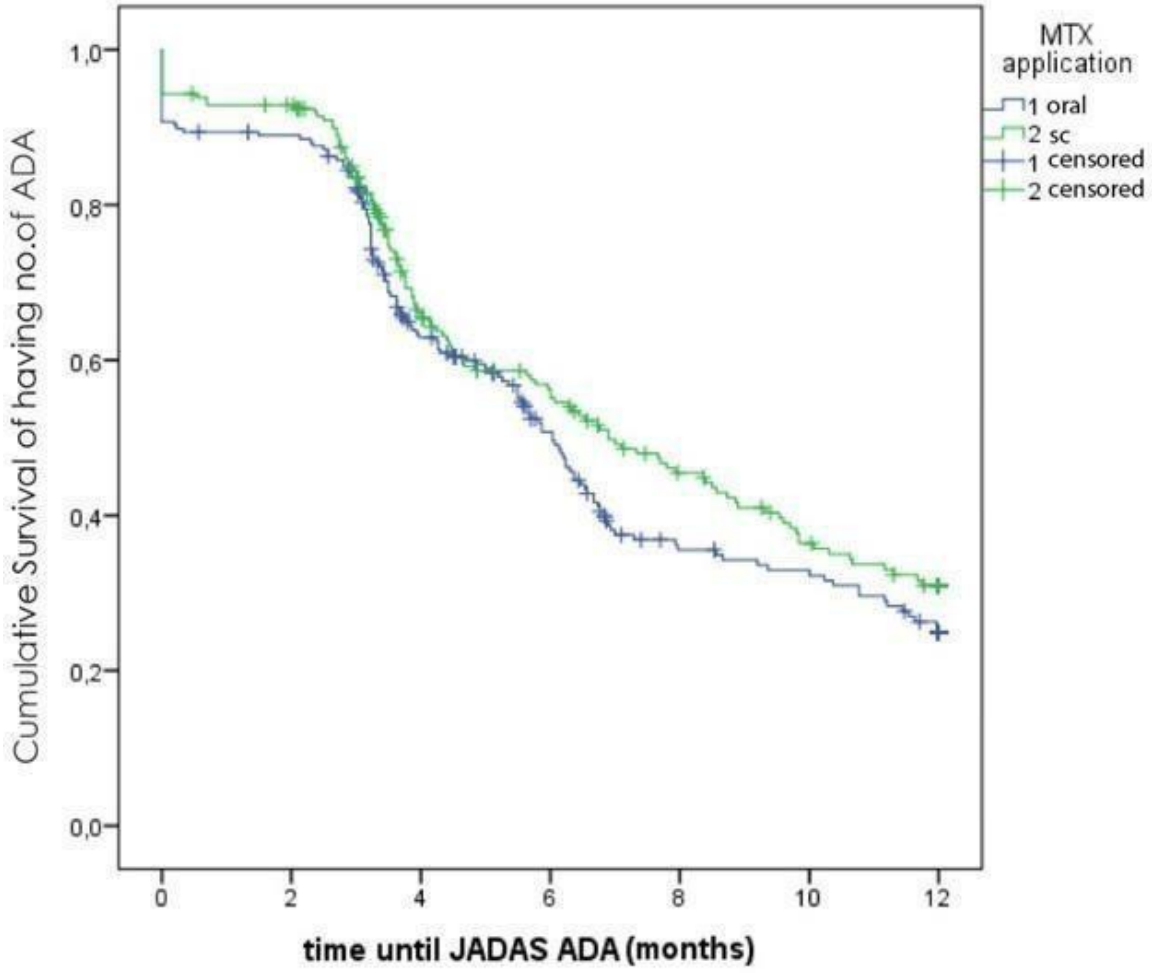

Fig. 15: Kaplan-Meyer until definition of JADAS acDA during the first year of treatment

3.3.6 JADAS10 Minimal disease activity response (MDA)

Fig. 16 shows no superiority of sc MTX over oral MTX in reaching definition of minimal disease activity during the first year of treatment in as observed and intention to treat population (44.2 % orally vs 47.9 % sc, p=0.440).

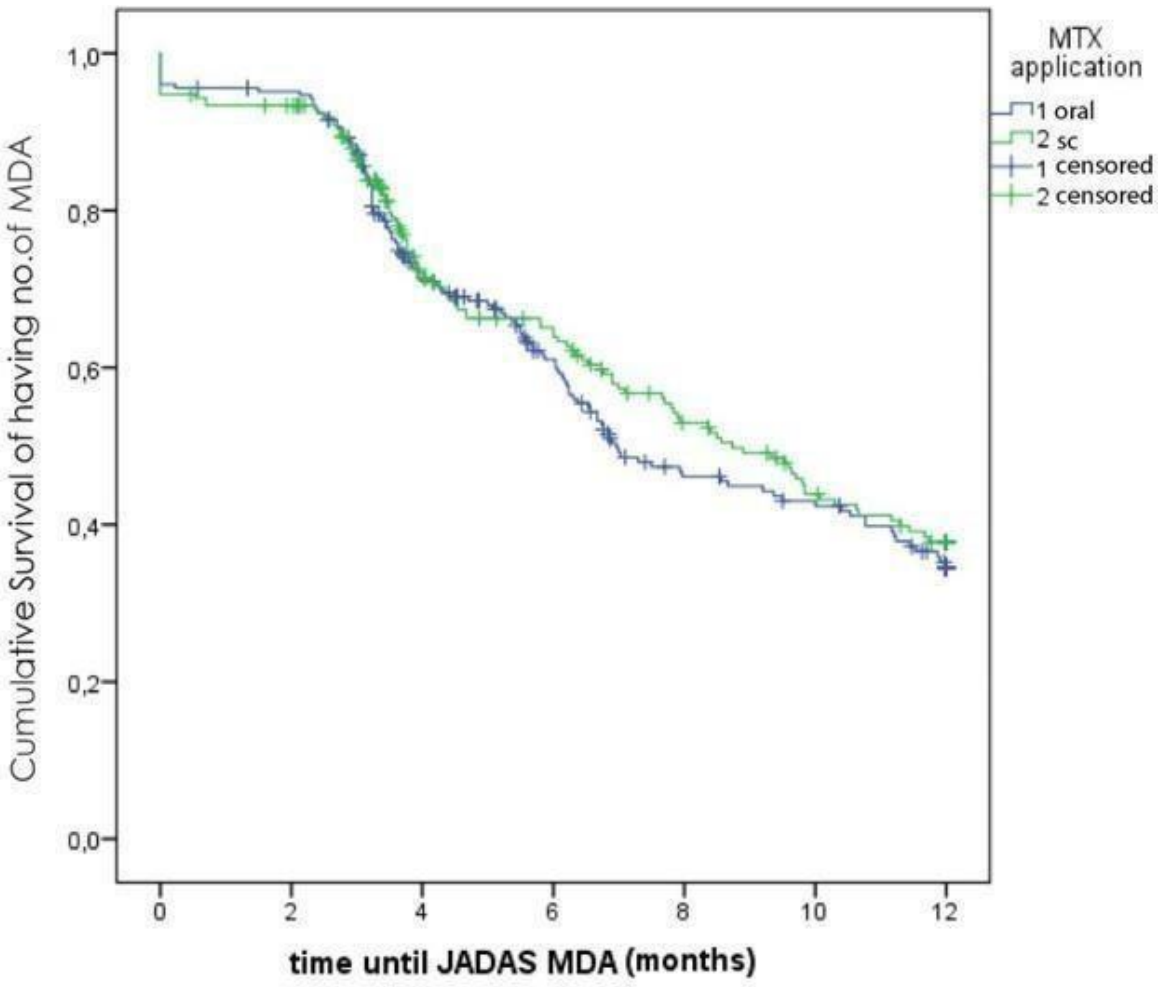

Fig. 16: Kaplan-Meyer until definition of JADAS MDA during the first year of treatment

3.3.7 JADAS10 Remission response

Fig. 17 shows that the survival time of the oral and the sc cohorts in as observed and in intention to treat population to reach definition of JADAS10 remission during the first year of treatment was statistically not significant (74.3 % orally vs 80.1 % sc, p=0.152).

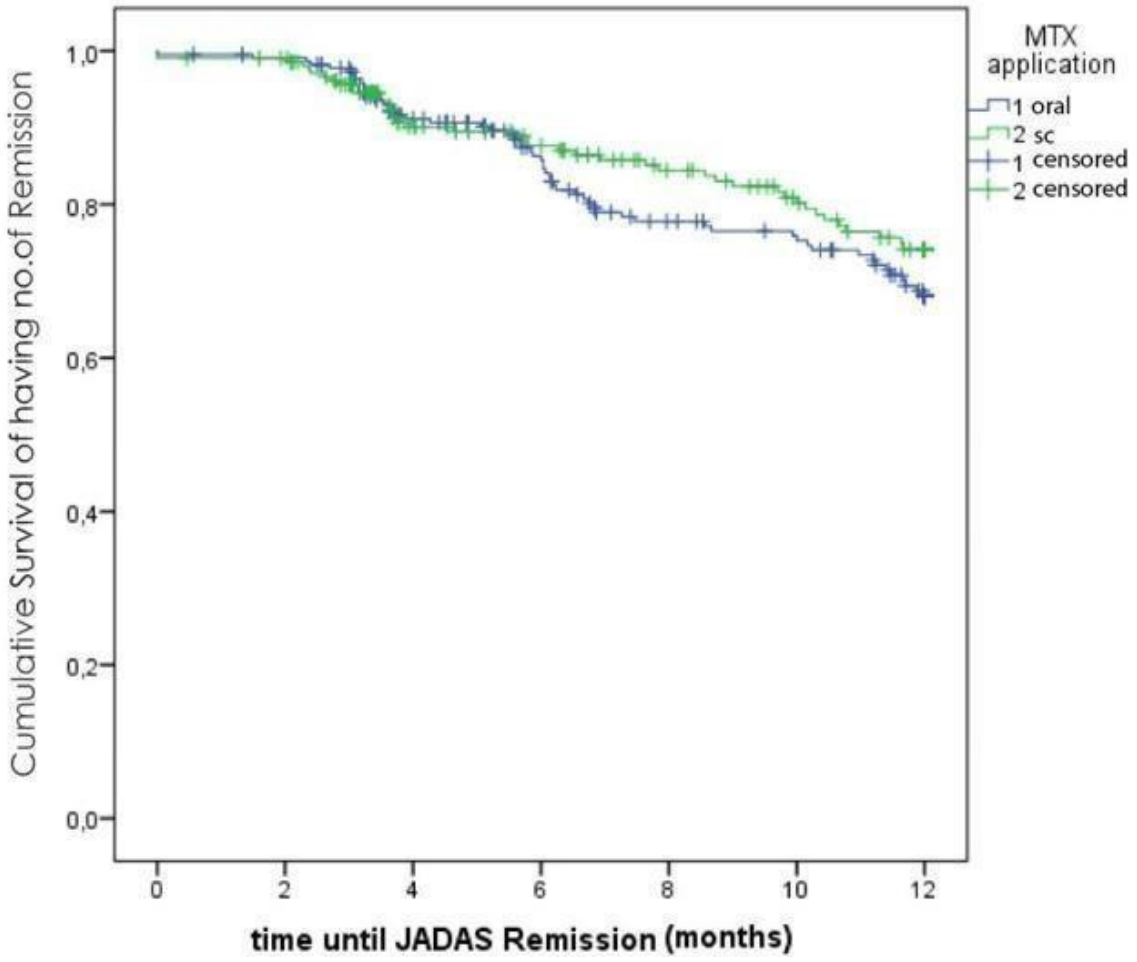

Fig. 17: Kaplan-Meyer until definition of JADAS Remission during the first year of treatment

3.4 Safety

There were side effects reported as adverse events through the treatment of MTX (Tab. 22). Analysis of our data showed that there was no significant difference between oral and sc cohorts in term of neutropenia, gastritis, loss of appetite or the occurrence of serious adverse events. On the other hand, there were significantly more adverse event such as URTI, nausea, vomiting and increased liver enzymes in the sc cohort.

Tab. 22: Side effects of MTX among oral and sc Cohort

		oral n=410	sc n=384	χ^2-test P, odd's ratio [95%CI]
AE	Viral infections			
	Flue	2 (0.5%)	4 (1%)	n.s
	Gingivitis	0 (0%)	3 (0.8%)	n.s
	Lymphadenitis	1 (0.2%)	0 (0%)	n.s
	URTI	23 (5.6%)	37 (9.6%)	P=0.032;1.7[1.0-3.08]
	Varicella	1 (0.2%)	3 (0.8%)	n.s
	Bronchitis	11 (2.7%)	9 (2.4%)	n.s
	Gastroenteritis	9(2%)	15 (4%)	n.s
	Bacterial infection			
	Tonsillitis	6 (1.5%)	7 (1.8%)	n.s
	Otitis media	3 (0.7%)	5 (1.3%)	n.s
	UTI	4 (1%)	3 (0.8%)	n.s
	GIT side effects			
	Nausea and vomiting	144 (35%)	198 (51%)	P>0.000;1.9[1.47-2.6]
	Increased liver enzyme	43 (10%)	71 (18.4%)	P=0.0001;1.9 [1.3-2.9]
	Loss of appetite	3 (0.7%)	5 (1.3%)	n.s
	Diarrhea	5 (1.2%)	3 (0.8%)	n.s
	Gastritis	2 (0.5%)	4 (1%)	n.s
	Others			
	Leukopenia	4 (1%)	6 (1.6%)	n.s
	Leukemia	1 (0.5%)	1 (0.26%)	n.s
SAE	Patients with at least one SAE	2(0.5%)	0(0%)	n.s
	Fracture	4(1%)	3(0.8%)	n.s
	Infection	5(1.2%)	3(0.8%)	n.s
	Neutropenia	0(0%)	3(0.8%)	n.s

URTI= upper respiratory tract infection, AE=adverse events, SAE=serious adverse events, UTI=urinary tract infection, sc=subcutaneous

3.5 Discontinuation

Out of 794 patients involved in the study, 175 patients discontinued MTX treatment. The main cause was due to inefficacy counting twenty percent in oral cohort vs. 20.5 % in sc MTX. 64 patients received MTX orally discontinued MTX because of adverse events, which is comparable to patients who received treatment parentally. Other reasons for discontinuation are listed in Tab. 23.

Tab 23: Reason for discontinuation MTX in patients taking oral and Subcutaneous MTX

	Oral MTX N=410	SC MTX N=384	2-test
Total No. of discontinuation	90 (23%)	85 (20.7%)	n.s
Total No. of AEs	64 (15.6%)	62 (15%)	n.s
Total No. Inefficacy	82 (20%)	84 (20.5%)	n.s
Total No. of remission	29 (7%)	27 (6.6%)	n.s
Discontinuation on demand	54 (13%)	54 (13%)	n.s
Discontinuatio from the n study due to starting biologics.	77 (18.7%)	72 (18.7%)	n.s
Others	84 (20.4%)	77 (19%)	n.s
In some patients, more than one reason for discontinuation were given, resulting in overlapping, no main reason was pointed.			

4. Discussion

The aim of this study was to analyze if there is a superiority of parenteral MTX over oral MTX in term of strength or kinetic of response, the velocity of response and safety. In this study, the cohort of patients was collected from the German Biker Registry founded in 2001, which has been collecting data prospectively to follow the efficacy and safety of long term treatment with MTX from 2005 on, the year in which MTX became approved for treatment of polyarticular JIA in Germany. Data of patients admitted to the registry until July 2011 have been analyzed. Recruiting was stopped because the target of 1500 JIA patients was reached of whom 1000 had polyarticular JIA.

Methotrexate is an effective second-line agent currently used to treat rheumatoid arthritis (RA) and Juvenile idiopathic arthritis (JIA). A controlled study for comparison of efficacy and safety of oral to parenteral MTX in JIA is lacking. Although it may have modest immunosuppressive effect at the doses used in RA, the rapid onset of action and predictability of disease flare after discontinuation suggest that its anti-inflammatory properties contribute to its efficacy. MTX appears to interfere directly with action of pro- inflammatory cytokines such as IL-1. It also increases the release of endogenous adenosine by connective tissue cells, which might decrease neutrophil adherence to endothelial cells and fibroblast. The effect of MTX on cytokines production is particularly important in RA, since factors like IL-1 and TNFα likely play a major role in the perpetuation of synovial inflammation. IL-1 and TNFα are present in inflammatory joint effusion and are derived primarily from synovial macrophages. This will result in lower level of collagenous production by adjacent fibroblast-like synoviocytes. IL-1 and TNFα are also potent inducer of metalloproteinase gene expression by FLS (Alvaro-Gracia JM,1990). Data suggest that altered collagenase: TIMP 1 (tissue inhibitor of metalloproteinase 1) ratio contribute to MTX mediated joint protection in RA (Gary S, et al.,1994).

The total number of patients in our retrospective study was 794 patients, who were diagnosed as JIA, according to ILAR definition and with JIA categories for which MTX is recommended (RF negative polyarthritis, RF positive polyarthritis, Extended oligoarthritis and Psoriatic arthritis) and who fulfilled all inclusion criteria and none of the exclusion

criteria. Endpoint of analysis was reached if patients discontinued MTX, switched mode of application, or started on biologic treatment (F M Balis, et al.,1988).

Two set of patients were analyzed; 1) as observed analysis, including patients on treatment, 2) Intention to treat analysis; including patients who reached endpoint and were labelled as non-responders. MTX was given almost equally in dosing in both cohorts (oral and parenteral) in mean of 12.5 mg/kg/week +/- 5.3 for oral patients. The majority of our patients were female and had RF negative polyarthritis. Disease duration was slightly longer in the oral population than the sc population (p=0.04). The analysis of demographic, clinical, articular and laboratory characteristics were made at baseline. Analysis of our data showed that patients with more severe clinical characteristics, including active joints, number of tender joints, number of swollen joints, and joints with limited range of motion, were started on parenteral MTX more often. Patients who were started on sc MTX also had higher laboratory indices of active disease at baseline including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). They also had higher values of JADAS and CHAQ. These differences must be considered for the discussion of the result (Tab. 4 and 5).

Evaluation of response to treatment in our study was based on PedACR score 30/50/70 and 90 which based on improvement from baseline on 3 out of 6 variables (physical global assessment, parent's global assessment, number of active joints. Number of limited range of motion, CHAQ and ESR with no more than one of the remaining variables worsened by more than 30%) and on JADAS.

One trial for 563 patients, whom were extracted from the PRINTO database, to evaluate the predictor of poor response to 6-month course of methotrexate in polyarticular patients (RF negative, psoriatic arthritis and enthesitis related arthritis excluded) concluded that the subgroup of patients with longer disease duration, ANA negative, higher disability and presence of wrist activity were significantly associated with a poorer response to a 6 month MTX course (CA.Wallace,et al., 2011).

After 24 month of treatment with MTX, analysis showed no statistical significant difference in number of patients who reached definition of PedACR 30, 50 and 70 and JADAS10

acceptable disease activity and JADAS10 minimal disease activity in the observed population. Number of patients in the observed population who reached definition of PedACR 90 and JADAS10 remission response after 6 month of treatment showed superiority of sc MTX over oral MTX (p=0.0004) (Fig. 7 and 10). In the intention to treat population, sc MTX was superior over oral MTX at 18th and 24th month of treatment in reaching PedACR 30, 50, 70 responses. Sc MTX was also more effective in reaching PedACR 90 response starting at 6th month of treatment. There was also statistical significant difference at 6th month of treatment with MTX in reaching JADAS10 minimal disease activity and JADAS10 remission response in the intention to treat population, favoring sc MTX.

In Kaplan-Mayer analysis, endpoints were defined as reaching JIA-ACR30-90, JADAS-minimal disease activity or JADAS-remission. Patients who discontinued MTX due to inefficacy or intolerance, who switched route of administration or started biologics were censored. No difference was shown in term of intensity or velocity of reaching JIA-ACR or JADAS response detected in both groups.

Analysis by Kaplan-Meier, showed no statistical significant between oral and sc MTX in reaching definition of PEDACR 30,50,70 and 90 and JADAS10 acceptable disease activity, minimal disease activity and remission in term of kinetic of response. Three prospective study, the TRIMECA trial, the MD-pedigree study and the PharmaChild registry, had included 79 patients to compare the efficacy of oral vs sc methotrexate in inducing sustained disease remission in children with oligoarthritis. Efficacy was assessed by comparing the rate of inactive disease (ID) and clinical remission on medication (CRM) at 12 months, the rate of patients changing the route of MTX administration or requiring a biologic medication due to treatment failure. Safety was assessed by comparing the frequency of treatment interruption due to side effects of MTX. Results showed increased efficacy of MTX in inducing sustained disease remission when it is administered subcutaneously after 12 month of treatment.

This small study supports our results despite the lower number of patients involved in the study. Another prospective study of 79 patients conducted in Italy to compare efficacy in inducing sustained disease remission in children with oligoarthritis which showed more

children receiving sc MTX achieved ID (inactive disease) (84.9% vs 43.8%, P<0.001) and CRM (clinical remission on medication) at 12 months (22.9% vs 6.5%, P=0.024) (Chiara Trincianti1, et al. 2017).

Another study, a short-term, prospective, open label trial in a single pediatric rheumatology center in Italy, enrolled 257 JIA patients (127 treated orally and 130 intramuscularly). All patients received 10mg/m^2 of MTX each week. The response rate after 6 months of MTX therapy was 58% in the oral group and 61% in the intramuscular group, with similar results in terms of safety and efficacy (A.Ravelli et al, 1998).

55 JIA patients were enrolled in retrospective study to document the clinical practice based on the treat-to-target approach in order to support the concept that better therapeutic effect achieved with an optimal dose of parenteral MTX is associated with clinically acceptable adverse effects comparable to those reported for oral treatment. 81.8% were started on parenteral MTX and results were. Patients were evaluated every 3 month for 12 months. They concluded that, subcutaneous MTX is associated not only with a high response rate within the first 12 months of treatment, but also with a relatively low rate of significant adverse effects that would lead to the treatment termination. It allows early recognition of MTX non-responders and addition of biologic therapy but longer term evaluations is needed to address the ongoing extension of the study

Comparing this result to the adult population, one prospective study conducted in rheumatology clinic under the department of medicine of Bangabandhu Sheikh Mujib Medical University from December 2004 to December 2005 to assess the efficacy, safety and compliance of subcutaneous methotrexate (MTX) in active rheumatoid arthritis (RA) patients. A total of 92 active rheumatoid arthritis patients according to American College of Rheumatology (ACR) criteria were recruited for the trial for six months. Among them 46 cases belonged to injectable MTX group and 46 cases belonged to oral MTX group. The outcome of response rate was significantly higher for the minimal ACR20 in the subcutaneous group (93% vs 80%, P=0.02) and the same for somewhat higher ACR50 response (89% vs 72%, P=0.03). This superiority was not observed for ACR70 (11% vs 9%, P=0.72).

Adverse events were analyzed in our study which showed no significant difference in number of patients who developed neutropenia, loss of appetite or gastritis in both cohorts. However, there was increased number of patients who developed viral upper respiratory tract infection, in the sc group compared to the oral MTX group (9.6% vs 5.6%, P=0.032). Similarly, patients who received sc MTX were more prone to develop nausea and vomiting then those who received the MTX orally (51% vs 35%, P>0.0001). Sc MTX lead to more hepatotoxicity and increased liver enzyme then oral MTX since 43(10%) patients showed to have increased liver enzyme during the management duration compared to 71(18.4%) patients for those who had MTX parenterally (P=0.0001). These observation was also made in our analysis where JIA patients on sc MTX had a higher adverse event rate of vomiting and elevated transaminases than those in the oral MTX cohort.

One previous observational study of 411 patients comparing efficacy and safety of oral and parenteral methotrexate concluded that, patients with subcutaneous MTX treatment showed a higher rate of adverse events then the oral cohort without reaching significant differences. One of the methods of treating methotrexate intolerance in juvenile idiopathic arthritis is using eye movement desensitization and reprocessing (EMDR). This open prospective study was performed in Garmisch-Partenkirchen in Germany, where 14 patients had MTX intolerance which was determined using the Methotrexate Intolerance Severity Score (MISS) questionnaire and health related quality of life was determined using the PedQL, at 3 time points.

Patients were treated using the tenderized EMDR protocol with 8 sessions over time of 2 weeks. They concluded that MTX intolerance in children with JIA can effectively be treated using an EMDR protocol, with lasting effect over 4 months. This intervention could potentially increase quality of life in affected patients and enable continued treatment with MTX.

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During treatment with MTX, number of patients had to discontinue medication in both cohorts (23% from oral population versus 20.7% from sc population) due to different reasons. There was no statistical difference in the analysis of causes in both populations. The causes were due to: development of side effects, inefficacy, remission, starting biologic treatment, discontinuation upon patient's desire or other reasons. Some patients had more the one reason to stop medication.

By looking at the Kaplan-Meyer ACR 90 response, there was earlier response in the sc cohort than the oral cohort, this might be due to more patients change route of administration from oral to sc or biologic medication was added at this point.

There are several limitations in our study. First, it is an open and nonrandomized study. Second, we could not be sure about the compliance of MTX when it is taken orally by the patient comparing to injection given by parents. A number of patients changed from oral to subcutaneous application or from subcutaneous to oral MTX. The reasons for this were

not recorded on our data. Finally, based on our baseline disease characteristics, patients with more severe active disease were started on parenteral MTX more frequently. However, some centers predominantly use one route of administration; others use oral and subcutaneous MTX equally.

In conclusion, result of our retrospective study showed some favor of sc Methotrexate in term of efficacy but not safety. Probably due to higher blood levels reached with injected Methotrexate typical side effects such as nausea, vomiting, and elevated transaminases were significantly more frequent upon sc than upon oral application. Such side effects markedly limit the continuation of treatment and must therefore been seen as an important disadvantage.

Furthermore, oral Methotrexate avoids injections, which is especially important for younger children and finally it must not withhold that sc. Methotrexate is much more expensive with yearly cost of about 1000 € compared to 100 € for oral Methotrexate. For definite recommendations for the sc. route of application of MTX treatment, controlled randomized prospective studies are required in children and juvenile patients.

5. Summary

Juvenile idiopathic arthritis is an umbrella term used to describe different group of diseases with arthritis starting before the age of 16 years. It is the most chronic rheumatic illness in children and it is responsible for short and long-term disability. MTX has shown to be the most common first-line disease modifying antirheumatic drugs (DMARDs) according to several national treatment guidelines. MTX is given once weekly through two different route of administration, oral and subcutaneous. Until now there is no conclusion as to which route is to be preferred in term of efficacy and safety.

The aim of this comparative retrospective study is to analyze the hypothesis of superiority of sc MTX over oral MTX in term of kinetic of response, velocity of response and safety. The cohort of patients was collected from the German Biker Registry founded in 2001. Data of patients admitted to the registry until July 2011. Total number of patients included in our study who fulfilled inclusion and exclusion criteria were 794 patients. 410 patients received MTX orally and 384 patients received it parenterally. Two set of analysis were performed. “As observed population analysis” and “Intention to treat population analysis”. Patients who had more active and sever disease were started on parenteral MTX based on analysis of the baseline laboratory and clinical characteristics of both groups. Evaluation of response was made based on the American Collage of Pediatric Rheumatology (PedACR) criteria and the Juvenile Disease Activity Score (JADAS10). The kinetic of reaching the response to MTX was analyzed using Kaplan-Meyer analysis. After 24 month of treatment with MTX, results showed no statistical significant difference in the number of patients who reached definition of PedACR 30, 50, 70 and JADAS10 acceptable disease activity between oral and sc population in the observed cohort. There were more patients reaching PedACR90 ($p=0.0004$) and JADAS remission ($p=0.019$) in the sc cohort after 6 months of MTX treatment in the observed population analysis. Whereas, there was no statistical significance in the kinetic of reaching the response to MTX by Kaplan-Meyer analysis in reaching PedACR 30,50,70 and 90 and JADAS10 acceptable disease activity, minimal disease activity and remission between both cohorts. Results of adverse events analysis showed more side effects with parenteral MTX compared to oral MTX. These results could be related to the sc MTX or to the high disease activity for those patients who were started on sc MTX. There are number of limitation in

our study. First, it is an open retrospective nonrandomized study. Second, compliance remain always questionable, especially with oral administration, because it can be easily missed by the patient comparing to the parenteral route, which is mainly given by the caretaker. Third, the reason of changing the mode of administration was not recorded on our registry. Finally, there is no clear guidelines when to start oral or sc MTX While some centers use one route predominantly, others use the oral and subcutaneous route equally. In conclusion, this retrospective study could recommend sc over oral MTX in management of non-systemic JIA due to its higher effectiveness. However it is associated with more adverse events, obligatory injection and higher costs than oral MTX. For definite recommendation for the preferred route of administration, a controlled randomized prospective studies are required to be conducted.

6. List of figures

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8. References

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