Pediatric rheumatology, one of the most stimulating and challenging areas in all of medicine, may deal with the broadest spectrum of diseases, although chronic arthritis has always been the core of this branch, the broader scope of the discipline gradually emerged with the recognition in children of systemic lupus erythematosus (SLE), dermatomyositis, vasculitis, infection-related disorders and, most recently, the autoinflammatory disorders **(Cassidy and Petty, 2011).**

Systemic rheumatic diseases are characterized by systemic autoimmunity leading to chronic inflammation in target organs and systems. Although the inciting event is not known for any of these conditions, it most likely results from a complex interaction of genetic and environmental factors. A general model of pathogenesis is that in a genetically susceptible individual ;an initial breakdown in tolerance creates primary self-reactive cells, which then propagate the autoimmune response by a variety of mechanisms that include positive-feedback amplification loops, such as T and B lymphocyte activation, autoantibody production, complement activation, immune complex deposition, and leukocyte infiltration of target organs. Although the relative importance of these abnormalities may be different in various diseases, they do share common effector pathways, which may present attractive therapeutic targets. The commonly used wide-spectrum immunosuppressive and anti-inflammatory drugs such as systemic corticosteroids have clinical benefit, but are

associated with significant side effects and do not induce long-lasting tolerance in humans. Their use is based mainly on empirical evidence of efficacy and not on the understanding of their mechanism of action on the immune system. Therefore, targeted interference with key components of inflammation provides the hope of more effective therapies **(Shirota et al., 2008).**

Over the past 25 years, dramatic advances in understanding the nature of inflammation and the possibility of specifically regulating the aberrant immune inflammatory response are revolutionizing the treatment of rheumatic diseases of childhood. Previous treatments with conventional drugs nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids (systemic or intra-articular) were only partially effective in treating the symptoms of arthritis and reducing long-term complications. Disease modifying antirheumatic drugs (DMARDs) have the ability to slow or modify disabling ability of most cases,so they met the gold standard of the disease in which they appear to lead to better disease control, with higher numbers of children achieving remission, and fewer children suffering long-term joint damage **(Kemper et al., 2012).**

DMARDs are dividing into two main categories:

1. Synthetic (non biologic or traditional) DMARDs which include: methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, cyclophosphamide, mycophenolate mofetil, azathioprine,cyclosporineA,tacrolimus,dapsone ,minocycline and thalidomide.

2. Newer biologic DMARDs which include: TNF-α inhibitors, selective costimulation modulation, interleukin 1 inhibitors, selective B-cell blockers, interleukin 6 inhibitors and intravenous immunoglobulins **(Miller and Ranatunga, 2012).**

The use of biologic DMARDs for the treatment of autoimmune and rheumatologic diseases is rapidly expanding, owing to the good efficacy and safety profiles of these drugs, and the better understanding of the initial targets of altered immune regulation and activity in various diseases. Although some of the biologic therapies have been found to be useful in more than one disease, others are specific for a single disease. Research is ongoing to identify other molecular targets **(Rosman et al., 2013).**

Our study will go through the most important and the most commonly used DMARDs (synthetic and biologic) in pediatric age group, regarding their mode of action, pharmacology, efficacy, dosage and safety.

To review the medical literature for study of the effectiveness, complications (short and long term) and economic value of biologic DMARDs compared with the traditional DMARDs and compared to conventional treatment (non-steroidal anti-inflammatory drugs [NSAIDs] and/or corticosteroids) in their use for the management of children with different Pediatric rheumatic diseases.

Methotrexate

Methotrexate, (MTX), a folic acid analog and a potent inhibitor of several enzymes within the folate pathway, was initially developed during the 1940s to inhibit dihydrofolate reductase (DHFR) for treatment of malignancies especially leukemia and choriocarcinoma. The clinical potential of MTX in treating rheumatoid arthritis [RA] was initially suggested by Gubner in1951, after studying the effects of MTX in six patients diagnosed with RA **(Gubner et al., 1951)** and was confirmed by further studies conducted during the 1980s. MTX possessed anti-inflammatory effects in RA patients, as trial subjects demonstrated improved function, global assessments, joint scores and marked decreases in pain **(Weinblatt et al, 1985).** In 1988, it was approved by the U.S. Food and Drug Administration (FDA) to treat RA. Over the years, this treatment option has expanded to include additional inflammatory and autoimmune diseases such as cancer,psoriasis and various rheumatic and other chronic inflammatory diseases. **(Stamp et al., 2006).**

Mode of action:

MTX is a folic acid analogue. Its exact mechanism of action is under intense study. There are currently several proposed mechanisms for the anti-inflammatory effects of low dose MTX.

The first hypothesis is based on the inhibition of dihydrofolate reductase (DHFR).Inhibition of DHFR leads to depletion of the tetrahydrofolate (THF) cofactors that are required for the synthesis of purines and thymidylate **(Boxtel, 2008).** By preventing synthesis of purines and pyrimidines required for cellular proliferation, inhibition of proliferation of the most rapidly dividing lymphocytes or other cells responsible for the synovial inflammation occurs. Thus, some workers have reported that MTX diminishes pyrimidine synthesis by T cells and prevents antigen-dependent proliferation **(Quemeneur et al., 2003).**

The second biochemical explanation is that MTX inhibits the synthesis of potentially toxic compounds (the transmethylation products spermine and spermidine) that accumulate in chronically inflamed tissues. By inhibiting DHFR, MTX inhibits the formation of THF which donates a methyl group during the synthesis of methionine from homocysteine. Methionine can be further converted to *S*-adenosyl-methionine, which serves as a methyl donor in a large number of cellular reactions, including the synthesis of the polyamines spermine and spermidine. Thus, MTX may inhibit the accumulation of polyamines that contribute to tissue injury in RA **(Cronstein, 2005).**

A third proposed mechanism, is that MTX reduces intracellular glutathione levels by an oxidant-associated mechanism leading to diminished macrophage and lymphocyte recruitment and function **(Phillips et al., 2003).** In addition, the

inflamed synovium is filled with cells that generate reactive oxygen metabolites (neutrophils and macrophages), and prior studies have clearly shown evidence of oxygen radical-mediated injury in synovial cells from patients with RA before any therapy; MTX has been shown to suppress, either directly or indirectly, the generation of toxic oxygen metabolites **(Sung et al., 2000).**

A fourth mechanism has been proposed, supported by in vitro, in vivo, and clinical data, in which adenosine, released in high concentrations from cells and tissues after treatment with MTX, mediates the anti-inflammatory effects of it **(Chabner et al., 1985).** MTX and its major metabolite 7-hydroxymethotrexate are taken up by cells and polyglutamated. MTX -polyglutamates have been shown to be even more active than the parent drug as inhibitors of a variety of folate-dependent enzymes, but the enzyme inhibited most effectively by methotrexate polyglutamates is AICAR (5-aminoimidazole-4-carboxamide ribonucleotide) transformylase **(Allegra et al., 1985; Baggott et al., 1986).** The inhibition of AICAR transformylase by MTX would be expected to lead to intracellular AICAR accumulation. Because AICAR inhibits AMP deaminase and AICAR's dephosphorylated metabolite AICARiboside directly inhibits adenosine deaminase, AICAR accumulation could lead to the release of AMP (which may be dephosphorylated to adenosine) which is a potent endogenous anti-inflammatory mediator **(Hasko and Cronstein, 2004).** More studies in an animal model of RA further support the role of adenosine, acting at its receptors, as the mediator of the anti-inflammatory effects of MTX. In these studies, adenosine

receptor antagonists theophylline and caffeine reverse the effects of MTX on the development of adjuvant arthritis **(Montesinos et al., 2000).**

It is most likely that some combination of these mechanisms is responsible for the potent anti-inflammatory effects of MTX. (**Figure** 1)

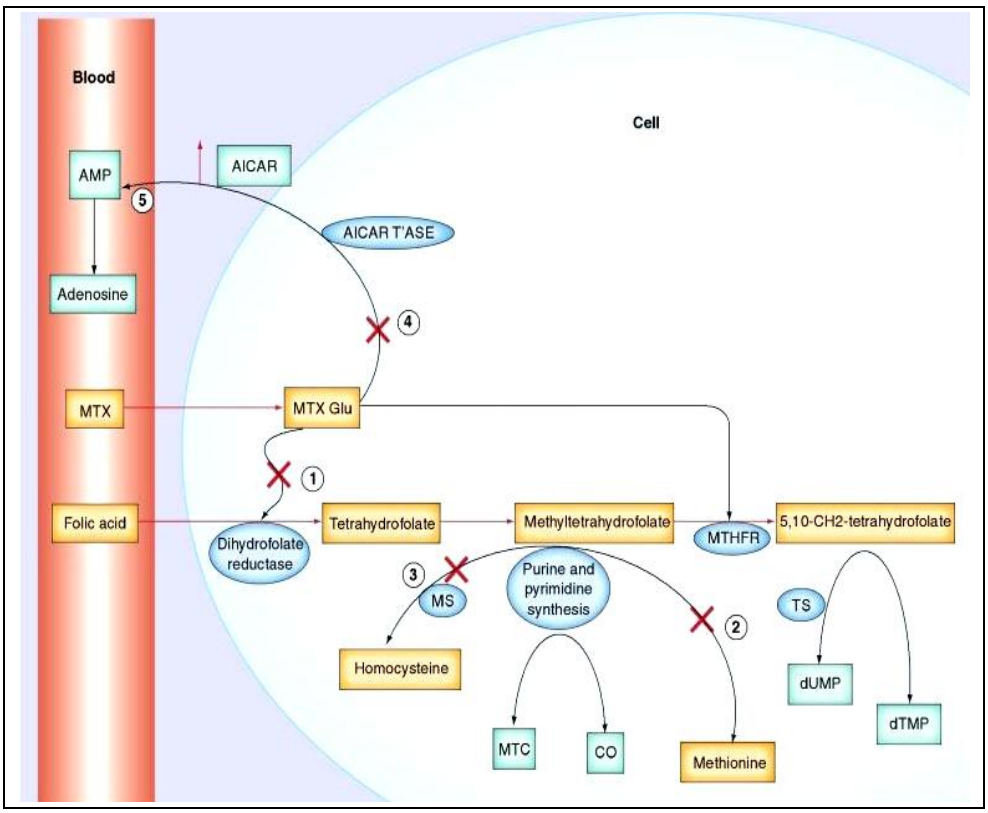

Figure (1): **Mode of action of methotrexate**

AICAR: Aminoimidazole carboxamidoribonucleotide; AICAR T'ASE: AICAR transformylase;AMP:Adenosine monophosphate;CO: Cobalamine; dTMP: Deoxy thymidine monophosphate; dUMP: Deoxy uridyl monophosphte;MS: Methionine synthase; MTC: Methyl cobalamine; MTHFR: Methylene tetrahydrofolate reductase; MTX: Methotrexate; MTX Glu:Polyglutamated methotrexate; TS: Thymidyl synthase **(Kaltsonoudis et al., 2012).**

Pharmacology:

MTX is the most common second-line therapeutic agent used to treat juvenile idiopathic arthritis (JIA) worldwide. Regardless of age or disease subtype, considerable interindividual variability in clinical response and adverse reactions exists with MTX, and thus far, there have been no predictive variables for outcomes in patients taking this medication **(Becker et al., 2010).**

MTX has been best studied at the cellular level. It is known that MTX acts as a folate antagonist, entering the cells primarily through the reduced folate carrier (*RFC/SLC19A1*). Once intracellular, MTX is bioactivated to a polyglutamated form by folylpolyglutamyl synthase (*FPGS*), which enhances the pharmacological activity and intracellular retention of MTX. In the RA and pediatric oncology literature, current evidence indicates that the enzymatic addition of glutamate residues to the MTX molecule *in vivo* (polyglutamation/MTXglu_n) is critical for pharmacologic activity by increasing the intracellular concentration of the drug and increasing its affinity for its therapeutic targets, thereby allowing more opportunity for its inhibitory effects to be exerted upon its target enzymes **(Schroder and Fogh, 1988).**

Genetic variation may explain individual differences in drug biotransformation. However, the pediatric population has an additional factor to consider, namely, the ontogeny of gene

expression, which may invariably affect the relative expression of genes within the pathway as one carbon resources which are allocated to the different functions of the folate cycle (purine and pyrimidine biosynthesis, homocysteine remethylation to methionine, one carbon donor for methyltransferases) during periods of dynamic change in folate supply and demand.This may explain the higher rate of subcutaneous administration and the higher doses of MTX used in children compared to adults. There are marked differences between racial groups in pharmacogenetics **(Becker et al., 2010).**

MTX at low doses is well absorbed from the gastrointestinal tract.It is better to be taken on empty stomach with water, citrus, or carbonated beverage .High doses should be administered intravenously. Approximately 50% is protein bound and may be displaced from plasma albumin by a number of drugs. MTX is mainly cleared by glomerular filtration and active tubular secretion with a terminal half-life of approximately 8–10 hours. The concurrent use of drugs that reduce renal blood flow such as NSAIDs, that are nephrotoxic, or that are weak organic acids can delay drug excretion and lead to severe myelosuppression **(Boxtel, 2008).**

Efficacy:

MTX is the most studied DMARD and good-quality studies support its efficacy.A new era of treatment started in 1992 with a randomized controlled trial showing MTX

administered weekly at 10 mg/m^2 was superior to placebo or 5 mg/m^2 **(Giannini et al., 1992).** In 2004 Ruperto and colleagues showed that by increasing the dose of MTX to 15 mg/m^2 per week and giving MTX parenterally was effective for most patients not responsive to 10 mg/m^2 per week. They also reported that there was no additional advantage to giving the higher doses of up to 30 mg/m^2 per week **(Ruperto et al., 2004).** The greatest efficacy of MTX was seen in patients with extended oligoarthritis, while in a randomized study no significant effect was found in patients with systemic arthritis **(Woo et al., 2000; Ravelli et al., 1999; Halle and Prieur, 1991).** Two small uncontrolled series have demonstrated that MTX may decrease the rate of progression of radiographic joint damage **(Ravelli et al., 1998; Harel et al., 1993).**

Foell and colleagues investigated whether longer MTX treatment during remission of JIA prevents flares after withdrawal of medication and whether MRP 8/14 biomarkers (phagocyte activation marker) identify patients at risk for flares **(Foell et al., 2010).** The study was a prospective, open, medication withdrawal randomized clinical trial including 364 patients with JIA. The primary outcome was relapse rate and the secondary outcome was time to relapse. In patients with JIA in remission, a 12-month *versus* 6-month withdrawal of MTX did not reduce the relapse rate. Higher MRP8/14 concentrations were associated with risk of relapse after discontinuing MTX, suggesting subclinical activity which was not apparent when the MTX was discontinued **(Foell et al., 2010).**

MTX is also used in many other rheumatic disorders, including SLE, some vasculitides,sarcoidosis, systemic sclerosis, scleroderma, and uveitis. The evidence for the efficacy of MTX in these conditions is less strong, however, and often is based on open, uncontrolled studies or extrapolated from the experience in adults, which is not always valid **(Cassidy and Petty, 2011).**

- **MTX resistance:** The mechanisms that can cause resistance include decreased transport of MTX into the cells, a decreased affinity of the antifolate for dihydrofolate reductase, increased concentrations of intracellular DHFR and decreased thymidylate synthetase activity **(Boxtel, 2008).**

Dose and monitoring:

Options include oral and subcutaneous administration, but intramuscular and intravenous administration are possible, although less practical in the outpatient setting. Before being taken into the body, contributors to variability that cannot be overlooked include patient compliance, differences in administered dose, and route of administration **(Becker et al., 2010).**

In general, for children with JIA, MTX therapy is started at a dose of 10–15 mg/m2/week or 0.3–0.6 mg/kg/week. However, children seem to tolerate much higher doses than adults and some series describe using up to 20–25 mg/m2/week in children with refractory disease, with relative safety in the

short term. At doses more than 15 mg/m2/week the parenteral route may be better because of the decreased oral bioavailability of the drug at high doses. It has been shown that subcutaneous administration of MTX has a 10–12% increased absorption compared with oral preparations. At the standard dose regime, 60–75% of patients with JIA benefit significantly from MTX therapy, with the maximum therapeutic effect usually becoming apparent 4–6 months after the beginning of treatment. Oral treatment is satisfactory in most patients as a single weekly dose. Occasionally the liquid preparation is needed, but there are issues around handling a liquid cytotoxic in the community where instructions for handling of spillage and disposal of empty containers need to be clear. Subcutaneous MTX may be required and provided in prefilled syringes to the home, for self administration. The time of adolescence can add compliance difficulties. The education and organisation of parents, children, and health professionals is essential to facilitate adherence, optimise efficacy, and monitor MTX safety **(Ramanan et al., 2003).**

Regarding clinical monitoring: improvement should be seen by 6-12 wk,clinical follow up should be done every 3-6 months depending on the course of illness. CBC with WBC count, differential, platelet count, MCV, AST, ALT, albumin are required every 4-8 wk initially, then every 12-16 wk. Reduction of the dose or discontinuation of MTX is done if clinical or laboratory adverse events has happened **(Cassidy and Petty, 2011).**

At present, it is impossible to make firm recommendations about routine folate supplementation in children receiving MTX treatment. Based on the data from adult studies and the small trial in children with JIA, it seems that low-dose (1 mg/day) folic acid supplementation does not have any detrimental effect on disease control and confers a beneficial effect in terms of GI and mucosal toxicities associated with low-dose weekly MTX treatment. Folic acid supplementation should be considered at least in symptomatic patients. High-dose folinic acid rescue should be reserved for patients with severe, life-threatening toxicity (e.g., aplastic anemia) **(Cassidy and Petty, 2011).**

Drug interactions are rarely significant at the low doses used in rheumatology and NSAIDs can be safely used together with MTX. Guidelines on immunization in the immunocompromised child should be followed. In particular, the use of live attenuated vaccines should be avoided and use of live polio vaccines in family members avoided. Children who are varicella zoster non-immune may be at risk of severe chickenpox infection and may require zoster immune globulin if in close contact, or treatment with oral or intravenous acyclovir if they acquire an infection with the virus **(Cronstein, 2005).**

- **Adverse effects**

Overall, although many patients experience adverse events during MTX treatment, they are generally mild and

withdrawals of MTX for toxicity are less common than for most other DMARDs. The results remain inconclusive for the risk of cirrhosis and malignancies, including lymphoma **(Salliot and van der Heijde, 2009).**

- **Gastrointestinal and liver:** Nausea and GIT complaints are common in children taking MTX.Side effects of MTX include oral ulcerations, nausea and rarely significant liver enzyme abnormalities. Tests to monitor complete blood cell counts, liver-related enzymes and renal function are recommended although it is unclear how often this testing should be done. Folic acid 1 mg taken daily has been shown to decrease occurrence of nausea, oral ulcerations and perhaps liver-related enzyme abnormalities without decreasing the efficacy of MTX **(Ravelli et al., 1999; Hunt et al., 1997).** Prey and Paul found that supplementation with folic acid is effective to reduce adverse hepatic effects associated with MTX treatment as well. They also found that there is no difference in benefit between folinic acid and folic acid, but the lower cost of the folic acid encourages its use **(Prey and Paul, 2009).**
- **Central nervous system:** Headache, fatigue, or impaired ability to concentrate may occur and some patients may develop a psychological aversion to the MTX and may benefit from cognitive behavioral therapy and relaxation techniques **(van der Meer et al., 2007).**