Journal of Orthopaedics and Clinical Rheumatology

Research Article Open Access

Drug Interaction of Methotrexate with its Adjuvant Drugs for Treatment of Rheumatoid Arthritis

Sarbjeet Singh[1]*, HC Patil[2] and RK Patil[3]

[1]*Department of PharmarmacyAdesh Institute of Pharmacy and Biomedical Sciences, Bathinda, Punjab*

[2]*Department of Pharmaceutics, Adesh Institute of Pharmacy and Biomedical Sciences, Bathinda, Punjab*

[3]*Department of Pharmacy Practices, Adesh Institute of Pharmacy and Biomedical Sciences, Bathinda, Punjab*

***Correspondence to:** RK Patil, Department of Pharmacy Practices, Adesh Institute of Pharmacy and Biomedical Sciences, Bathinda, Punjab, E-mail: rajjipatil@gmail.com

Received: 29 September 2020; **Accepted:** 19 November 2020; **Published:** 26 November 2020

Copyright: © 2020 PatilRK, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Methotrexate (MTX) is used as a DMARDs for some autoimmune illnesses, inclusive of rheumatoid arthritis, juvenile dermatomyositis, psoriasis, psoriatic arthritis and plenty of sorts of vacuities. Low-dose, weekly MTX (10 to 25 mg/week) used as both monotherapy or in mixture with other drugs, has an advanced efficacy profile as defined in placebo-managed trials and comparable efficacy to different medicines which include anti-TNF remedy. Patients suffering from rheumatoid arthritis (RA) may have some comorbid conditions that require a combination of a lot of medicinal drugs. For these comorbidities, prescription show polypharmacy and these medicines may additionally regulate the efficacy or growth of the toxicity of methotrexate (MTX). Interactions among drugs (DDIs) among the prescribed drugs are the reason behind the ADRs and these adverse effects are commonly seen in the aged patients (above 65) due to poly-pharmacy in prescription. In truth, poly-therapy boom the complexity of the therapeutic management and thereby the risk of a clinically applicable drug interaction. In this review, we report the interactions between MTX and the other tablets commonly used in the control of rheumatoid arthritis. The usage of google scholar, PubMed, PCM, NCBI website and reference lists. we studied the study material posted until 2019 and file the most common drug-drug interaction founds in the prescription of RA patients treating with MTX. In the context of a cure for MTX and NSAIDs like COX-1, COX-2 inhibitor, and among glucocorticoids or immunosuppressive medicinal products e.g., azathioprine, and cyclosporine, clinically important DDIs are identified. DDIs play a major role in both the production of ADRs and therapeutic failure in the treatment of MTX and specific medications.

Keywords: Methotrexate (MTX), Rheumatoid Arthritis, Drug-Drug Interaction, Poly-therapy, ADRs.

Background

There are numerous kinds of rheumatic diseases, but rheumatoid arthritis is probably the maximum commonplace. In rheumatoid arthritis, human beings typically have numerous inflamed joints. This causes the joints to gradually end up deformed and stiff. The first signal of rheumatoid arthritis is frequently the swelling of joints, causing pain and stiffness, especially inside the finger joints. Other signs typical of rheumatoid arthritis may additionally develop over the years, consisting of muscle weakness. Rheumatoid arthritis is autoimmune. Because of this, our immune system attacks our body. The immune system mistakenly identifies our body's cells as foreign substances and assaults them. This reasons an inflammatory response that specifically affects the joints in humans who have rheumatoid arthritis [1].

Table 1: Drugs used for the treatment of Rheumatoid Arthritis

On the basses of newly developed criteria, patients suffering from arthritis with the involvement of at least one joint may require DMARD therapy with appreciate to a different component of standards. Rheumatoid arthritis can be taken into consideration a probably curable situation all through the evolutionary procedure (from inflammatory arthritis to established condition) and the disease path can be modified with the aid of early suitable competitive treatment. Particularly DMARDs (ailment-modifying antirheumatic arthritis capsules), NSAIDs (non-steroidal anti-inflammatory pills), Immunosuppressive retailers like cyclosporine, azathioprine and so forth and agent that block the proinflammatory cytokine tumour necrosis factor-a (anti-TNF- a) can be used (table 1). NSAIDs (non-steroidal anti-inflammatory drugs) are generally used to deal with rheumatoid arthritis. They help control the continual pain, inflammation, and swelling which might be characteristic of RA however now not the disorder's progression: but long-term use of NSAIDs as a monotherapy cause unfavourable drug reactions (ADRS) [2-4].

Drugs for Symptomatic treatment		DMARDs		Immuno-suppressants		
NSAIDs	Topical	Corticosteroids	Opioids	Nonbiological	Biological	
Etoricoxib	Capsaicin	Prednisolone	Tramadol	Hydroxychloroquine	Anti-TNF-α agents	Cyclosporine
Celecoxib	Diclofenac 1%	Prednisone	Oxycodone	Leflunomide	Anti-CD20	Azathioprine
Ibuprofen	Diclofenac 2%	Methylprednisolone	Meperidine	Methotrexate	Anti-CD80/86	
Naproxen		Dexamethasone	Hydrocodone	Sulfasalazine	Anti-IL-1	
Aspirin		Betamethasone		Minocycline	Anti-IL-6	
Diclofenac						

Although some controversy exists in the medical sciences about the function of topical NSAIDs, current treatment guidelines endorse topical NSAIDs as a first choice and even first-line therapy for the treatment of knee OA, mainly among elderly sufferers [5]. Capsaicin is a remarkably selective and powerful exogenous agonist (low nanomolar affinity) for the TRVP1 receptor, a complex trans-membrane-ion pathway, offering integrated temperature, PH and endogenous lipid responses [6]. Corticosteroids are steroidal medicines given to RA patients to reduce inflammation and help alter the autoimmune activity. Corticosteroids were used for over 5 many years to help deal with RA symptoms [7-9]. Many corticosteroids known as glucocorticoids can be detected. In conjunction with NSAIDs and DMARDs, many RA therapies tend to use corticosteroids because inflammation no longer decreases, but they can help protect joint and organ against damage to destiny as well. DMARDs are one of the main medication groups for many forms of arthritis such as RA (Rheumatoid Arthritis), PSA (Psoriatic Arthritis) and so many, and they are used for many purposes in the treatment of arthritis [10-12]. DMARDs are immunosuppressive and immunomodulatory drugs and are categorized into two categories, one is traditional DMARDs or other is biologic DMARDs. Usually used traditional DMARDs include methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine. Biologic DMARDs were introduced within the early 1990s and are normally prescribed after the failure of traditional DMARDs remedy (ongoing ailment pastime, or clinical or radiographic disease development). Biologic DMARDs are exceptionally particular and goal a particular pathway of the immune machine. Methotrexate is the maximum generally used agent as an initial treatment. RA treatment is complex, with a variety of decision-making considerations including the occurrence and severity of illnesses, co-morbidities and patient preferences (including costs, administration routes and monitoring frequencies). RA treatment may be either monotherapy or combination therapy, although some randomized controlled trials demonstrated a biological DMARD combination therapy dominance with traditional DMARD such as methotrexate over either agent alone [13-16].

Drugs	Uses	Doses	Adverse Effect	Mechanism
Infliximab	Moderate or severe Rheumatoid Arthritis with MTX	3mg/kg iv	Rashes, headache, fever, vertigo, asthenia and higher plasma transaminases level	Anti-TNF-α
Adalimumab	Severe Rheumatoid Arthritis	40mg sc.	Myositis, rash, headache, hypertension, vomiting	Anti-TNF-α
Anakinra	As monotherapy in moderate to severe RA	100mg/die sc.	ABD pain, increase gut mobility, fever, asthma	Anti-IL-1
Rituximab	Moderate to severe RA	1000 mg IV infusion	Angioedema, Asthenia, chills, dizziness, fever, headache, Pruritus, Rash, Abdominal Pain, diarrhoea, nausea, vomiting	Anti-CD20
Tocilizumab	Severe RA	162 mg sc.	UTI infection, Nasopharyngitis,Headache, Hypertension, ALT increased, Bronchitis, Rash, Dizziness	Anti-IL-6
Abatacept	Monotherapy in moderate to severe RA	500/1000 mg iv	Headache, blood hypertension, infection, vertigo and severe infection	Anti-CD80/86

Table 2: List of disease-modifying antirheumatic drugs (DMARDs)

Although maximum traditional DMARDs have comparable adverse outcomes, there are several adverse effects results precisely to each agent. (Table 2) Bacterial infection, fungal infection and viral infections are the not unusual and extreme infections are caused by the uses of or are the most common adverse effect of all biologic DMARDs. Several other drugs used to treat RA can affect, or enhance the effectiveness of, the pharmacokinetic effect or pharmacodynamic effect of DMARDs and can also enhance the risk of adverse effects, with non-steroid anti-inflammatory agents (NSAIDs), Corticosteroids, antacids, calcium supplements, PPI and sulfasalazine. [17-20].

Material and Methods

Our objective became to decide what medicines are used with the DMARDs for the remedy of rheumatoid arthritis may boom the aspect effect or toxicity of methotrexate or lower its efficacy. Making use of applicable key phrases, we perform systematic literature seek using google scholar, PubMed, PCM, NCBI net site. The secondary search protected articles mentioned in reference lists identified by using the number one search. Data were first screened earlier than entire text papers for eligibility evaluation by title/abstract. Papers are considered eligible if the type of sentences is protected: "Rheumatoid arthritis", "RA", "DMARDs", "organic DMARDs", "drug-drug interaction". "NSAIDs in rheumatoid arthritis". All citations had been downloaded inside the Endnote software version x9.3.3, and duplicates were deleted.

Methotrexate Pharmacology

Pharmacokinetic

A couple of older research styles supporting the proper absorption at low doses of MTX have stressed that the absorption of this drug after oral use will be relatively weak and unpredictable[21, 22]. Methotrexate is a drug that is folate analogue that after absorption, distribute to various cell and tissue mainly in the non-fatty tissue of the body[23, 24]. Transport of MTX across the capillary and cellular membranes of the liver, kidney, and pores and skin is speedy so that equilibrium ratios of tissue to plasma concentrations (plasma concentrations > 1 μm) are established on a time scale regular with plasma flow limitation. The essential metabolite of MTX, produced by way of the action of hepatic aldehyde oxidase, is 7-hydroxy MTX (7-OH-MTX)[25,26]. 7-OH-MTX is only 1% as powerful an inhibitor of DHFR as is MTX[27]. This metabolite is also less water-soluble than MTX and can make a reason for the renal toxicity regularly seen after excessive doses of the antifolate[28]. The clearance of the MTX from the body is done by both biliary and urinary routes. Maximum of the drug excreted into the bile passes through the intestine and is excreted focally, but the drug likewise issues to partial intestinal reabsorption and metabolism via enteric microorganism[29,30]. MTX also undergoes hydroxylation utilizing liver aldehyde oxidase to form 7-hydroxymethotrexate, a metabolite with a long half-life-the existence of 24 h in human beings.

Pharmacodynamics

RA patients acquire polyamines from synovial tissues, synovial fluid, PBMCs and urine, sperm and spermidine. Polyamines can be converted into hydrogen peroxidase and ammonia lymphotoxins by using monocytes. Methotrexate depletes tetrahydrofolate and methyl-tetrahydrofolate (5-CH3-THF) with the aid of the inhibiting DHFR. Both compounds typically act in the form of methionine and s-adenosylmethionine (SAM) and polyamines as methyl donors[31]. The following: This mechanism proposes that MTX, by inhibiting the DHFR, decrease the downstream mediators and also decrease the methionine and SAM, for this reason, decrease the process of methylation and the next step of formation of polyamines and consequently lymphotoxins.

But research has shown that the inhibition of polyamine is much less likely to justify the effectiveness of methotrexate in RA. Transmethylation inhibitor 3-deoxyadenosine has not shown any therapeutic efficacy in RA. It is also well-known that by way of methionine but inverted by the use of folinical acid plus sam, methotrexate inhibits chemotaxis and the formation of superoxide in monocytes [32]. Hence, polyamine inhibition should possibly make a contribution to methotrexate efficacy in a few manners but does no longer seem like the predominant mechanism.

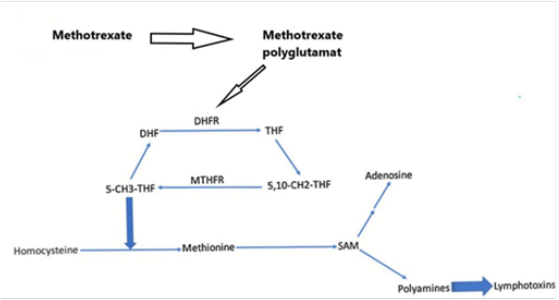

Figure 1: Mechanism of Action of Methotrexate in the inhibition of polyamine andlymphotoxin formation. Source [31]

Methotrexate's Interaction with Drugs Commonly Used In Ra Treatment

Drug-drug interactions (DDIs) are considered preventable medication-associated troubles; however, in scientific exercise, DDIs are regularly chargeable for adverse drug reactions (ADRs) and can lead to an extended hazard of hospitalization and better health care charges [33–37].

MTX with NSAIDS

A cohort takes a look at became carried out in Denmark and display that concomitant use of low‐dose methotrexate and NSAIDs turned into associated with a notably extended chance of significant adverse activities. [38] however, a few observe indicates that excretion of methotrexate from the body is inhibited, when MTX is given with the NSAIDs like indomethacin, aspirin several studies have confirmed the efficacy of low-dose methotrexate in treating patients who have rheumatoid arthritis[39-40]. Inside the early ninety's numerous case reports describing poisonous and on occasion deadly interactions between NSAIDs and methotrexate had been posted. [41-44] A case report shows co-management of MTX and NSAIDs may also result in extensive toxicity. Clinical manifestations, inclusive of pancytopenia and renal failure, have been proven while patients received both high-dose or low-dose MTX collectively with NSAIDs[45]. Some recent studies show that Etoricoxib which is a selective COX-2 inhibitor is also capable of inhibiting the human organic anion transporter-3 (HOAT-3) in the human body with a dose-dependent manner [46]. The document demonstrates that the affected person was re-evaluated and become identified with stevens-johnson syndrome-poisonous epidermal necrolysis (SJS-TEN) whilst she becomes below the remedy with methotrexate and etoricoxib[47].

A few observe indicates that celecoxib, a cyclooxygenase (COX-2) inhibitor, shows inhibitory effects on methotrexate accumulation in S2-HOAT3 cells. Celecoxib inhibited the methotrexate accumulation mediated by using HOAT3 in a concentration-based manner. [48]

however, celecoxib does not affect the PK of MTX[49]. Some studies indicate that rofecoxib does not affect MTX plasma concentrations and the MTX renal clearance in patients with RA at a dosage of 12.5-50 mg OD[50].

Drugs	Effect/MOA	Reference
NSAIDs (COX-1 Inhibitor)	Increased chance of severe negative effects,NSAIDs minimize body excretion of MTX,Human Organic Anion Transporter 349 Inhibited	[38]
Etoricoxib	Reduce MTX excretion by inhibiting HOAT-3	[39,40]
Celecoxib	Inhibition of deposition of methotrexate in S2-HOAT3 cells	[46]
Tubular secretion competition through the organic renal anion transporter 3 (OAT3) Competition		[48]

Table 3: Drug-Drug Interaction between MTX and NSAIDs

MTX with Non-biological DMARDS:

An examine explains the multiplied efficiency of the MTX-HCQ aggregate over MTX as a single agent and additionally the sustained outcomes of MTX while administered with HCQ. In addition to this, during the co-administration lessening of the adverse effect of the liver may be explained by the reduction of Cmax of methotrexate observed during the co-administration. Greater vigilance for MTX detrimental consequences at some point of aggregate remedy with HCQ is usually recommended, specifically if the renal characteristic is thought to be reduced[51]. The threat of pancytopenia at some point of leflunomide remedy seems to be elevated when the drug is mixed with methotrexate and in older sufferers. Onset can be behind schedule, and ongoing monitoring of blood counts is important [52]. Use of methotrexate with leflunomide will increase the threat of pancytopenia compared with the use of leflunomide alone [53-55]. We concluded that the combinations of MTX with G, HCQ, SASP and MNC in RA have been pretty properly tolerated. No boom in toxicity as compared with MTX by myself became discovered. The lowest rate of facet effects was noted in group 1, even as institution four offered the best discontinuation rate[56]. The exposed patients had substantially more risks of developing renal, gastrointestinal and pulmonary activities, and drastically extra fitness care aid utilization and fees[57] [58].

Drugs	Effect/MOA	Reference
Hydroxychloroquine	The increased capacity of the MTX raised mean AUC for the MTX and lowered average MTX concentration	[51]
Leflunomide	Inhibits lymphocyte and other cells that are easily divided and are rarely associated with life-threatening pancytopenia pyrimidine synthesis	[52-55]
Sulfasalazine	No interaction	[56]
Minocycline	No interaction	[56]
Cyclosporine	Renal impairment, GIT disturbance	[57-58]

Table 4: Drug-Drug interaction between MTX and other Non-biological DMARDs

MTX with Corticosteroids:

Hepatocellular impairment occurs due to decrease in the elimination of the MTX from biliary and due to this there is an increase in the concentration of MTX in the liver and this condition contribute in the hepatotoxicity of the MTX while administrated with dexamethasone. Furthermore, the influence of dexamethasone on protein expression of anionic capsules transporters inside the liver and kidney changed into confirmed[59-61]. The impact of methotrexate and betamethasone on a following phototoxic reaction to 8-methoxy psoralen and lengthy-wave ultraviolet light (PUVA) was studied within the mouse. Excessive PUVA doses had been no longer inspired by way of the two drugs examined. Each methotrexate and betamethasone tended to decrease the PUVA response while psoralen becomes given in a medium dose[62]. Using methotrexate collectively with methylprednisolone can increase the blood level or upload to the adverse effects of methotrexate[63]. However some studies don't show any interaction and side effect[64].

Drugs	Effect/MOA	Reference
Dexamethasone	Hepatocellular impairment	[59-61]
Betamethasone	Diminish the PUVA response	[62]
Methylprednisolone	No Interaction	[63-64]
Prednisolone	No data found	[65]

Table 5: Drug-Drug Interaction between MTX and Corticosteroids

MTX with Biological DMARDs:

A 69-year-vintage English man laid low with rheumatoid arthritis with a record of type-2 diabetes mellitus turn out to be mentioned the hospital for treatment of rheumatoid arthritis. We describe a patient with RA who developed pancytopenia complicated by disseminated Cryptococcus neoformans while receiving low dose MTX and infliximab[66] [67]. Throughout the etanercept treatment (subcutaneous dose) plus MTX (oral dose), no pharmacokinetic DDIs were nevertheless recorded[72]. Many medical studies have ended with improved RA signs and symptoms in patients who have energetic RA without adequate MTX-response with the addition of adalimumab without improving pharmacokinetic DDIs [73]. Under the modern MTX management, the absence of pharmacokinetic DDI, plus rituximab, tocilizumab, certolizumabpegol or golimumab have been recorded in different evidence [74-76]. The t-lymphocyte activation modulator, approved to cure lively RA, for DMARD non-response sufferers was recommended along with MTX and anti-TNF-Ⅱ[77].

Drugs	Effect/MOA	Reference
Infliximab, Adalimumab,	Increased risk of infections	[66-67]
Golimumab		
Etanercept	No DDIs	[68]
Adalimumab	No DDIs	[69]
Tocilizumab, certolizumabpegol, and golimumab	No DDIs	[70-72]
Abatacept	No DDIs	[73]

Table 6: Drug-Drug Interaction between MTX and Corticosteroids

Conclusion

The loss of folate and cell inability to synthesize DNA at the same time describe the antirheumatic and anti-inflammatory effects of MTX. Specific parameters are necessary to control the suppressive effects MTX on the hematopoietic system and the risk of fibrosis, cirrhosis or gastric ulcers. Folic acid supplementation helps reduce the toxicity of the MTX [74]. The importance of pharmacovigilance in MTX patients is also associated with the dangers of DDIs that can boom MTX toxicity. Upon absorption of MTX, it is confined to the blood serum albumin for dissemination into various body parts and thus can be transferred through various MTX medications. The remediation risk for livers and bone marrow repression can be improved by using NSAIDs or DMARDs, with pills with comparable ADRs [74, 75]. The remedy the enhance kidney clearance with NSAIDs. In short, for the period of treatment with MTX, it should be taken into account the possibility of DDIs that may raise the risk of hepatotoxicity, nephrotoxicity and other toxic effects.

Discussion

It is very critical that you are safe against developing ADRs or therapeutic failure. MTX is a low-dose medication for patients with RA who are taking other anti-Rheumatic drugs because certain DDIs may occur. An increase in MTX toxicity may be linked to the relationship MTX + NSAIDs. The liver toxicities and/or blood toxicity may also result from the MTX + leflunomide or the sulphasalazine association. Very little detail has been made available on the relationship of MTX to organic DMARDs. To order to ensure that you boost DDIs, it is important to raising the MTX or co-administered medication dose. With ADRs at some stage during the procedure, the plasma concentration of the drug can be measured in miles.

References

1. Finckh A. "Early inflammatory arthritis versus rheumatoid arthritis". Curr Opin Rheumatol 21(2009):118-123.

2. Gor AP, Saksena M. "Adverse drug reactions of nonsteroidal anti-inflammatory drugs in orthopedic patients". Int J Res Pharmacol Pharmacother 2(2011):26.

3.Lapeyre-Mestre M, Grolleau S, Montastruc JL. "Association Française des Centres Régionaux de Pharmacovigilance (CRPV). Adverse drug reactions associated with the use of NSAIDs: a case/noncase analysis of spontaneous reports from the French pharmacovigilance database 2002–2006". Fundam Clin Pharmacol 27 (2013):223-30.

4.Lapeyre-Mestre M, De Castro AM, Bareille MP, Pozo JG, Requejo AA, et al. "Non-steroidal anti-inflammatory drug-related hepatic damage in France and Spain: analysis from national spontaneous reporting systems". Fundam Clin Pharmacol 20(2006):391-395.

5. Rodriguez-Merchan EC. "Topical therapies for knee osteoarthritis". J Postgrad Med130(2018) 607-612.

6. Alawi K, Keeble J. "The paradoxical role of the transient receptor potential vanilloid 1 receptor in inflammation". Int J Res Pharmacol Pharmacother 125 (2010):181-95.

7. Hench PS, Kendall EC, Slocumb CH, Polley HF. "Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions: A study in clinical physiology". Arch Intern Med 85 (1950):545-666.

8. Byron MA, Mowat AG. "Corticosteroid prescribing in rheumatoid arthritis—the fiction and the fact". Rheumatology 24 (1985):164-166.

9. Saag KG, Koehnke R, Caldwell JR, Brasington R, Burmeister LF, et al. "Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events". Am J Med 96 (1994):115-123.

10. Gregori D, Giacovelli G, Minto C, Barbetta B, Gualtieri F, et al. "Association of pharmacological treatments with long-term pain control in patients with knee osteoarthritis: a systematic review and meta-analysis". Jama 320(2018):2564-2579.

11. Lyseng-Williamson KA. "Anakinra in Still's disease: a profile of its use". Drugs Ther Perspect 34(2018):543-553.

12. Abbasi M, Mousavi MJ, Jamalzehi S, Alimohammadi R, Bezvan MH, et al. "Strategies toward rheumatoid arthritis therapy; the old and the new". J Cell Physiol 234(2019):10018-10031.

13. Buckley F, Finckh A, Huizinga TW, Dejonckheere F, Jansen JP. "Comparative efficacy of novel DMARDs as monotherapy and in combination with methotrexate in rheumatoid arthritis patients with inadequate response to conventional DMARDs: a network meta-analysis". J Manag Care Spec Pharm 21(2015):409-423.

14.Singh JA, Hossain A, Ghogomu ET, Mudano AS, Tugwell P, et al. "Biologic or tofacitinib monotherapy for rheumatoid arthritis in people with traditional disease-modifying anti-rheumatic drug (DMARD) failure: a Cochrane Systematic Review and network meta-analysis (NMA) ". Cochrane Database Syst Rev (2016):12437.

15.Jansen JP, Buckley F, Dejonckheere F, Ogale S. "Comparative efficacy of biologics as monotherapy and in combination with methotrexate on patient reported outcomes (PROs) in rheumatoid arthritis patients with an inadequate response to conventional DMARDs–a systematic review and network meta-analysis". Health Qual Life Outcomes 12(2014):102.

16.Guyot P, Taylor P, Christensen R, Pericleous L, Poncet C, et al. "Abatacept with methotrexate versus other biologic agents in treatment

of patients with active rheumatoid arthritis despite methotrexate: a network meta-analysis". Arthritis Res Ther 13(2011):204.

17. Gallelli L, Ferreri G, Colosimo M, Pirritano D, Guadagnino L, et al. "Adverse drug reactions to antibiotics observed in two pulmonology divisions of Catanzaro, Italy: a six-year retrospective study". Pharmacol Res 46(2002):395-400.

18. Gallelli L, Guadagnino V, Caroleo B, Marigliano N, De Sarro GB, et al. "Bilateral skin ulceration after injection of pegylated interferon-α-2b in a patient with chronic hepatitis C". Clin Drug Invest 23(2003):615-619.

19. Gallelli L, Ferraro M, Mauro GF, De Sarro G. "Generalised Dermatitis Induced by Pegylated Interferon-α-2b in a Patient Infected with Genotype-1 Hepatitis C Virus. Clin Drug Invest 25(2005):281-284.

20. Scicchitano F, Giofre C, Palleria C, Mazzitello C, Ciriaco M, et al. "Pharmacovigilance and drug safety 2011 in Calabria (Italy): Adverse events analysis". Res Med Sci17(2012):872-875.

21. Chungi VS, Bourne DW, Dittert LW. "Drug absorption VIII: kinetics of GI absorption of methotrexate". Pharm Sci 67(1978):560-561.

22. Henderson ES, Adamson RH, Oliverio VT. "The metabolic fate of tritiated methotrexate: II Absorption and excretion in man". Cancer Res 25(1965):1018-1024.

23. Balis FM, Savitch JL, Bleyer WA. "Pharmacokinetics of oral methotrexate in children. Cancer Res 43 (1983):2342-2345.

24. Kearney PJ, Light PA, Preece A, Mott MG. "Unpredictable serum levels after oral methotrexate in children with acute lymphoblastic leukaemia". Cancer Chemother Pharmacol 3(1979):117-120.

25. Fabre G, Seither R, Goldman ID. "Hydroxylation of 4-amino-antifolates by partially purified aldehyde oxidase from rabbit liver". Biochem Pharmacol 35(1986):1325-1330.

26. Johns DG, Loo TL. " Metabolite of 4-amino-4-deoxy-N10-methylpteroylglutamic acid (methotrexate) ". Pharm Sci 56(1967):356-359.

27. Erttmann R, Bielack S, Landbeck G. "Kinetics of 7-hydroxy-methotrexate after high-dose methotrexate therapy". Cancer Chemother Pharmacol 15(1985):101-104.

28. Jacobs SA, Stoller RG, Chabner BA, Johns DG. "7-Hydroxymethotrexate as a urinary metabolite in human subjects and rhesus monkeys receiving high dose methotrexate". Clin Invs 57(1976):534-538.

29. Breithaupt H, Kuenzlen E. "Infusions of High-Dose Methotrexate". Cancer Treat Rep 66(1982):1733-1711.

30. Zaharko DS, Dedrick RL. "Pharmacokinetics of methotrexate in animals and man". InFolate Antagonists as Therapeutic Agents 2(1984):97-163.

31. Chan ES, Cronstein BN. "Methotrexate—how does it really work? ". Nat Rev Rheumatol 6(2010):175-178.

32. Nesher G, Moore TL, Dorner RW. "In vitro effects of methotrexate on peripheral blood monocytes: modulation by folinic acid and S-adenosylmethionine". Ann Rheum Dis50(1991):637-641.

33. Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. "Drug-drug interactions among elderly patients hospitalized for drug toxicity". JAMA 289 (2003):1652-1658.

34. McDonnell PJ, Jacobs MR. "Hospital admissions resulting from preventable adverse drug reactions". Ann Pharmacother36(2002):1331-1336.

35. Strandell J, Bate A, Lindquist M, Edwards IR. "Swedish, Finnish, Interaction X-referencing Drug-drug Interaction Database (SFINX Group). Drug-drug interactions-A preventable patient safety issue". Br J Clin Pharmacol 65(2007):144-146.

36. Pirmohamed M, James S, Meakin S, Green C, Scott AK, et al. "Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients". BMJ 329(2004):15-19.

37. Aparasu R, Baer R, Aparasu A. "Clinically important potential drug-drug interactions in outpatient settings". Res Social Adm Pharm 3(2007):426-437.

38. Svanström H, Lund M, Melbye M, Pasternak B. "Concomitant use of low-dose methotrexate and NSAIDs and the risk of serious adverse events among patients with rheumatoid arthritis". Pharmacoepidemiol Drug Saf 27 (2018):885-893.

39. Statkevich PA, Fournier DJ, Sweeney KR. "Characterization of methotrexate elimination and interaction with indomethacin and flurbiprofen in the isolated perfused rat kidney". Pharmacol Exp Ther 265(1993):1118-1124.

40. Daly H, Boyle J, Roberts C, Scott G. "Interaction between methotrexate and non-steroidal anti-inflammatory drugs". The Lancet 327(1986):557.

41.Stewart CF, Fleming RA, Germain BF, Seleznick MJ, Evans WE. "Aspirin alters methotrexate disposition in rheumatoid arthritis patients". Arthritis Rheum 34(1991):1514-1520.

42. Zuik M, Mandel MA. "Methotrexate–salicylate interaction: a clinical and experimental study". Surg Forum 26(1975):567.

43. Stewart CF, Fleming RA, Arkin CR, Evans WE. "Coadministration of naproxen and low-dose methotrexate in patients with rheumatoid arthritis". Clin Pharmacol Ther 47(1990):540-546.

44. Furst DE, Herman RA, Koehnke R, Ericksen N, et al. "Effect of aspirin and sulindac on methotrexate clearance". J Pharm Sci (1990)79(9):782-786.

45.Frenia M L, Long KS, Hartshorn EA. "Methotrexate and Nonsteroidal Antiinflammatory Drug Interactions". Ann Pharmacother 26(1992):234–237.

46. Honjo H, Uwai Y, Iwamoto K. "Inhibitory Effect of Selective Cyclooxygenase-2 Inhibitor Etoricoxib on Human Organic Anion Transporter 3 (hOAT3) ". Drug Metab Lett 5(2011):137–140.

47. Rachana PR, Anuradha HV, Mounika R. "Stevens Johnson syndrome-toxic epidermal necrolysis overlap secondary to interaction between methotrexate and etoricoxib: A case report". J Clin Diagn Res JCDR 9 (2015):FD01.

48. Maeda A, Tsuruoka S, Ushijima K, Kanai Y, Endou H. "Drug interaction between celecoxib and methotrexate in organic anion transporter 3–transfected renal cells and in rats in vivo". Eur J Pharmacol

(2010)640:168–171.

49. Karim A,Tolbert D, Piergies A, Hunt T, Hubbard R, et al. "Celecoxib, a specific cox-2 inhibitor, lacks significant drug-drug interactions with methotrexate or warfarin". J Rheumatol 41(1998):315.

50. Schwartz JI, Agrawal NGB, Wong PH, Bachmann KA, Porras AG, et al. "Lack of Pharmacokinetic Interaction between Rofecoxib and Methotrexate in Rheumatoid Arthritis Patients". J Clin Pharmacol 41 (2001): 1120–1130.

51. Carmichael SJ, Beal J, Day RO, Tett SE. "Combination therapy with methotrexate and hydroxychloroquine for rheumatoid". J Rheumatol 29(2002):2077-2083.

52. Chan J, Sanders DC, Du L, Pillans PI. " Leflunomide-associated pancytopenia with or without methotrexate". Ann Pharmacother 38(2004): 1206-1211.

53. McEwen J, Purcell PM, Hill RL, Calcino LJ, Riley CG. "The incidence of pancytopenia in patients taking leflunomide alone or with methotrexate". Pharmacoepidemiol Drug Saf 16(2007):65-73.

54. Toyokawa Y, Kingetsu I, Yasuda C, Yasuda J, Yoshida K, et al. "Pancytopenia, including macrocytic anemia, associated with leflunomide in a rheumatoid arthritis patient". Mod Rheumatol 17(2007):436-440.

55.Emery P, Breedveld FC, Lemmel EM, Kaltwasser JP, Dawes PT, et al. "A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis". Rheumatol (2000)39:655-665.

56. Elkayam O, Yaron M, Zhukovsky G, Segal R, Caspi D. "Toxicity profile of dual methotrexate combinations with gold, hydroxychloroquine, sulphasalazine and minocycline in rheumatoid arthritis patients. Rheumatol Int (1997)17:49-53.

57. Saurat JH, Guérin A, Andrew PY, Latremouille-Viau D, Wu EQ, et al. "High prevalence of potential drug-drug interactions for psoriasis patients prescribed methotrexate or cyclosporine for psoriasis: associated clinical and economic outcomes in real-world practice". Dermatol 220(2010); 128-137.

58. Gerards AH, Landewe RB, Prins AP, Bruijn GA, Laan RF, et al. "Cyclosporin A monotherapy versus cyclosporin A and methotrexate combination therapy in patients with early rheumatoid arthritis: a double blind randomised placebo controlled trial". Ann Rheum Dis 62(2003):291-296.

59. Fuksa L, Brcakova E, Kolouchova G, Hirsova P, Hroch M, et al. "Dexamethasone reduces methotrexate biliary elimination and potentiates its hepatotoxicity in rats". Toxicology 267(2010:165-171.

60. Lin H, Abida WM, Sauer RT, Cornish VW. "Dexamethasone–Methotrexate: An Efficient Chemical Inducer of Protein Dimerization In Vivo". Amer Chem Soci (2000) 122:4247-4248.

61. Wolff JE, Hauch H, Kühl J, Egeler RM, Jürgens H. "Dexamethasone increases hepatotoxicity of MTX in children with brain tumors". Anticancer research 18(1998):2895-2899.

62. Ljunggen B, Moller H. "Interaction of methotrexate and betamethasone with experimental phototoxic inflammation to PUVA (Psoralen and UVA) in mice. Arch Dermatol Res 264(1979):257-260.

63. Van der Veen MJ, Bijlsma JW. "The effect of methylprednisolone pulse therapy on methotrexate treatment of rheumatoid arthritis. Clin Rheumatol 12(1993):500-505.

64. Liu JT, Zhang S, Gu B, Li HN, Wang SY, et al. "Methotrexate combined with methylprednisolone for the recovery of motor function and differential gene expression in rats with spinal cord injury". Neural Regen Res 12(2017):1507.

65. Lafforgue P, Monjanel-Mouterde S, Durand A, Catalin J, Acquaviva PC. " Is there an interaction between low doses of corticosteroids and methotrexate in patients with rheumatoid arthritis? A pharmacokinetic study in 33 patients". J Rheumatol (1993):263-267.

66. True DG, Penmetcha M, Peckham SJ. "Disseminated cryptococcal infection in rheumatoid arthritis treated with methotrexate and infliximab". J Rheumatol 29(2002):1561-1563.

67. Luong BT, Chong BS, Lowder DM. "Treatment options for rheumatoid arthritis: celecoxib, leflunomide, etanercept, and infliximab". Ann Pharmacother 34(2000):743–760.

68. Zhou H, Mayer PR, Wajdula J, Fatenejad S. "Unaltered etanercept pharmacokinetics with concurrent methotrexate in patients with rheumatoid arthritis". J Clin Pharmacol 44(2004):1235–1243.

69. Weisman MH, Moreland LW, Furst DE, et al. "Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: a pilot study". Clin Ther 25(2003):1700–1721.

70. RoActemra (Tocilizumab) Roche Registration Ltd. Summary of product characteristics(2009).

71. Cimzia (Certolizumab pegol) UCB Inc.US Prescribing information (2007).

72. Oldfield V, Plosker GL. "Golimumab: in the treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis". BioDrugs 23(2009):125-135.

73. Kyburz D, Tyndall A, Zufferey P, Villiger PM. "Use of abatacept in rheumatoid arthritis". Swiss Med Wkly 11 (2012):142.

74. Thompson AE, Bashook PG. "Rheumatologists' recommended patient information when prescribing methotrexate for rheumatoid arthritis". Clin Exp Rheumatol 28(2010):539.

75. Van Roon EN, van den Bemt PM, Tim LT, Houtman NM, van de Laar MA, et al. "An evidence-based assessment of the clinical significance of drug-drug interactions between disease-modifying antirheumatic drugs and non-antirheumatic drugs according to rheumatologists and pharmacists". Clinical therapeutics 31 (2009):1737-1746.

Citation: Singh S, Patil HC and Patil RK. "Drug Interaction of Methotrexate with its Adjuvant Drugs for Treatment of Rheumatoid Arthritis." J Ortho ClinRhuem(2020): 001 doi: 10.47755/J Ortho Clin Rhuemtol.2020.1.001