International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 15, Issue 2, 2023

Review Article

EFFECTIVENESS AND SIDE EFFECTS OF USING METHOTREXATE AND ADALIMUMAB IN THE TREATMENT OF RHEUMATOID ARTHRITIS PATIENTS

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Received: 20 Aug 2022, Revised and Accepted: 27 Oct 2022

ABSTRACT

Rheumatoid arthritis (RA) is one of the diseases autoimmune systemic progressively characterized by inflammation of the membrane synovial that coating joints. Methotrexate (MTX) and adalimumab are one of the drugs that are commonly used in Rheumatoid arthritis treatment. This study is aimed to look at the effectiveness and safety of both either in monotherapy and a combination of them. This study is a review of the article of experimental studies with data retrieval retrospectively on a database that has been set, namely PubMed, Google Scholar, and Portal Garuda were conducted for 6 mo. The use of adalimumab showed improvement based on the value DAS28-4(ESR) and HAQ-DI when compared with methotrexate. The side effects caused by MTX showed the risk was more than 2% than adalimumab. Several drug carriers are determinants of therapeutic efficacy, such as sRNA (small interfering-RNA), LPNP (hybrid lipid-polymers nanoparticles), FRβ (Folate-receptor β), NF-κB (nuclear factor kappa-light-chain-enhancer of activated B-cells), β-GP (β-Glycerophosphate). The use of adalimumab monotherapy has slightly better effectiveness than methotrexate but has more diverse side effects but less risk. The use of the combination does not have a significant difference, but the risk of side effects from both is lower than when used alone.

Keywords: Rheumatoid arthritis, Methotrexate, Adalimumab, Monotherapy and combination therapy

DOI: https://dx.doi.org/10.22159/ijap.2023v15i2.46158. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Rheumatoid arthritis (RA) is a form of development of progressive of diseases autoimmune systemic, which is characterized by inflammation of the membrane synovial that coating joints. This inflammation can cause pain, stiffness, swell and even cause cartilage erosion and deformity resulting in damage to function and irreversible disability [1, 2].

In addition to its high incidence, the presence of this disease can also increase the risk of death. Women aged over 18 y have a two to three times risk level for suffering this disease compared to men and attacks someone in a long period (chronic) of about 6 mo to 1 y. Rheumatoid arthritis cannot be cured completely but only control (remission) of the symptoms that occur so as to minimize the risk of bone damage and even death [3, 4].

Based on the data released by the World Health Organization (WHO) in 2010 fig. incidence of the disease have reached 0.5 to 1% of the total population of the world or estimated approximately 69.23 million inhabitants (the number of inhabitants 2010 world around 6.923 billion). But in 2012 the number increased to 25%. However, the prevalence rate in Indonesia is not too high compared to other regions in Europe [5, 6].

Medical therapy in Indonesia refers to the National Formulary that has been stipulated in the Decree of the Minister of Health of the Republic of Indonesia Number HK.01.07/MENKES/813/2019. Medication therapy rheumatoid arthritis using the drugs methotrexate (MTX) as a *first line* that works with inhibiting the proliferation of cells of inflammation, neutrophil to reduce the of proteins pro-inflammatory such as TNF-α and IL-1B via increased adenosine release [7].

In addition, the carrier compounds contained in the drug will also greatly determine the efficacy of a drug. Changes in the binding of a drug in the systemic pathway can change due to the drug carrier. This is another matter that affects the efficacy of using drugs, especially MTX and Adalimumab. The factors are influence such as changes in the application of heat, pH, and activation by light. Drug carriers are also used to improve pharmacokinetic and pharmacodynamic properties. Several varieties of drug carrier systems have been developed and studied, each of which has advantages and disadvantages. One of the more popular types of drug carriers include liposomes, polymeric micelles, microspheres, and nanoparticles [8].

The use of drugs for long-term therapy on rheumatoid arthritis is certainly to achieve and the best effectiveness and minimize the side effects. This review was conducted to see the most efficient use of drugs for RA disease.

MATERIALS AND METHODS

This study used a narrative review on articles that have experimental methods with data collection in the last 10 y, starting from 1st June until 30th December 2020. Database of article used in this study is *Portal Garuda, Google Scholar* with using keywords "*Rheumatoid Arthritis, Methotrexate, Adalimumab, and Combine of them*". All articles obtained were screened with inclusion criteria such as articles containing the treatment of rheumatoid arthritis, using the drug *methotrexate, adalimumab,* and a combination of them, containing data on the efficacy or side effects of using methotrexate, adalimumab, or a combination both. Articles can be accessed in full papers and published articles in 2010-2020.

The exclusion criteria in this journal review include articles containing MTX or *Adalimumab* for cancer therapy. This article indicated a conflict of interest in the publication or research process. The article indicated duplication, and the article with the subject patient geriatric, pediatric, or pregnancy.

RESULTS

Rheumatoid arthritis is an autoimmune disease that can affect both men and women. Because it is related to the immune system, hormonal influences should not be ruled out for the prevalence of RA.

However, the percentage prevalence of both can be seen by clearly in table 1 as follows.

Quality assessment

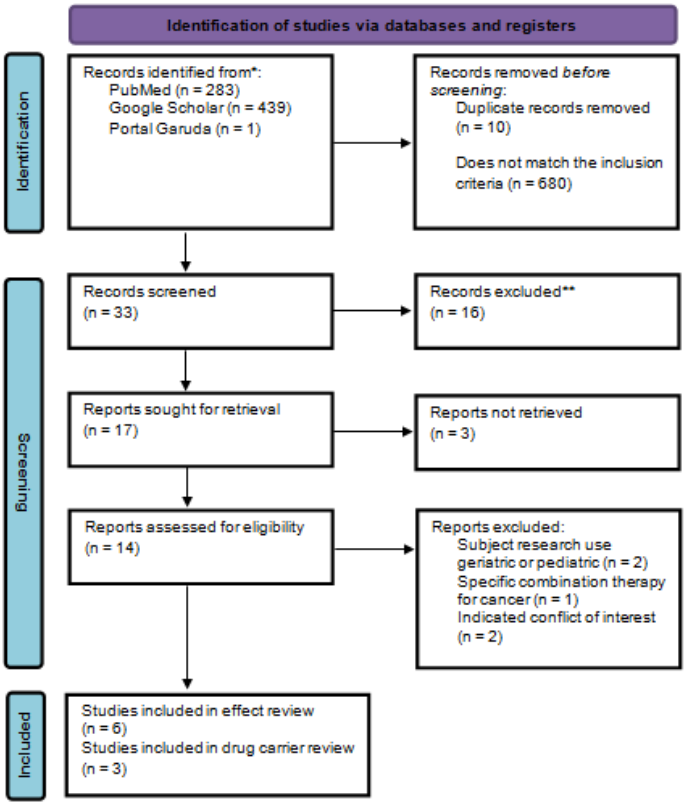

Fig. 1: Assessment review chart [9]

Table 1: Patient's baseline characteristics

No	Author	Total patient	Gender		Average age (Years)	Reference
			Male	Female		
1.	Conaghan	109	19	90	48,8	[10]
2.	Keystone	140	43	97	50,5	[11]
3.	Chen	396	47	349	47,7	[12]
4.	Burmester	6.610	1278	5332	53,7	[13]
5.	Furst	606	101	505	55,4	[14]
6.	Fleischmann	1.146	196	950	50,1	[15]
Total		9007	1684 (18,69%)	7323 (81,31%)	51,03	

Base on that study consisting of 1684 male (18,69%) and 7323 female patients (81,31%) with an average age of about 51 y ago, knowing that this rheumatoid arthritis did attack all races and could not be guessed for specifically, the ratio between men and women suffering from this disease was 1:4 and mostly attacks on women. This is in accordance with the results of studies related to the relationship between sex and the incidence of rheumatoid arthritis that women are 4,016 times more risk than men. This is because women have hormone estrogen which can stimulate autoimmune events, causing rheumatoid arthritis and an inappropriate diet and lifestyle also trigger this disease.

Methotrexate

Single or combination use in therapy is often a separate choice according to the effectiveness and rationality, but in the use of MTX in a single way MTX can influence RA patients based on DAS28-4 (ESR) "disease activity score in 28 joints with 4 variable including erythrocyte sedimentation rates". In table 2 can be seen the results from an analysis related to protective policies on how to treat rheumatoid arthritis patients.

Patients taking methotrexate have shown an improvement and a decrease in inflammation in the synovium as described by RAMRIS (*Rheumatoid Arthritis MRI Score*). However, the results were not better than the comparison drug from the Janus Kinase Inhibitor (JAK Inhibitor) group, which showed better improvement [10]. JAK Inhibitor works by blocking the binding between inflammatory cytokines in the auto-immune response so that the inhibition of inflammation will be more visible. Methotrexate works in several pathways, one of them is the inhibition of the aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase (ATIC), which triggers the release of adenosine. Still in the same effect but in a different pathway, MTX can inhibit nuclear activation factors that also play in role in the release of adenosine. It is known that adenosine will bind to the cell surface to suppress inflammatory reactions and immune reactions. MTX also works by inhibiting dihydrofolate reductase which can increase the sensitivity of T cells that play an important role in the immune response. MTX is known to modulate specific cells such as macrophages, fibroblast-like synoviocytes and endothelial cells that play an important role in the pathogenesis of RA. MTX also plays a role in the transcription process of apoptosis inhibiting genes, where this process increases the cure rate from RA in the use of MTX [1]. Although the decrease in DAS28-4 (ESR) is not good as well as the group of JAK Inhibitor, but overall, the mechanism of MTX can be exploited to suppress the autoimmune response that occurs in RA's patients by other pathways.

Table 2: The result of the review of methotrexate

No.	Author	Method	Research result	Reference
1	Chen	Multicentre RCT, double blind	From the decrease value of DAS28-4 (ESR) shows that the effectiveness of using the method alone is not better if it is used in combination with other drugs.	[12]
2	Conaghan	RCT *double blind*	The use of MTX did not show any better improvement when used alone than a JAK Inhibitor (Tofacitinib). This can be seen from the value of DAS28-4 (ESR) around<3.2.	[10]

DAS28-4(ESR) (*disease activity score in 28 joints with 4 variable including erythrocyte sedimentation rate), MTX (Methotrexate), JAK Inhibitor (Janus Kinase Inhibitor*), RCT (*Randomized Controlled Trial)*

Adalimumab

Adalimumab is TNF-α inhibitor that modifies monochromatic antibodies and inactivates tumor necrosis factor-alpha (TNF-α). It is recommended for patients who are ineffective with conventional DMARD. It also diminished signs and symptoms in RA patients. From the articles reviewed in table 3. With double-blind RCT method showed that adalimumab was able to show good effectiveness in its use. Even in combination using, it can give a double effect of using MTX.

Table 3: Result review of adalimumab effectiveness

No	Author	Methods	Research result	Reference
1	Burmester	RCT	Using adalimumab for more than 5 y has a good clinical response and its effectiveness can be maintained during long-term observation	[13]
2	Furst	RCT double-blind	Using adalimumab showed improvement in symptoms and signed of RA. Adalimumab is also effective use for patient who do not show improvement in conventional DMARD such as MTX.	[14]

RCT (Randomized controlled trial), RA (Rheumatoid arthritis), DMARD (disease modifying anti rheumatic drugs), MTX (Methotrexate)

Specifically, adalimumab works directly by inhibiting TNF-α so that it inhibits inflammation. Based on the value of DAS28-4(ESR) in using adalimumab for approximately 5 y showed a consistent decrease, not only that from the HAQ-DI (Health Assessment Questionnaire Disability Index), indicating that the patient is able to achieve normal conditions for joints.

On table 3, the treatment therapy of RA using adalimumab monotherapy was started at a dose of 40 mg per week injected subcutaneously. Adalimumab in active RA patients who have receive various anti-rheumatic drugs with a duration of illness of 10,4 y with 27,5 of TJC value (Tender Joint County i.e. an assessment of the presence of tenderness in 28 joints) and 21,1 of SJC value (Swollen Joint County i.e. an assessment of the presence of swelling in 28 joints). At week 24, patients who taking adalimumab got statistically superior scores compared to placebo group. In this study showing the results that the addition of adalimumab, after the use of RA therapy for conventional DMARD was discontinued, it was able to provide good clinical response.

Both Methotrexate and Adalimumab have side effects that can appear randomly in certain patients. The results of the following article review in table 4. showed the side effects that arise due to use of Methotrexate and Adalimumab monotherapy as well as duel therapy.

Table 4: The result of review of the safety of the use of methotrexate and adalimumab either as monotherapy or a combination of them in rheumatoid arthritis patients

No	Author	Methods	Side effects	Amount (%)
1	Burmester [13]	RCT	Using Adalimumab	N = 6610
			TB	35 (0,52%)
			Sepsis	35 (0,52%)
			Malignancy	121 (1,83%)
			Lymphoma	15 (0,22%)
			NMSC *(non-melanoma skin cancer)*	43 (0,65%)
			CHF (*Congestive Heart Failure*)	47 (0,71%)
			Cerebrovascular	56 (0,84%)
			Hepatic Disorder	58(0,87%)
2	Keystone [11]	RCT *double blind*	Using MTX	N = 56
			NMSC *(non-melanoma skin cancer)*	2 (3,5%)
			Reaction at the Injection Site	2 (3,5%)
			Dead	2 (3,5%)
			Infection	41 (73,2%)
3	Fleischmann [15]	RCT *double blind*	Using Adalimumab dan MTX	N = 386
			Serious Infection	6 (1,55%)
			Herpes zoster	6 (1,55%)
			Opportunistic Infection	2 (0,51%)
			MACE (*mayor adverse cardiovascular event)*	2 (0,51%)

RCT (Randomized Controlled Trial), DMARD (disease modifying anti-rheumatic drugs) NMSC (non-melanoma skin cancer, MACE (mayor adverse cardiovascular event)

In the incidence of infections due to the use of adalimumab, it shows that there is a risk from mild to serious. The greatest infections occur include the respiratory system, such as sinusitis, influenza to TB, sepsis, and pneumonia for cases of serious infection. In lymphoma and malignancy, it has also been identified that there is a close relationship with adalimumab binding to receptors [16].

Besides that, some side effects were also seen due to the inhibition of monochromatic antibodies, such as NMSC (non-melanoma skin cancer), lymphoma, up to respiratory tract infections. However, the small percentage and only<2% indicate that the effectiveness of adalimumab is still greater than the side effects to worry about. The use of methotrexate itself has a>2% risk of side effects from allergic reactions, NMSC (Non-Melanoma Skin Cancer) or infections. Infections that occur in accordance with the results of previous studies that used MTX can cause abnormalities in WBC due to the complex mechanism of action of MTX. This comparison shows fewer side effects than adalimumab, although the efficacy of using two alone is not much different. So, maybe this is a clinical consideration in choosing MTX as the first line in some cases of RA. This interesting thing can be seen in the use of the combination of them, the risk of side effects is smaller and less, but it still must pay attention to the dose of the two drugs. Opportunistic infections are believed to occur from the suppression of the immune system due to both drugs that work together both in cytokine, T cell exposure, and macrophage. Use a combination of both showed a response that is not much different with a single treatment in rheumatoid arthritis, but for side effects, it can be suppressed. From a safety point, it might be more, but from economic point might burden patients [17].

Effect methotrexate and adalimumab from the drug carrier side

Drug carrier is any substrate used in the process of drug delivery which serves to improve the selectivity, effectiveness, and safety in drug dispensing. Drug carriers are primarily used to control the release a drug into the systemic circulation body.

Table 5: The review of the drug carrier of methotrexate and adalimumab

No.	Drug	Author	Target cell	Drug carrier	Reference
1	Methotrexate	Duan	NF-κB	siRNA	[18]
		Zhao	FRβ	LPNPs	[19]
2	Adalimumab	Chen	Corneal epithelial cells (HCEC) and retinal pigmen epithelial cells (ARPE 19)	β-GP	[20]
3	Methotrexate	Ahuja	LHRH	siRNA Gold half-shell nanoparticle	[21, 22]
			FPGS	Arginine glycine	

siRNA (small interfering-RNA), LPNP (hybrid lipid-polymers nanoparticles), FRβ (Folate-Receptor β), NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), β-GP (β-Glycerophosphate), LHRH (Luteinizing hormone-releasing hormone), FPGH (Foly-Poly Glutamyl Synthase).

NF-κB system is the important therapeutic target for inflammatory response and NF-kB has role in signaling pathways and reduced the expression of pro-inflammatory cytokines. The combination siRNA and methotrexate can be reduced risk for pathogenesis of rheumatoid arthritis in the joints. Nanocarriers targeted at folate receptors showed suppression of arthritis progression directly due to siRNA accumulation. This indicated there is a good therapeutic efficacy and safety level in the treatment of RA using methotrexate.

In LPNPs, which have high biocompatibility in circulation, the drug will last longer in the bloodstream but can accumulate quickly in tumor tissue because it has a high permeation and retention effect, which will increase vascular permeability. This makes it excellent as a drug delivery agent for RA. The advantages that result from a selective delivery system in MTX, will make the effect better and the risk of side effects lower because the release of MTX into the blood circulation is shorter.

LPNPs are very responsive to pH where the state of inflammatory tissue pH is 6.5, which is lower than blood, which is 7.4. FRβ is a cell that can over-activate macrophages in several inflammatory diseases such as RA. These two things are interrelated in the success of therapy because the good responsiveness of LPNPs to pH and accelerated drug release under acidic conditions indicate the inhibition of activated FRβ so that cell proliferation is inhibited and can reduce the development of inflammation, especially in rheumatoid arthritis (RA).

β-GP shows good biocompatibility when used with adalimumab. β-GP causes increased permeability and efficacy in both corneal and retinal cells. When viewed in the treatment of rheumatoid, it can be said that the role of β-GP as a drug carrier can work if used topically due to increased membrane permeability.

In general, the use of MTX is more widely used either as monotherapy or in combination with other DMARDs in RA disease with high to low severity [23]. The silencing achieved with small interfering RNAs (siRNAs) is transient. Therefore, new strategies have been developed and reported for a longer period of silence. The programmed strategy of vectors such as short hairpin RNA (shRNA) can also be used for a long-term stable cell silencing method. siRNA has been encapsulated in fully charged particles that provide effective protection against seroconversion and off-target immune effects. Mediators such as growth factors, proinflammatory cytokines, chemokines, cell adhesion molecules, and proteases play an essential role in the development of RA. In this plan, angiogenesis and inflammation are conditions implicated in the progression of RA [21].

DISCUSSION

The use of MTX or Adalimumab in rheumatoid patients is a clinician's choice in therapy. However, its use sometimes does not see whether effectiveness and safety are directly proportional. This study provides a clinical picture of how the effectiveness and safety of its use in patients in single or combination therapy can be considered by doctors in considering the effect. In addition, the description of the drug carrier involved can be a reference for pharmacologists in assessing the mechanism of action of drugs that are suitable for patients with rheumatoid.

In the safety point for the use of MTX alone, there are several side effects such as a decrease in WBC (White Blood Cells), respiratory tract infections, rash, urinary tract infection, adenopathy, pulmonary infections up to abnormal stools. On pulmonary infection, side effects in the use of MTX was associated with the activation of T cells. The fact is that MTX release of cytokines by type 2 alveolar cells cause alveolitis because of inflammations that occurs. MTX is directly stimulates new fibroblast and epithelial cells to induce the recruitment of eosinophils and neutrophils. This explains how a decrease in the WBC can occur in the use of MTX [24].

Platelet or chemical complications of thrombocytopenia can occur, which can be followed by the development of leukoneutropenia, which usually occurs 1 w after the use of MTX. Hematologic disorders on the use of MTX are associated with folic acid deficiency to the risk of kidney disorders. Although renal impairment due to the use of MTX is rare, the risk of acute renal failure can occur due to obstruction and decreased ClCr (creatinine clearance) of the kidney due to high levels of MTX in blood which triggers oxygenation and affects the tubular epithelium and causes vasoconstriction in the renal arteriole. While the effect on digestive system disorder is usually caused by the dose effect of MTX, so that dose management in MTX users must be considered. Damage to the liver is not yet clear and increased serum aminotransferase elevations are associated not only with infectious factors, alcohol, diabetes, and obesity also with the effect of folic acid in the body [24].

Cytokines play an important role in any disease as a means of cell communication and cell activation and cytokine regulation is an important factor in the regulation of diseases such as rheumatoid arthritis. For example, NF-κB is activated in the synovial membrane of RA patients. Disease-modifying antidepressant drugs (DMARDs)"modify" the disease process in all these respects, and

once a DMARD is effective, no further symptomatic treatment is needed. Examples include methotrexate [25].

Patients with RA do not adhere to their DMARDs prescriptions. Interventions and educational programs should incorporate individual beliefs about medications and improve adherence to DMARDs that will subsequently improve the effectiveness of medical treatments and FPGS polymorphism have associated with side effects [22,26]. These changes were attributed to MTX-induced increases in both oxidative and nitrosative stress because of exposure of the liver to high concentrations of MTX oxidative metabolites. Inhibition of the cytosolic de novo synthetic pathway for purines, pyrimidines, and polyamines by methotrexate reduces hepatic folate reservoirs, limits folate entry into mitochondria, and affects S-phase nucleic acid synthesis [27].

Single-use in RA therapy for both Methotrexate and Adalimumab had a slight difference in effectiveness, although adalimumab had slightly greater effectiveness but fewer side effects than methotrexate. However, adalimumab's side effect presentation is also smaller than methotrexate.

Increased permeability due to the target cell drug carrier factor is also an important factor in terms of efficacy and safety. if viewed more broadly, the drug carrier becomes a determinant for a drug to maintain its bioavailability. However, the patient's disease condition also influences the effectiveness of the drug.

Knowledge the effectiveness in the treatment of rheumatoid, the efficacy in treatment that uses high costs as in other autoimmune diseases can also have a positive effect. Efficient treatment by reducing the risk of side effects and increasing protection in other autoimmune diseases could be a step in the field of medicine, especially for diseases that use MTX and Adalimumab in therapy. Medical science that continues to develop and undergo adjustments in the future does not rule out the possibility to the genetic stage. With the drug carrier data into consideration, the effect of treatment to the choice of individual therapy.

CONCLUSION

Use of Adalimumab is a little better than methotrexate in the basis of monotherapy with a small risk of side effects but diverse. In the use of a combination of both for rheumatoid arthritis, there is no significant difference compared to monotherapy, but the risk of side effects can be reduced by using the combination.

ABBREVIATION

DAS28-4(ESR) = *disease activity score in 28 joints with 4 variable including erythrocyte sedimentation rate.*

MTX = Methotrexate.

JAK Inhibitor = Janus Kinase Inhibitor.

RCT = *Randomized Controlled Trial.*

RA = Rheumatoid Arthritis.

DMARD = Disease modifying anti rheumatic.

NMSC = *non-melanoma skin cancer.*

MACE = *mayor adverse cardiovascular event.*

siRNA = small interfering-RNA.

LPNP = hybrid lipid-polymers nanoparticles.

FRβ = Folate-Receptor-β.

NF-κB = Nuclear factor kappa-light-chain-enhancer of activated B cells.

β-GP = β-Glycerophosphate.

WBC = White Blood Cells

ClCr = Creatinine Clearance

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

There are no conflicts of interest.

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