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A Narrative Review: Efficacy and Safety the Used of Corticosteroids as an Adjunct Therapy for Rheumatoid Arthritis

Hendra Herman[1], Irma Rachma Hanifah [2], Andi Maulana Kamri [3]
[1] Faculty of Pharmacy, Universitas Muslim Indonesia, Makassar, Indonesia, & Clinical Pharmacy, Ibnu Sina Hospital, Makassar, Indonesia
[2] Faculty of Pharmacy, Universitas Muslim Indonesia, Makassar, Indonesia
[3] Faculty of Pharmacy, Universitas Muslim Indonesia, Makassar, Indonesia, & Clinical Pharmacy, Islamic Faisal Hospital, Makassar, Indonesia

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Corresponding Author:
Hendra Herman
Faculty of Pharmacy,
Universitas Muslim Indonesia,
Makassar, Indonesia
Clinical Pharmacy, Ibnu Sina
Hospital, Makassar, Indonesia
Email:
hendra.herman@umi.ac.id

ABSTRACT

Rheumatoid Arthritis (RA) is an autoimmune disease characterized by inflammation of the joints. The selection of corticosteroids with broad indications is used as an adjunct therapy because of its anti-inflammatory activity and immune suppression. The research aimed to determine the efficacy and safety profile of corticosteroids in rheumatoid arthritis patients. The method used was a literature review with a narrative review design based on inclusion and exclusion criteria through the PubMed and Google Scholar databases. The results showed that the Prednisone group with varying doses of 5 mg; 6.25 mg; 10 mg gave better efficacy than the placebo group or Methotrexate monotherapy against disease activity with the DAS28 parameter. Prednisone safety was observed from the side effects, hypertension; hyperglycemia and adverse events, headache; reported diarrhea. The review show that the use of Prednisone tab 10 mg/day provided the best efficacy in the first 3 months ($p<0.001$) with the DAS28 parameter which achieved the greatest clinical remission. The side effects of Prednisone could not be concluded between the effect of dose and the level of drug safety.

Keywords:
Corticosteroids, Glucocorticoids, Rheumatoid Arthritis, Efficacy and safety.

1. INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation of the joints and synovium that is symmetrical and systemic. Seeing the activity of RA attacking the joints, serious attention is needed because joint inflammation makes it difficult for a person to carry out their daily activities. A more severe impact, RA causes paralysis and even death because the systemic effects caused are able to attack other organ systems in the body [1],[2].

According to Riskesdas, patients with RA based on doctor's diagnosis in patients over 15 years old in Indonesia reached 7.3% and the province with the highest prevalence was in Aceh 13.3%. As the number of RA sufferers in Indonesia increases, the level of knowledge and information about RA is very low. Many people think that RA is just an ordinary arthritis, so it is too late to take treatment [3].

Research on the management of RA therapy has been carried out. Disease Modifying Anti Rheumatic Drugs (DMARDs) are the main choice of therapy, while corticosteroids are used as adjunctive therapy for DMARDs [2]. The important thing to achieve in the management of RA is to control symptoms and suppress disease activity. For this reason, most of the management of RA involves anti-pain and anti-inflammatory drugs to control the pain that is so intense.

Corticosteroids are often used to treat RA because of their anti-inflammatory and immunosuppressive properties. Consideration of the use of corticosteroids at the beginning of treatment is done if symptoms are not controlled with DMARDs. Before research results of 90% of 30 RA patients received corticosteroid therapy alone or in combination with DMARDs and the use of corticosteroids was effective in controlling symptoms in RA [4].

Corticosteroids are often called life saving drugs or divine drugs because of the wide range of clinical indications. However, the indications produced are also proportional to the side effects caused by the drug. In the research of analyzed data on 1066 patients using corticosteroids for a period of more than 6 months, there was a side effect of increasing blood pressure in the dose range <5 mg/day to >7.5 mg/day by 23.0% [5].

Other side effects that can arise are osteoporosis, hyperglycemia, glaucoma and cataracts. For this reason, the use of corticosteroids must be carried out carefully starting from the lowest but effective dose because even the lowest dose can cause other side effects in the form of infection. In addition, the duration of corticosteroid use needs to be considered because long-term use can increase the risk of side effects [2].

The use of corticosteroids does not escape the huge side effects that await, however, given the large role of corticosteroids in RA therapy, it is hoped that through the right dose the side effects can be minimized in order to achieve recovery and improve the patient's quality of life. For this reason, a narrative review study was conducted to determine the safe dose of corticosteroid use.

2. METHOD

This study uses a literature review method or literature review with a narrative review design. The research was conducted by reviewing the literature in the form of articles conducted from February 2021-May 2021 through a database of international journals (PubMed and Google Scholar), and by considering certain inclusion and exclusion criteria. Article searches are carried out using keywords to make searching easier. The keyword variations used are corticosteroid, glucocorticoid, rheumatoid arthritis, efficacy and safety.

2.1. Inclusion Criteria

The inclusion criteria in this study are, articles published in international journals (in English), time of publication of articles from 2010-2021, articles available with free full text, articles comparing between more than one group using corticosteroids as a comparison drug, and articles have an ISSN number.

2.2. Exclusion Criteria

The exclusion criteria in this study were the article did not discuss the use of corticosteroid drugs in the treatment of rheumatoid arthritis, the article was a research review, and the article did not state the drug and dose of corticosteroid medication.

3. RESULTS AND DISCUSSION

This study aims to review articles related to the efficacy and safety of using corticosteroids as adjunctive therapy in rheumatoid arthritis patients. The final result to be achieved is to find out how the efficacy and safety profile of the use of corticosteroid drugs for rheumatoid arthritis patients.

Table 1. Results of a Review Article on the Use of Corticosteroids in Rheumatoid Arthritis Patients

No.	Researchers	Method	Intervention	Patients	Result	P value (DAS28)
1.	Frank Buttgereit *et al*. German (2012) [6]	RCT, 3 month	MTX+PDN tab 5 mg/day **VS** MTX+placebo	350 (231:119)	Prednisone 5 mg/day provides good efficacy in reducing disease activity and controlling symptoms, compared to the placebo group	p< 0,001
2	Marije F. Bakker *et al.* Dutch (2012) [7]	RCT, 24 month	MTX+PDN tab 10 mg/day **VS** MTX+ placebo	236 (117:119)	Prednisone 10 mg/day provides good efficacy in reducing disease activity and controlling symptoms, compared to the placebo group	p< 0,001
3.	Carlomaurizio Montecucco *et al.*Italy (2012) [8]	RCT, 12 month	MTX+PDN tab 6,25 mg/day **VS** MTX monotherapy	220 (110:110)	Prednisone 6.25 mg/day provides good efficacy in reducing disease activity and symptom control in early RA, compared to the monotherapy group.	p< 0,05

*DAS28, *disease activity score 28 joints*; DMARDs, *disease modifying anti rheumatic drugs*; MTX, metotreksat; PDN, prednison; RCT, *randomized controlled trial*; Tab, tablet.

Based on Table 1, the three articles were obtained using the RCT method. The use of the RCT method is the golden standard of experimental research. There were 2 articles using a double-blind RCT with placebo (articles 1 & 2) and 1 other article using a non-blind or open label RCT without placebo (article 3). If examined based on the method used in the study, the level of confidence in the double-blind article is higher than the non-blind. The non-blind method reduces the confidence level of the article because it is feared that there will be a bias effect that gives suggestions to both parties, both patients and researchers [9].

He presence of a placebo in the RCT method also minimized the effect of bias in the results of the study. The use of a placebo can confirm whether the improvement effect "simply" comes from the test drug and not from

suggestions [9]. Thus, of all the articles reviewed, the third article [8] provides a lower level of confidence than other articles.

The research time for the first article was shorter (3 months) than the other 2 articles (24 months and 12 months). Varied and quite different study times did not affect the determination of drug efficacy, because the determination of efficacy was observed when 3-4 months of corticosteroid use and at that duration showed good symptom control [10]. This is done by observing the DAS28 values which have different significance values. In contrast to the determination of efficacy, to see the safety profile of drug use observed from the side effects reported in the review article, it can be assumed that the longer the research time, the more monitoring time it is expected to provide more valid data. Based on the year of publication of the article, all three articles have the same publication year, namely 2012. When compared to the time when the article review was conducted, the time span is far enough that there is concern that data updates will be missed. However, seeing from the absence of a definite dose of corticosteroid use in RA therapy but using a dose range, this article from the 2012 publication year can be used because it still meets the dosage range requirements data.

3.1. Review of Corticosteroid Efficacy

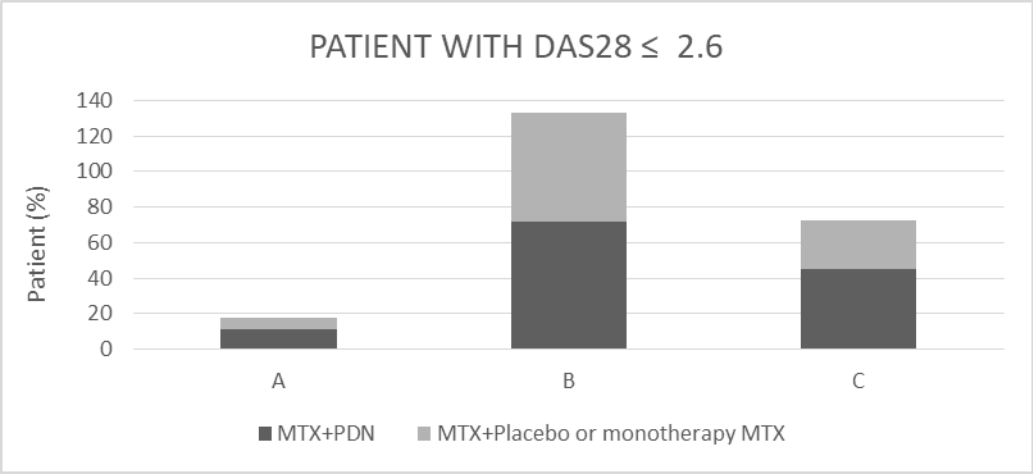

Figure 1. Frequency of RA Patients Reaching DAS28≤ 2.6.

Based on Figure 1 the three articles gave similar results with regard to the efficacy of corticosteroids, that corticosteroids provided an improvement in the control of RA symptoms. The efficacy parameter was evaluated from the DAS28 value that achieved remission or provided an improvement in disease activity. It is said to be in remission if the DAS value is 28≤2.6 (Perhimpunan Reumatologi Indonesia, 2014). From the data obtained, the frequency of patients achieving DAS28≤2.6 remission was significantly higher in the MTX+PDN group than in the placebo or MTX monotherapy group.

The higher frequency of patients achieving remission in the MTX+PDN group compared to the placebo or MTX monotherapy group ($p<0.05$) indicates that the use of corticosteroids provides better results in symptom control of RA. In this case, the most widely used corticosteroid is prednisone tablets. The presence of high remission in the MTX + PDN group cannot be separated from the characteristics of prednisone which has a dominant glucocorticoid effect so that it becomes the choice for anti-inflammatory, anti-pain and immunosuppressive indications [11].

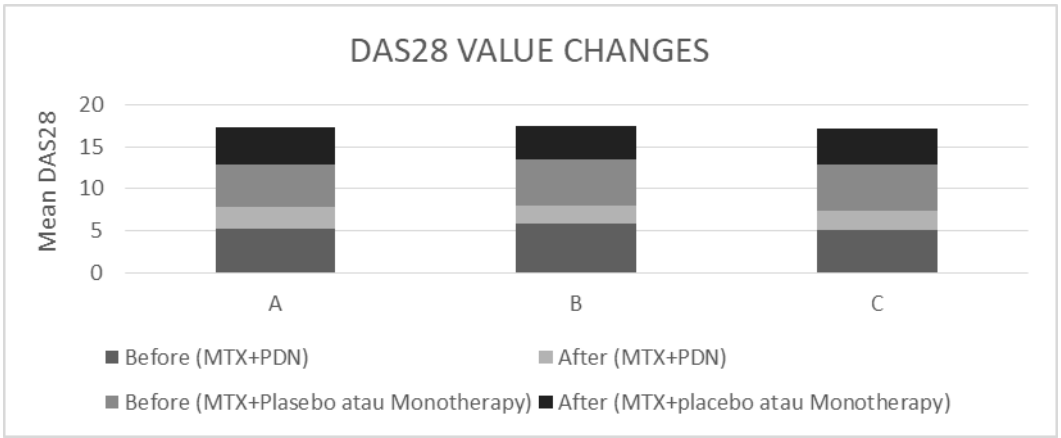

Figure 2. DAS28 Value Before and After Use of PDN

Based on the articles reviewed, there are 3 variants of PDN dosage, namely 5 mg; 6.25 mg; and 10 mg. From the data in Figure 2, the largest difference in remission of DAS28 values is in PDN 10 mg (difference in value of 3.6). This difference illustrates a very significant improvement in the DAS28 value, meaning that high-dose PDN activity is better in controlling RA symptoms than low-dose PDN. The dose of PDN to achieve good efficacy in treatment is carried out with low-dose corticosteroid management starting from a dose of 5 mg-10 mg / day. This is in accordance use of low-dose corticosteroids PDN 10 mg/day (or equivalent) and the use of therapy time < 3 months.

The more significant value of DAS28 at 10 mg PDN is supported by research that the higher the dose, the greater the effect. However, keep in mind that the management of corticosteroids should start from the lowest effective dose and in a short time [11]. The minimize the number of unwanted events. In addition, monitoring of RA management must continue to be carried out periodically to ensure the dose is safe enough for the patient [12].

3.2. Review of Corticosteroid Safety

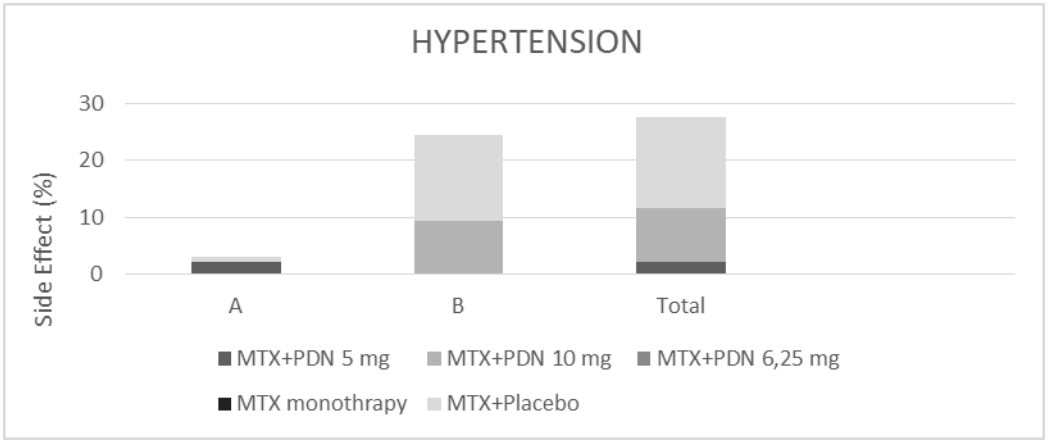

Figure 3. Hypertension Incidence in RA Patients After Receiving Intervention.

In Figure 3 the highest percentage of hypertension occurred in MTX+placebo (15.9%) followed by MTX+PDN 10 mg (9.4%). The incidence of hypertension in the use of PDN is a side effect of corticosteroids. This side effect is caused by fluid and sodium retention resulting in an increase in blood volume and an increase in peripheral resistance which results in an increase in blood pressure. Furthermore, when viewed from the dose used, the percentage of hypertension in PDN 10 mg is higher than PDN 5 mg. This is supported by the theory that the higher the dose, the greater the side effects produced.

In patients taking MTX in 2 articles [6],[7] hypertension side effects were higher on placebo compared to PDN. This incident is not known for certain. Based on the literature the use of MTX does not cause hypertension side effects. Referring to the literature, the percentage of placebo should be lower than that of PDN, so further research is needed to find out the reasons for these results [2].

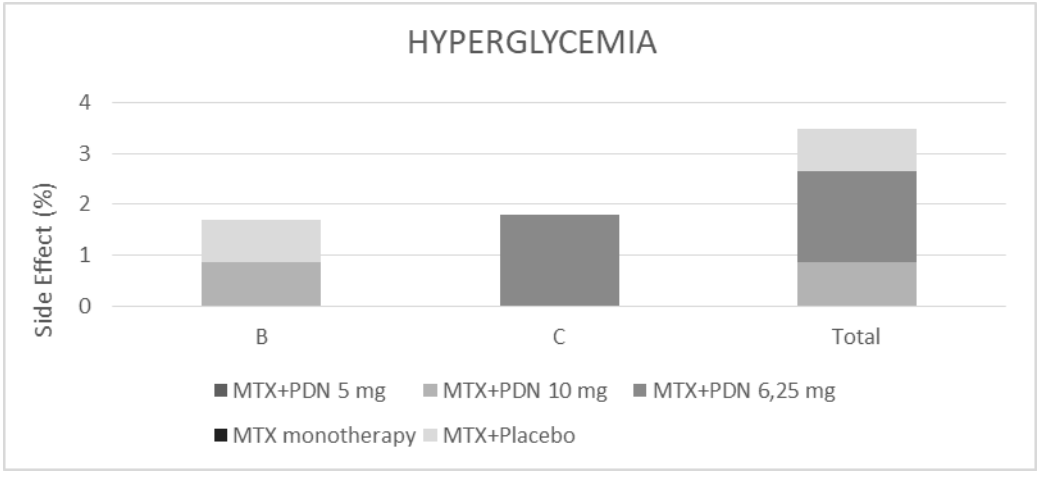

Figure 4. Incidence of Hyperglycemia in RA Patients After Receiving Intervention.

In Figure 4 the highest percentage of hyperglycemia occurred in MTX+PDN 6.25 mg (1.8%) followed by MTX+PDN 10 mg (0.85%). Similar to hypertension, hyperglycemia is a side effect of corticosteroids, the occurrence of hyperglycemia is related to the characteristics of PDN glucocorticoids that mimic cortisol and then affect the metabolism of carbohydrates, fats and proteins so that they can stimulate gluconeogenesis.
The high percentage of hyperglycemia of PDN 6.25 mg compared to PDN 10 mg has not been found for a definite reason because if referring to the "The dose alone makes poison" the higher the dose, the greater the side effects produced. Meanwhile, there is no literature that supports why hyperglycemia occurs in the placebo group because when viewed from the point of view of the use of MTX it does not cause side effects of hyperglycemia [2].

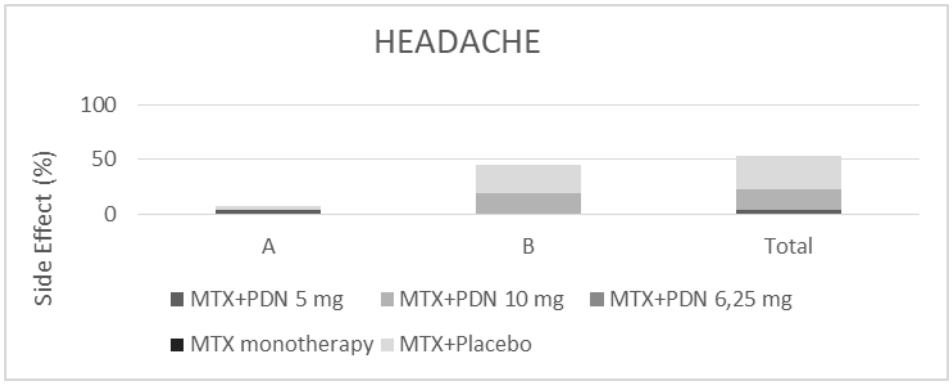

Figure 5. Headache Incidence in RA Patients After Receiving Intervention.

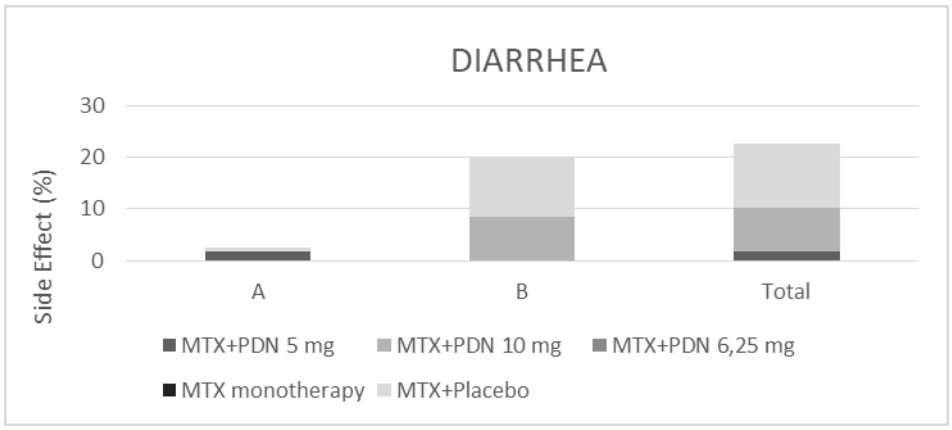

Figure 6. Diarrhea Incidence in RA Patients After Receiving Intervention

Different with hypertension and hyperglycemia case, in Figure 5 and Figure 6 the cause of headache and diarrhea cannot be known with certainty, because it is not related to the mechanism of action of PDN. For this reason, both are called adverse events [2],[3],[14].

Rheumatoid arthritis (RA) is thought to be an autoimmune condition. Rheumatoid factor (RF), anti-perinuclear factor (APF), anti-keratin antibodies (AKA), anti-collagen antibodies, and antibodies to nuclear antigens such Epstein-Barr nuclear antigen and RA33, anti-Sa, and anti-p68 antibodies are all strongly associated with the condition. The majority of these antibodies respond to and interact with citrullinated proteins [15–18]. There has been substantial advancement in RA treatment and disease remission without joint deformities. Despite this, a sizable part of RA patients do not respond well to the available treatments, necessitating the urgent need for novel medications [19],[20].

Nonsteroidal anti-inflammatory medicines (NSAIDs), corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and some biological agents are the most often used treatments for rheumatoid arthritis. However, none of the known treatments can lead to drug-free remission, which is the ultimate aim of treatment [21],[22],[23]. Despite the development of newer biologics, methotrexate (MTX) remains the cornerstone of the treatment of rheumatoid arthritis (RA). Fast acting, with the best efficacy:toxicity ratio, and also less expensive is MTX [24],[25],[26] .

4. CONCLUSION

Corticosteroids provide good efficacy in the treatment of rheumatoid arthritis. Prednisone tablets are the most used type of corticosteroid. Prednisone 10 mg/day provided the best efficacy at the start of treatment around the first 3 months ($p<0.001$) with the DAS28 parameter achieving clinical remission. Prednisone side effects found were hypertension and hyperglycemia, while the adverse events reported were headache and diarrhoea. Based on the level of safety, it cannot be fully concluded that the effect of the dose on the level of safety of the drug is because the results obtained are contrary to the existing theory

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