INTRODUCTION

Methotrexate is the first choice of Disease Modifying Antirheumatic Drugs (DMARDs) for therapy of RA. Improvement and effectiveness of therapy of RA can be measured through instruments such as Disease Activity Score 28 (DAS28). Its score is low for therapy effectiveness. DAS28 has been widely used clinically with a combination number of the tender joints, the swollen joints, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), and global clinical assessment by the patient.

Long-term therapy with adjusted doses of methotrexate is needed in order to achieve the remission condition for RA. Doses of methotrexate and length of therapy has been proven as a contributing factor to therapy efficacy, with regimen therapy of methotrexate with starting doses of 7.5-12.5 mg and usage interval of once weekly.2 The previous research conducted by Yamakata et al. (2007) said that there was a positive correlation in statistically between an average dose of methotrexate > 8 mg per week and DAS28 score < 3.2.3 The results of this study can be used by clinicians and pharmacists for evaluating the dose and length of therapy methotrexate in RA patient.

MATERIALS AND METHODS

The research was done at the Rheumatology Polyclinic of Saiful Anwar Hospital (RSSA), Malang from February-July 2018 and has been given ethical clearance number 400/SK/K.3/30/2018 by the ethics commission of RSSA. The research is a cross-sectional study, with quantitative analysis is the research method for acknowledging the correlation between methotrexate dosages as well as length of therapy and RA disease activity. The subjects who became involved in the study was calculated using the purposive sampling method and the subjects agreed to sign a consent form. In this study, the inclusion subjects are men and women > 20 years old who have been diagnosed with RA, have used only methotrexate for at least 3 months, possess laboratory results as differential diagnosis, and were proven to have RA with ESR. Patients did not possess other disease complications (such as IBD, SLE, or cancer). The exclusion are patients who smoke and/or drink alcohol. Data was collected through sheets that provide patient information by medical records, in addition to methotrexate doses, length of therapy, DAS28 component, and ESR results. Calculation of scoring results from DAS28 is performed using mathematical equations such as the following:4

\[
\text{DAS28} = 0.56 \times (\text{TJC28}) + 0.28 \times (\text{SJC28}) + 0.70 \times (\text{ESR}) + 0.014 \times \text{GH}
\]

Note: TJC = tenderness in 28 joints, SJC = swelling in 28 joints, ESR = erythrocrit sedimentation rate in the first 1 hour, GH = Patient's Assessment of General Health measured by VAS (Visual Analog Score).

Rheumatology Association.1 divides RA disease activity into the four severity degrees of remission, low activity, medium activity, and high activity, for which the classification is detailed in Table 1.

<table>
<thead>
<tr>
<th>Severity Level</th>
<th>DAS28 Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>≤ 2.6</td>
</tr>
<tr>
<td>Low activity</td>
<td>&gt; 2.6 to ≤ 3.2</td>
</tr>
<tr>
<td>Medium activity</td>
<td>&gt; 3.2 to ≤ 5.1</td>
</tr>
<tr>
<td>High activity</td>
<td>&gt; 5.1</td>
</tr>
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Statistical analysis included both Pearson and Rank-Spearman correlation in order to analyze the link of methotrexate doses and length of therapy to DAS28 score (<0.05).

RESULTS

The highest age prevalence at 46-55 years was 30 patients (table 2). The incidence of RA in women is influenced by the hormone estrogen which can reduce the immune response and secretion of proinflammatory cytokines. Estrogen can inhibit the formation of osteoclasts and synovial pannus so RA progression can be inhibited.5

The methotrexate dose given to patients differ based on disease conditions and tolerability. The target of RA therapy is remission with a DAS28 score ≤ 2.6. The results of this study showed 16 patients achieved remission. The result of cumulative dose of 16 patients are 120-2155 mg, an average doses of 6.25-12.5 mg and a maximum doses of 7.5 mg-15 mg. If we pay attention to the use of methotrexate doses in research, patients has not reached the maximum dose of 25 mg/week. It can be recommended for clinicians to provide therapeutic doses up to 25 mg in RA patients who have not yet reached remission. Increasing the dose can be done if after 4 weeks have not reached remission. Likewise with the initial dose of MTX can be recommended to increase the dose of 2.5-5 mg every 2-6 weeks depending on the severity of the disease, until reaching a maximum dose of 25 mg/week.6 The decision take a combination therapy using other conventional DMARDs or biological agents, will be applied to the patient therapy regimen if the condition of the patient worsens.6

Out of 16 of 88 patients who achieved the remission condition (DAS28 < 2.6) and have been receiving methotrexate for 120-240 weeks and the longest length of therapy was 624 weeks. The shortest length of therapy out of 88 patients was 12 weeks. Although statistically there is no significant relationship, the length of therapy with MTX can reduce the DAS28 score. This is in line with the effectiveness of MTX therapy. Half life (½) of methotrexate has different based on dosage. Half-life (½) of methotrexate on low doses is 3-10 hours, while on higher doses of 10-15 hours. The metabolic process of methotrexate produces active metabolites namely which hydroxymethotrexate.5 This metabolite has a half-life (½) of 12 hours. Half-life (½) of methotrexate affects the length of time influence in the body and also the effectiveness in regulating the dose and interval of therapy giving therapy. The success of methotrexate therapy not only depends on the dose and duration of therapy, but adherence to treatment therapy also plays an important role. Methotrexate also requires steady state time (6-8 weeks)9,10. The maximum dose and duration in the therapy single use of methotrexate was required to achieve remission in Rheumatoid Arthritis disease.

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REFERENCES