Combination Therapy with Rituximab and Methotrexate in the Management of Rheumatoid Arthritis

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Abstract
This study was conducted to evaluate the response and safety of rituximab combination with methotrexate with the aim of improving the quality of life in patients with active rheumatoid arthritis in Mosul city, Iraq. The study was done at Al-Salaam Teaching Hospital in Mosul City. Patients were well educated about the therapeutic profile of rituximab, including both risks and benefits. Enrolled patients: Male or female patients ≥ 18 years with active RA for at least 6 months before the study, inadequately responded to methotrexate therapy. The disease activity was assessed by measuring Disease Activity Score (DAS28). Indication of disease activity was swollen joint and tender joint count ≥ 8 and DAS28-ESR >5.1. Patients were excluded if: < 18 years or over 65 years, concomitant treatment with any DMARDs (other than methotrexate), chest infection, tuberculosis, hepatitis, diabetes, low immune patients, pregnant or breast feeding women. A detailed history and complete physical examination in all patients preceded rituximab therapy. The treatment included rituximab(MabThera1000mg) infusion on days 1 and 15 in addition to methotrexate. Patients were assessed at baseline, at the follow-up at 2 and 12 weeks post treatment, for disease activity score and for the safety outcomes. Remission rate was defined as DAS-28 < 2.6, swollen joints< 4, tender joints< 2, pain score <10 mm and ESR less than 20 mm/h. Sixty three patients with active RA were enrolled, aged 18–65 years. The duration of the disease was 0.6–30 years. Rheumatoid factor was positive in 59% of patients. The reduction in mean DAS28 and its component was highly significant (P < 0.0001) over the time. The reduction in mean DAS28 was highly significant (P < 0.0001) over the time. It was higher at the baseline (9.6) compared with its value (4.6) after first dose and (2.7) second dose, respectively. The disease activity suppressed in 96% of patients within 3 months, the remission was achieved in 50% of patients and 46% patients achieved low disease activity. While only 2 patients showed persistent disease activity (DAS >5.1). Of note, joint pain, and swelling were improved and most patients reduced their analgesic intake. Regarding the safety, the most commonly observed adverse events were infusion related reactions. They were developed in 29% of patients during the first infusion. They included, throat irritation, urticaria/flushing and headache. They were mild to moderate in severity. 8% of patients showed immediate improvement after the symptomatic treatment. While13 patients experienced serious infusion related reaction, consisted mainly of anaphylactic reactions, dyspnea, chest pain, tachycardia, tingling, edema, elevated blood pressure. As a result, the infusion were definitively stopped and these patients were withdrawn from the study according to the physician decision. Interestingly, subsequent infusion was well tolerated. Furthermore, no infections were noted during the period of study and no deaths were related to this outcome. Conclusion: B-cell depletion therapy is valuable in suppressing disease activity and improving outcome in patients with active rheumatoid arthritis. Rituximab in combination with methotrexate represents a safe alternative option for patients that fail to respond to other therapy, with no major adverse effects. Infusion related reaction is considered to be a main disadvantage; however, its incidence is lowered with corticosteroid pretreatment and with subsequent infusions.

Keywords: RA, rituximab, methotrexate, nurses, combinational therapy

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Introduction

Rheumatoid arthritis (RA) is a common systemic autoimmune disease that involve any tissues and organs but it primarily causes a chronic synovial inflammation of joints\(^1\). The cause of RA is enigmatic, various genetic and environmental factors are probably to be concerned in the vulnerability to RA, progression and its pathogenesis\(^2\). Inflammatory disease process is associated with pain, tiredness and disability which are chronic. Moreover, it can result in deformity, destruction of joints and to substantial loss of function and quality of life\(^3,4\). In addition to significant morbidity, it associated with reduced life expectancy\(^5,6\). Treatment of RA requires a multidisciplinary approach with both pharmacological and non-pharmacological interventions, such as physical therapy, exercise, education and possibly surgery\(^7\). Since there is no cure for RA, the treatment goals are a remission of symptoms, as well as a return to full function and maintenance of the joints. However, pain, swelling, in addition to permanent joint injury and risk of disability, can be controlled by early intervention\(^8,9\). Disease modifying anti-rheumatic drugs (DMARDs), anti-inflammatory medications, stays the preferred primary treatment for RA; they are usually used to help with the symptoms. In addition, they reduce disease activity, delay joint erosions, and improve patients’ quality of life\(^10,11\).

Methotrexate (MTX), a traditional DMARDs, is generally effective as first-line treatment. Unfortunately, several patients either fail to respond adequately or quit the therapy because of their adverse effects\(^12\). The aim of achieving effective treatment options RA was the reason for the development of biologic agents. Biologic therapies have shown success in patients that do not respond to DMARDs\(^13\). They are a group of disease modifying drugs that target particular components of the immune system that play an essential role in RA\(^14\). Biologic agents have the ability to control the signs and symptoms of RA, and prevent structural damage of the joints\(^15\). Rituximab (RTX) is one such a biological agent. It is a monoclonal antibody that targets the CD20 molecule on the surface of B cells\(^16\). It was used primarily for the management of non-Hodgkin’s lymphoma and later on approved for the management of RA which does not respond sufficiently to DMARDs. Due to safety and cost-effectiveness reasons, biologic agents are used after failure to respond to conventional DMARDs\(^17\). RTX, in combination with MTX, has become an important therapeutic option in the management of RA\(^18\).

Hence it was decided to conduct this study to evaluate the response to this combination in patients with active RA in Mosul city, with the aim of improving the quality of life for these patients.

Patients and Methods

This study was conducted at Medical Unit / Department of Medicine at Al-Salam Teaching Hospital in Mosul City, between July 2018 and April 2019, under supervision of Rheumatologists. The local hospital ethics committee approved the study. Patients were well educated about the therapeutic profile of RTX, including both risks and benefits. All the patients agreed for participation. Inclusion criteria for patients to be enrolled were: Male or female patients ≥ 18 years, who had presented with active RA for at least 6 months prior to the study. They were inadequately responded to MTX therapy. The disease activity was assessed by using Disease Activity Score (DAS28-ESR)\(^18,19\).

< 18 years or over 65 years of age, concomitant treatment with any DMARDs (other than MTX) or biologic therapy, chest infection, active or previous tuberculosis (Tb), hepatitis, diabetes, pancytopenia, leucopenia, low immune patients, pregnant or breast feeding women. Initiation of RTX was preceded by receiving a detailed history (concerning chronic or new comorbidity including, cardiovascular, pulmonary diseases, infections and allergies), in addition to a total physical examination to all participants, in order to exclude probable contraindications, particularly the elderly patients. After screening, all eligible patients had admitted to the hospital, and blood samples were taken from each patient. The baseline characteristics for each patient age, gender, disease duration, were recorded. Patients were assessed at baseline before the treatment, and at the follow-up, at 2 and 12 weeks post treatment, for DAS-28 which measures swollen joint count (SJC), tender joint count (TJC), and biological parameters (ESR and/or CRP), pain on visual analogue scale (VAS) for patient’s global assessment (0-100mm). In addition to the assessment of blood pressure, fasting blood sugar, renal and liver function tests and complete blood picture. Also, chest radiography was carried out. Enrolled patient received the following treatment, RTX (MabThera1000mg) as intravenous (IV) infusion over 3 hours on days 1, as first dose, and on day 15 as a second dose of treatment. Prior to each infusion of RTX, all patients received premedication which included methylprednisolone100mg, acetaminophen and an antihistamine intravenously. In addition to concomitant MTX tablets (12.5 mg/week) at a stable dose. Data for the safety outcomes was collected retrospectively for every patient after each dose of treatment, including infusion related reactions (IRR), cardiovascular effects, serious infections, gastrointestinal effects, central nervous system (CNS) effects, pulmonary effects and dermatologic effects. Response assessment according to standards of care for therapies with biological agents and MTX, compared the changes in DAS-28 from study baseline to
follow-up. The efficacy endpoints included the percentage of patients achieved DAS28-ESR remission. Remission rate was defined as DAS-28 <2.6, pain score <10 mm, less than 4 swollen joints, less than 2 tender joints and ESR less than 20 mm/h.

Statistical analysis was carried out using SPSS (V24; IBM SPSS Statistics USA). Results were presented as mean, range and percentage. Responses to RTX at 2 and 12 weeks after therapy were compared with baseline. Normality of the data distribution was assessed by Shapiro-Wilko test. Differences between means were tested for significance by student t–test, when data followed normal distribution, or Mann-Whitney test. P values ≤ 0.05 were considered a statistically significant.

Results

In this study there were 63 RA patients met the criteria for inclusion; of these, 57(90.5%) were females and 6(9.5%) were males, with ages ranging 18 - 65 years and mean of 49 years. The disease duration was between 0.6 – 30 years (mean 9 years). Rheumatoid factor (RF) was positive in 59%. Regarding concomitant therapy, all patients had concomitant MTX 12.5 mg/week orally at a stable dose. The demographic characteristics of patients are summarized in Table 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result: No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex distribution:</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (9.5)</td>
</tr>
<tr>
<td>Female</td>
<td>57 (90.5)</td>
</tr>
<tr>
<td><strong>Age(years): range(mean)</strong></td>
<td>18 - 68 (49)</td>
</tr>
<tr>
<td><strong>Disease duration(years): range(mean)</strong></td>
<td>0.6 – 30 (9)</td>
</tr>
<tr>
<td>Rheumatoid factor positive: no. (%)</td>
<td>37 (59)</td>
</tr>
</tbody>
</table>

*Thirteen patients were excluded from the study

In this study, DAS28-ESR was the primary efficacy outcome measure for evaluation of RTX treatment and for assessment of RA activity. It was evaluated at baseline and repeated at 2 and 12 weeks after treatment. In general, 79% of the patients achieved a statistically significant improvement in all individual components of the DAS28 as compared to baseline. The reduction in mean DAS28 was highly significant (P < 0.0001) over the time. It was higher at the baseline (9.6) compared with the its value (4.6) after first dose and (2.7) second dose, respectively. The percentages of improvement of DAS28 from baseline were 33% and 61% respectively (Table 2). Regarding the components of the DAS28-ESR, SJC, TJC, ESR, and VAS for patient global assessment, showed significant decline in their scores than baseline. At 2 weeks after the first dose of RTX, the percentages of improvement for SJC, TJC, ESR, and VAS were as follow, 72%, 68%, 42% and 50% respectively. At 12 weeks, further reduction in these values was reported. The percentages of improvement were 96%, 89%, 72%, and 87% respectively. **Thirty four (68%) patients achieved moderate disease activity (DAS28 ≤ 5.1 - 3.2) at 2 weeks after a single dose of RTX.** At the same time, low disease activity (DAS28 ≤ 3.2 - 2.6) was reported in 6 (12% ) patients. Finally, the disease activity was continuing to decline in 96% of patients within 3 months, the remission (DAS28 < 2.6) was reported in 25 patients (50%) and 23 patients (46%) achieved low disease activity. While only 2 patients showed persistent disease activity (DAS >5.1). Of note, joint pain, and swelling were improved and most patients reduced their analgesic intake.
Table 2. Baseline, 2-week and 12-week outcome measurements as assessed by DAS28 and its component changes, together with the percentage of improvement. Data are mean (range). N=50

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baseline</th>
<th>2 Weeks</th>
<th>Improvement%</th>
<th>12 Weeks</th>
<th>Improvement%</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28</td>
<td>6.9(5.2-9)</td>
<td>4.6(2.8-7)</td>
<td>33</td>
<td>2.7(1.8-6)</td>
<td>61</td>
</tr>
<tr>
<td>SJC</td>
<td>10(8-26)</td>
<td>2.8(0-12)</td>
<td>72</td>
<td>0.4(0-7)</td>
<td>96</td>
</tr>
<tr>
<td>TJC</td>
<td>17(8-30)</td>
<td>5.5(0-24)</td>
<td>68</td>
<td>1.8(0-12)</td>
<td>89</td>
</tr>
<tr>
<td>ESR mm/h</td>
<td>72(18-135)</td>
<td>42**(14-113)</td>
<td>42</td>
<td>20**(10-62)</td>
<td>72</td>
</tr>
<tr>
<td>VAS (0–100 mm)</td>
<td>70(25-100)</td>
<td>35*(10-90)</td>
<td>50</td>
<td>9*(0-60)</td>
<td>87</td>
</tr>
</tbody>
</table>

*P <0.0001 **P < 0.001. N: total number of patients.

Regarding safety concerns of RTX infusion, eighteen (29%) patients developed an infusion related reaction (IRR) during the first RTX infusion despite premedication with methylprednisolone. The most commonly reported side effects were throat irritation, urticaria/rash, flushing and headache (Table 3). These reactions were mild to moderate in severity, however, some cases required short discontinuation of infusion as well as additional interventions with IV paracetamol, antihistamines and/or hydrocortisone. Five patients (8%) showed immediate improvement after the symptomatic treatment. While 13 patients (21%) experienced serious IRR, even after symptomatic therapy, consisted mainly of anaphylactic reactions, dyspnea, chest pain, tachycardia, tingling, edema, elevated blood pressure in addition to skin itching, flushing, headache and throat irritation (Table 3). As a result, the infusions were definitively stopped at that time. Moreover, these patients were withdrawn from the study according to the physician decision. Interestingly, subsequent infusion was well tolerated. Furthermore, no infections were noted during the period of study and no deaths were related to this outcome.

Table 3. Summary of the adverse events of RTX infusion by treatment course

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>No. of patients(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients with AE</td>
<td>18(29)</td>
</tr>
<tr>
<td>Patients with serious IRR who withdrawal from the study</td>
<td>13(21)</td>
</tr>
<tr>
<td>Serious infection</td>
<td>0</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorder events</td>
<td>20(32)</td>
</tr>
<tr>
<td>Respiratory symptoms events</td>
<td>13(21)</td>
</tr>
<tr>
<td>CNS events</td>
<td>4(6)</td>
</tr>
<tr>
<td>Dermatological events</td>
<td>15(23)</td>
</tr>
</tbody>
</table>
Discussion

To the best of our knowledge, this is the first study in Iraq to evaluate the response of patients with active RA to the concomitant therapy of RTX with MTX. Even though the comparison among various clinical studies is not always possible because of differences in patient demographics, assessment of inclusion/exclusions criteria and management plans. The results obtained in this study were very encouraging. RTX was generally well tolerated by the most patients. Interestingly, even with resistant long-standing active RA, the disease activity continued to be suppressed in 96% of patients within 3 months, in addition to the remission of symptoms and the return to the joints’ function. The findings of this study demonstrate that the combination therapy of RTX with MTX is an important therapeutic option for treatment of ‘difficult-to-treat’ active RA, who show no response and/or experience reduced response to MTX with time, as evidence by good response in 79% of patients at 2 weeks and even higher (96%) as early as 12 weeks of the treatment. This observation was in accordance with the results of the REFLEX trial which confirmed that RTX plus MTX is more effective than placebo plus MTX20. In addition, Tak et al. reported that the combination of RTX with MTX improved the sign and symptoms of RA as well as slowed joint damage progression21. RTX therapy has been shown to be successful in suppressing disease activity as indicated by a dropping in the mean DAS28 from baseline by -2.3 at 2 weeks (P < 0.0001) and -4.2 at 3 months (P < 0.0001). Moreover, the improvement were noticed in each parameters of disease activity including SJC (P < 0.0001 at 2 weeks, P < 0.0001 at 3 months), TJC (P < 0.0001 at 2 weeks, P < 0.0001 at 3 months), ESR (P < 0.001 at 2 weeks, P < 0.0001 at 3 months) and VAS (P < 0.0001 at 2 weeks, P < 0.0001 at 3 months). Results from the REFLEX trial12 found that a mean DAS28 change of about -2.0 after RTX therapy. With regards to safety concerns, RA is an immunomodulatory chronic disease, it requires treatment administration for prolonged period, a condition that requests continuous awareness of safety events. Acute infusion reaction was the most common event reported in all previous study using RTX. Although most of these events are mild and transient, they can be serious in rare cases and should not be ignored22-24. The binding of RTX to CD20 antigen on the B lymphocyte’s surface might be responsible for the symptoms observed in IRRs to RTX25,26. IRRs were the main AEs observed in the present study. It was developed in 29% of our patients during first infusion, the same percentage was reported in meta-analysis by Volkmann et al.27. Five patients (8%) showed immediate improvement after the symptomatic treatment. While SAE that required inpatient hospitalization, were observed in 13 patients (21%), as a result, the infusion was definitively stopped at time and they were withdrawn from the study. Therefore, no infusion-related deaths. Which is also have noticed by Vollenhoven R et al7. SAE that have been observed consisted mainly of anaphylactic reactions, dyspnea, chest pain, tachycardia, tingling, edema and elevated blood pressure. These pattern of IRRs is similar to that described in clinical trials7,28,29. It was demonstrated that SAEs were developed in patients aged ≥ 52 years and their disease duration ≥ 3 years. This observation is agree with study done by Huhn et al. and Payet30,31. Consistent with previous reports, IRRs were less frequent over subsequent dose of RTX. This might confirm the hypothesis of reduction in cytokine release syndrome due to a lower B cell load with additional courses7. Of notice, premedication with corticosteroids and antihistamines was not protective against IRR but it reduced the frequency and severity of infusion reactions32. In addition, paracetamol premedication has an important role to reduce the occurrence of headache and fever/chill. Headache was noticed in 4 patients (6%), while no patient develop fever/chill. Moreover, the manufacturer recommends a slow rate of infusion administration to prevent an IRR30. Many studies attempted to prolong the infusion rate of RTX, with reported success33,34. In this study, infusion over 3 hours was well tolerated. Importantly, a detailed medical history in addition to complete physical examination as well as the inquiry about symptoms of TB and chest x-rays were performed before entry to the study. For these reasons, there were no cases of serious infections, TB or disseminated fungal infection, were noticed during the analysis period. Moreover, patients with RA are known to be at an increased risk of cardiovascular disease, either because of the disease process or as a result of therapy34. However, in our study, no patient was developed MI, which was one of the most common SAE that found in prior articles34,35. This result is consistent with the demonstration of Vollenhoven et al. who reported that, there was no evidence for the relationship of MI and RTX therapy in RA patients7. Future studies need to evaluate the longer-term efficacy and safety of the combination of RTX with MTX for RA treatment, as well as the optimal time of re-administration of these agents.

Conclusion

The observations of this study prove that B-cell depletion therapy is efficient in suppressing disease activity and ameliorating outcome in active RA patients. RTX in combination with MTX represents a safe alternative option for patients that fail to respond to other therapy, without reporting major adverse effects. IRR is considered to be a main disadvantage, however, their incidence is lowered with corticosteroid pretreatment and with subsequent infusions.
Conflict of interest

None of the authors have any conflicts of interest relevant to this research subject.

Ethical Approval

Ethical Committee of the Mosul health directorate approved the study. All patients’ consents were taken before inclusion in the study.

References


