# Treatment of Rheumatoid Arthritis in Combined Therapy with Methotrexate

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SUMMARY
In 2 years study, at Rheumatologic Department of University Clinic Centre in Pristina, it was done application of combined therapy with Methotrexate (tablets Methotrexate of 15 mg weekly, Sulphasalazine 2g daily, Hydroxychloroquine 400 mg) to patients with rheumatoid arthritis. Methods: During our investigation were treated 20 patients, 18 females and 2 males, in the treated group with Methotrexate, and 20 patients 16 female and 4 male in treated group with Methotrexate (MTX), Sulphasalazine (SSZ) and Hydroxychloroquine (HCQ). The diagnosis of rheumatoid arthritis was concluded on diagnostic criteria of American Rheumatism Association (ARA). The aim of this study is to compare medical results between group I (with tablets Methotrexate), as simple therapy and group II (with MTX, SSZ and HCQ), as combined therapy of drugs that modify rheumatic diseases (DMARDs), according to laboratory analysis, subjective and objective parameters, as well as side effects of drugs that were used. During application of DMARDs we were based on principals of drug applications. Results: To the investigated patients of group I and II that were of ages (23–72 years old vs. 21-69 years old) with average (46 vs. 45). Most of the patients of group 1 and 2 belong in 1st and 2nd functional stage according to Steinbrocker. Average value of morning stiffness for group 1 and 2 was (69.5 vs. 73 minutes) in the beginning of treatment, while in the end of the treatment was (26 vs. 21minutes, p<0.01). Average value of hands grip before the medication was (67 vs. 62 mm), while after medication (85 vs. 92 mm, p<0.01). Pain to all patients of group I and II before the medication was present, but after the medication changed intensively, had no pain (5 vs. 9 patients), had light pain ( 13 vs. 10 patients), while remained patients with strong pain ( 2 vs. 1 patients). Average value of swelling on proximal interphalangeal joints in group I and II in the beginning of medication was (70 vs. 67 mm), while after the medication was (68 vs. 62 mm). Average value of erythrocytes sedimentation before the medication was (33 vs. 38) while after the medication was (19 vs. 14). The positive rheumatoid factor was found to (15 vs. 17 patients). After the medication is achieved the reduction of titer (2 vs. 4 patients), while to others, the titer value remained unchanged. After the medication with DMARDs from side effects leucopenia was founded to (2 vs. 3 patients), while in two groups, only one patient had protein in urine, thrombocytopenia and pruritus, in group I and II in two patients were manifested gastrointestinal complications: with nausea, vomiting and gastric pain, in group II diarrhea, rush and alopecia. Conclusions: According to our results we concluded efficacy of the combination of DMARDs (MTX, SSZ, HCQ) as combined therapy compared with medication of simple therapy (MTX) to the patients with rheumatoid arthritis. The combined therapy of DMARDs caused visible clinic improvement, have decreased laboratory parameters, disease activity and have improved life quality.
**Key words: rheumatoid arthritis; DMARDs**

## 1. INTRODUCTION

Drugs that modify the rheumatic diseases (DMARD-a) in the treatment of early stage of rheumatoid arthritis we achieved slowing the progression of the disease, preventing disability and optimal normalization of the functions of the locomotor system (1,2,3). Within the DMARD system are gold salts, synthetic antimalarics (hydroxychloroquine-HCQ), sulphasalazine (SSZ), methotrexate (MTHX), and manifest indicated effects from 4 weeks to 12 months. The treatment begins at an early stage and the individualization of dosage depends on patient tolerance and therapeutic response. Methotrexate in combination with sulphasalazine hydroxychloroquine and compared with methotrexate as the only therapy showed to be much more effective.

Methotrexate (MTHX) amethropine, folic acid antagonist, is administered in patients with rheumatoid arthritis since 1983 (3,4,5). Hydroxychloroquine, sulphasalazine as an independent therapy was applied several years earlier. A few years later is introduced the application of methotrexate in the Rheumatology department at Pristina (6,7,8,9). In recent years applied is the triple-DMARD therapy. DMARD mechanism of action is unknown. Some authors have explained the result of action: through elimination of immunocompetent cells (10,11). So that immunosuppression as a result of action of cytostatic, is explained by the inhibition of cellular and humoral, immune responses.

In the course of applying DMARD authors noted reduction in titer of rheumatoid factor in serum. Antiflogistic action was explained by the product inhibition of inflammatory mediators (11). Effects Side effects are numerous

and are mostly in the gastrointestinal system, alopecia, hemorrhagic cystitis, stomatitis, and mycotic bacterial infections, leukopenia, thrombocytopenia, while late side effects are hepatitis, azo-or oligospermia, ovarian fibrosis and malignant diseases (12).

## 2. GOAL

The goal of the study is to present our experience in applying DMARD, following laboratory analysis, subjective and objective parameters and the side effects of these drugs, especially comparing the results in the treatment of patients with rheumatoid arthritis with methotrexate and patients with a combination of methotrexate with other drugs.

## 3. MATERIAL AND METHODOLOGY

The two-year study at the Department of Rheumatology, of the Clinic for Internal diseases we investigated 20 patients (l8 women and 2 men) in group 1 with rheumatoid arthritis, aged 23-72 years (mean age 46 yrs.) Treated with (MTX) and group 2, 20 patients (16 women and 4 men) aged 21-69 years (mean age 45 years) treated with triple therapy (MTX, SSZ, HCQ). Studied patients belonged to the: 1st and 2nd functional class according to Steinbrocker, diagnosed by ACR–American College of Rheumatology's 1991, and also Level 1 and 2 of anatomical-radiological changes. Application of DMARDs in all patients is consistent with ACR recommendations.

Introduced is laboratory evaluation before therapy of these parameters: blood count (erythrocytes, leukocytes, platelets, leukocytes formulas), transaminases, urine analysis, etc. From history we got information that the patients studied were not alcohol users, there were no cases of previous hepatitis. In therapeutically period there was no indication for radiological examinations of the lungs and spirometry. Further monitoring is done through laboratory tests every 14 days. Included are hematologic and biochemical analysis (erythrocytes sedimentation, blood count, transaminases, hepatogram, urine, rheumatoid factor, a functional test lungs, etc.). To evaluate the therapeutic effects of the drugs were used: subjective and objective parameters–the mean value of morning stiffness, hand grip, pain intensity and swelling. To assess pain we used methodology of descriptive by Likert (12).

Statistical analysis of collected results we calculated through: pointers of structure and calculating the arithmetic mean. The homogeneity of statistical series is indicated on the above statistical parameters: the interval of variation of standard deviation and coefficient of variation. Differences of arithmetic mean values were tested with T-test, arithmetic mean values for dependent small samples, while nonparametric finding are tested with the $X^2$-test. All obtained results were shown in tables.

## 4. RESULTS

In the two-year study, from the total number of tested patients 40, in the first group were 20 patients (l8 women and 2 men) with rheumatoid arthritis, aged 23-72 years (mean age 46 yrs.) Treated with (MTX) and group in second group, 20 patients (16 women and 4 men) aged 21-69 years (mean age 45 years) treated with triple therapy (MTX, SSZ, HCQ).

| Modes | Group 1 | | Group 2 | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Men | 2 | 10 | 4 | 20 |
| Women | 18 | 90 | 16 | 80 |
| Total | 20 | 100 | 20 | 100 |

Table 1. Gender structure of the patients in 1st and 2nd group treated with DMARDs

In comparison with the gender distribution our sample was dominated by women 90% than men 10%, with significant statistical difference ($p<0.003$). For the purpose of justification of therapeutic effects of DMARDs, we followed subjective and objective parameters and laboratory data before and after treatment as shown in Table 2.

| No | Parameters | Before treatment | | After treatment | | T-test |
|---|---|---|---|---|---|---|
| | | I | II | I | II | |
| 1 | Morning stiffness (min.) | 69.5 | 73 | 26 | 21 | $p<0.01$ |
| 2 | Hand grip (mm) | 67 | 62 | 85 | 92 | $p<0.01$ |
| 3 | joints swelling PIP (mm) | 70 | 67 | 68 | 62 | $p<0.01$ |
| 4 | ERS | 33 | 38 | 19 | 14 | $p<0.01$ |
| 5 | RF (Waaler-Rose titer) | 15 | 17 | 13 | 13 | $p<0.05$ |

Table 2. Mean value of subjective and objective parameters

The mean value of morning stiffness for patients from two groups was 69.5 or 73 min. at the beginning of treatment, whereas after treatment it was 26 or 21 minutes. Testing of mean we found significant statistical difference in duration of morning stiffness of the two groups, with the difference that the triple therapy had a better effect in shortening the duration of morning stiffness, compared to single therapy ($p<0.001$).

The mean value of the hand grip in both groups before treatment was 67 or 62mm; while after the treatment it was 85 or 92. Testing the mean value of this parameter before and after treatment, we also noted a significant statistical difference. The triple therapy was marked by a better therapeutic effect in terms of increasing hand grip force after treatment compared to single therapy ($p<0.01$).

In relation to the mean value of swelling in the PIP joints we also had good results. The baseline mean value of the swelling was 70 or 67 mm, after treatment the mean value of the swelling was 68 or 62 mm. Testing of the mean value of swelling in the PIP joints before and after treatment, we noted significant differences with the better effect of triple therapy in comparison to single therapy, in terms of reduction of the swelling in these joints (Table 2).

Erythrocytes sedimentation mean value before treatment was 33 or 38 for the first hour, while after treatment 19 or 14. Testing the mean also indicate significant statistical difference ($p<0.01$). Therapy with MTX, SSZ and CHQ, significantly enhance the value of erythrocytes sedimentation.

Positive rheumatoid factor was found in 15 or 17 patients, after treatment it was the same in the two groups -13 patients, therefore we observed a negative trend of rheumatoid factor, but without statistically significant differences ($p<0.05$). So the triple therapy did not affect the significant

larger reduction in titer of rheumatoid factor as compared to patients treated with single therapy.

| Pain modality | Code | Group 1 | | Group 2 | |
|---|---|---|---|---|---|
| | | No. | % | No. | % |
| Without pain | 0 | 5 | 25 | 8 | 40 |
| Slight pain | 1 | 13 | 65 | 12 | 60 |
| Moderate pain | 2 | 0 | 0 | 0 | 0 |
| Severe pain | 3 | 2 | 10 | 0 | 0 |
| Extreme pain | 4 | 0 | 0 | 0 | 0 |
| Total | | 20 | 100 | 20 | 100 |

Table 3. Structure of cases with rheumatoid arthritis by pain intensity

The intensity of pain during treatment significantly changes. So the patients before treatment had pain (mild, moderate and severe). After treatment with single and triple therapy it is reduced gradually. After treatment, the pain as a symptom has disappeared in 25% or 40%. Only 2 or 10% in the first group have strong pain persisted, while the majority of patients had mild pain in 65% or 60% (Table 3).

| Side effects | | Group 1 | | Group 2 | |
|---|---|---|---|---|---|
| | | No. | % | No. | % |
| With manifestation of side effects | Leukopenia | 2 | 10 | 3 | 15 |
| | Thrombocytopenia | 1 | 5 | 1 | 5 |
| | Proteinuria | 1 | 5 | 1 | 5 |
| | Itch | 1 | 5 | 1 | 5 |
| | GI side effects (nausea, vomiting, epigastric pain) | 2 | 10 | 2 | 10 |
| | Diarrhea, rush, alopecia | | | 1 | 5 |
| Subtotal | | 7 | 35 | 9 | 45 |
| Without manifestation of side effects | | 13 | 65 | 11 | 55 |
| Total | | 20 | 100 | 20 | 100 |

Table 4. Side effects in application of DMARDs therapy in 1st and 2nd group

Side effects after treatment with DMARDs manifested in 7 or 9 cases, of which the leukopenia was present in 2 or 3 patients, gastrointestinal disturbances in the sense of nausea, vomiting and epigastric pain were present in 2 patients, 1 patient with thrombocytopenia, proteinuria and itch, while in group 2 in one case a rush, diarrhea and alopecia (Table 4).

## 5. DISCUSSION

From the total number of patients in both groups, in the group 1 was 18 women and 2 men, while in group 2 there was 16 women and 4 men. This gender relationship is equivalent with other authors who also found similar findings, because as is well known that this disease encompasses more women than men (13). Improvement of subjective and objective parameters of morning stiffness which was before treatment (69.5 or 73min.) while after treatment it was (26 and 21min.), and hand grip (67 and 62), while after treatment (85 or 92), and the intensity of pain, which after treatment was gradually reduced and the other findings agrees with the findings of other authors, who also after DMARD therapy has achieved excellent results in treating patients with rheumatoid arthritis (13).

In our patients who had achieved vast improvements mentioned are the results achieved by the hand grip and duration of morning stiffness, but fewer results have been achieved in relation to the swelling of PIP joints. Also results of reducing the average erythrocytes sedimentation before and after treatment showed statistically significant difference, and our results agree with findings of other authors (13).

Reduction in titer of rheumatoid factor in serum in our patients was not statistically significantly difference, while others have found significant statistical difference after treatment with triple therapy (14). Side effects in our study were diverse, ranging from thrombocytopenia, leukopenia, pruritus, and side effects in the gastrointestinal system. The aforementioned results are compatible with the findings of side effects in the works of other authors (14,15).

## 6. CONCLUSION

The triple-therapy with DMARDs (MTX, SSZ, HCQ) is recommended in patients with rheumatoid arthritis. The total dose of MTX of 7.5-l5 mg/week, SSZ 1-2 grams and HCQ of 400mg, gives high scores to improve subjective and objective parameters. Hematological, biochemical and serological laboratory tests are improved after triple therapy. Gastrointestinal side effects, leukopenia, thrombocytopenia, rush, alopecia were of transitory character, and disappeared after the interruption of administration. DMARD therapy has not been stopped in any patients due to toxic effect.

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