Review Article

Rheumatoid Arthritis: Monotherapy versus Combination Therapy

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Abstract

Rheumatoid arthritis is an autoimmune disease characterized by joint destruction, disability and disability adjusted life years of a patient. Early diagnosis and appropriate treatment may improve outcome. Disease-modifying anti-rheumatic drugs suppress the disease progression. Recent guidelines advise early and sustained use of disease-modifying anti-rheumatic drugs of which methotrexate (MTX) and sulfasalazine (SSZ) are the most frequently used. Both drugs are effective, cheap, available and well tolerable. Now days MTX and SSZ are used as monotherapy and in combination. Basically the outcomes of two combinations of drugs are multiplicative. One drug promotes the action of the other. In daily practice interactions are often not well studied when using combinations of Disease Modifying Anti-Rheumatic Drugs (DMARDs). The aim of this study is the use of combination of MTX and SSZ is frequently used in the therapy for RA and has been tested in several clinical trials globally.

Keywords: Rheumatoid Arthritis(RA), Disease Modifying Anti-Rheumatic Drugs (DMARDs), Methotrexate (MTX), Sulfasalazine (SSZ). Non Steroidal Anti-Inflammatory Drugs (NSAIDs).

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Introduction

Rheumatoid arthritis is a chronic, autoimmune, inflammatory disorder of unknown etiology that is characterized by symmetric synovitis and the propensity to cause joint destruction, disability and premature death[1]. Optimal treatment in early disease may provide a window of opportunity leading to improved outcome[2]. Disease-modifying anti-rheumatic drugs (DMARDs) slow the natural course of the disease, reduce joint damage and pain, and retard loss of function and disability[3]. Disease modifying agents should be started as early as possible.

Current guidelines advise early and sustained use of disease-modifying anti-rheumatic drugs (DMARDs) of which methotrexate (MTX) and sulfasalazine (SSZ) are the most frequently used[4]. Both drugs are effective, have an acceptable toxicity and their cost is low. MTX and SSZ are used as monotherapy and in combination[5]. Although their mechanism of action remains unclear, several reports suggest that these drugs may differ in their effects on circulating cytokines and cytokine production[6].

Two studies using the combination of drugs used in this study[7]. In the first, a controlled open step-up study in 40 patients "resistant" to SSZ, the combination was significantly better than MTX alone. In the second[8], the individual drugs were compared with the combination in a parallel design from the outset. A modest trend favoring the combination of SSZ and MTX was seen, with comparable results from the two individual drugs. Nausea was documented as an adverse event more often in the combination group.

Epidemiology:

RA affects approximately 0.5-1% of the adult population worldwide. There is evidence that the overall incidence of RA has been decreasing in recent decades, whereas the prevalence has remained the same because individuals with RA are living longer. Both genetic and environmental factors appear to be involved in the pathogenesis of RA. The concordance rate of RA is higher in monozygotic (12-15%) than in dizygotic twins (3%), and there is an increased frequency of disease in first-degree relatives of patients. Up to 50% of the genetic susceptibility is due to genes in the HLA region. HLA-DR4 is the major susceptibility haplotype in most ethnic groups. Susceptibility is increased post-partum and by breastfeeding. Cigarette smoking is a strong risk factor for developing RA and also associates with greater severity.

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Pathophysiology:

Whatever the initiating stimulus, RA is characterised by infiltration of the synovial membrane with lymphocytes, plasma cells and macrophages. CD4+ T cells play a central role by interacting with other cells in the synovium. Activated T cells stimulate B cells to produce immunoglobulins including RF, and macrophages to produce pro-inflammatory cytokines. These act on endothelium, synovial fibroblasts, bone cells and chondrocytes to promote swelling and congestion of the synovial membrane and destruction of bone, cartilage and soft tissues.

The pro-inflammatory cytokine TNF- α plays an important role in this process by regulating production of other cytokines, whose actions are shown in. The B cells release immunoglobulins, including RF, which can form immune complexes within the joint and in extra-articular tissues, leading to vasculitis. Lymphoid follicles form within the synovial membrane. Inflammatory granulation tissue (pannus) spreads over and under the articular cartilage, which is progressively eroded and destroyed. Later, fibrous or bony ankylosis may occur. Muscles adjacent to inflamed joints atrophy and may be infiltrated with lymphocytes[9].

Criteria for diagnosis of rheumatoid arthritis (According to ARA 1987 revision)[9]

•Diagnosis of RA is made with four or more of the following:

- Morning stiffness (> 1 hr)
- Arthritis of three or more joint areas
- Symmetrical arthritis
- Rheumatoid nodules
- Rheumatoid factor
- Radiological changes
- Duration ≥6 wks

In 2010, a collaborative effort between the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) revised the 1987 ACR classification criteria for RA in an effort to improve early diagnosis with the goal of identifying patients who would benefit from early introduction of disease-modifying therapy. Application of the newly revised criteria yields a score of 0-10, with a score of ≥6 fulfilling the requirements for definite RA. The new classification criteria differ in several ways from the older criteria set.

Classification Criteria for Rheumatoid Arthritis (According to 2010 ACR/EULAR collaborative initiative)[10]

		Score
Joint involvement	1 large joint (shoulder, elbow, hip, knee, ankle)	0
	2-10 large joints	1
	1-3 small joints (MCP, PIP, Thumb IP, MTP, wrists)	2
	4-10 small joints	3
	>10 joints (at least 1 small joint)	5
Serology	Negative RF and negative ACPA	0
	Low-positive RF or low-positive anti-CCP antibodies (3 times ULN)	2
	High-positive RF or high-positive anti-CCP antibodies (>3 times ULN)	3
Acute-phase reactants	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
Duration of symptoms	<6 weeks	0
	>6 weeks	1

Note: These criteria are aimed at classification of newly presenting patients who have at least 1 joint with definite clinical synovitis that is not better explained by another disease.

Extra-articular manifestations of rheumatoid disease
Systemic

- Fever
- Weight loss
- Fatigue
- Susceptibility to infection

Musculoskeletal

- Muscle-wasting
- Tenosynovitis
- Bursitis
- Osteoporosis

Haematological

- Anaemia
- Thrombocytosis
- Eosinophilia

Lymphatic

- Felty's syndrome
- Splenomegaly

Nodules

- Sinuses
- Fistulae

Ocular

- Episcleritis
- Scleritis
- Scleromalacia
- Keratoconjunctivitis sicca

Vasculitis

- Digital arteritis
- Ulcers
- Pyoderma gangrenosum
- Mononeuritis multiplex
- Visceral arteritis

Cardiac

- Pericarditis
- Myocarditis
- Endocarditis
- Conduction defects
- Coronary vasculitis
- Granulomatous aortitis

Pulmonary

- Nodules
- Pleural effusions
- Fibrosing alveolitis
- Bronchiolitis
- Caplan's syndrome

Neurological

- Cervical cord compression
- Compression neuropathies
- Peripheral neuropathy
- Mononeuritis multiplex

Amyloidosis

Investigations and monitoring of rheumatoid arthritis:

To establish diagnosis:

Clinical criteria

Acute phase response (APR)

Serological tests (anti-CCP antibodies & RA factor)

To monitor disease activity and drug efficacy

Pain (visual analogue scale)

Early morning stiffness (minutes)

Joint tenderness

Joint swelling

DAS 28 score

APR

To monitor drug safety

- Urinalysis
- Biochemistry (Serum Creatinine, SGPT)
- Haematology (CBC)

Management:

Physical rest, targeted anti-inflammatory therapy and passive exercises are the mainstays, with the aim of relieving symptoms, suppressing inflammation, and conserving and restoring function in affected joints. A multidisciplinary approach is required, including doctors, nurses, physiotherapists and occupational therapists, and patient education and counselling play a key role. During treatment, periodic assessment of disease activity, progression and disability is essential. In the vast majority, management is outpatient-based, but hospital admission can be helpful in patients with very active disease for a period of bed rest, multiple joint injections, splinting, regular hydrotherapy, physiotherapy and education.

Drug Therapy: The medications used for the treatment of RA may be divided into broad categories:

a) Nonsteroidal anti-inflammatory drugs (NSAIDs);

b) Glucocorticoids, such as prednisone and methylprednisolone;

c) Conventional disease-modifying anti-rheumatic drugs (DMARDs); and

d) Biologic DMARDs

NSAIDs: NSAIDs were formally viewed as the core of all other RA therapy, but they are now considered to be adjunctive therapy for management of symptoms uncontrolled by other measures. Chronic use should be minimized due to the possibility of side effects, including gastritis and peptic ulcer disease as well as impairment of renal function.

Glucocorticoids: Glucocorticoids may serve in several ways to control disease activity in RA. First, they may be administered in low-to-moderate doses to achieve rapid disease control before the onset of fully effective DMARD therapy, which often takes several weeks or even months. Second, a 1-2 week burst of glucocorticoids may be prescribed for the management of acute disease flares, with dose and duration guided by the severity of the exacerbation. Chronic administration of low doses (5-10 mg/d) of prednisone (or its equivalent) may also be warranted to control disease activity in patients with an inadequate response to DMARD therapy.

DMARDs: DMARDs are so named because of their ability to slow or prevent structural progression of RA. The conventional DMARDs include hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide; they exhibit a delayed onset of action of approximately 6-12 weeks. Methotrexate is the DMARD of choice for the treatment of RA and is the anchor drug for most combination therapies. Short description of MTX & SSZ is given below.

Sulfasalazine:

Dosage: Initially 500 mg orally twice daily. Maintenance: 1000-1500 mg twice daily.

Serious Toxicities: Granulocytopenia &Hemolytic anemia (with G6PD deficiency)

Other Common Side Effects: Nausea, Diarrhea & Headache.

Initial Evaluation: CBC, LFTs & G6PD level.

Monitoring: CBC every 2-4 weeks for first 3 months, then every 3 months.

Methotrexate:

Dosage: 10-25 mg/week orally. Folic acid 1 mg/d to reduce toxicities.

Serious Toxicities: Hepatotoxicity, Myelosuppression, Infection, Interstitial pneumonitis, Pregnancy category X.

Other Common Side Effects: Nausea, Diarrhea, Stomatitis/mouth ulcers, Alopecia, Fatigue.

Initial Evaluation: CBC, LFTs, hepatitis B surface antigen, hepatitis C viral antibody & Chest X-ray.

Monitoring: CBC, creatinine, LFTs every 2-3 months.

Discussion

The level of activity was assessed in 334 out-patients who visited the Clinic of Physical Medicine at the Hanusch-krankenhaus[11]. The self-administered Health Assessment Questionnaire (HAQ) was used for that purpose by the authors. The mean HAQ-Score was low OJ>6 (25 percentile=0!) indicating only slight restrictions of personal activity. Older subjects presented with higher scores than younger people. The mean HAQ score was 03 in third decades, reached a plateau about 0.55 to 0.57 between 40 to 70 years and rises to 0.69 in the 8th decade and to 0.73 in subjects older than 80 years. Subjects with disease of the central nervous system such as hemiparesis after stroke or M.Par-kinson, and patients after amputation ranked highest. Patients after joint surgery, after fractures or contusion and also patients with tendovaginttis followed them in die score rank. The majority of out-patients was not highly restricted in activity.

Several new drugs for rheumatoid arthritis are available including leflunomide. Comparative studies of treatment with leflunomide (against methotrexate) report a better quality of life. In a study designed to evaluate the efficacy of combination of methotrexate and hydroxychlorquine with leflunomide, a new disease modifying antirheumatoid drug[12]. Analysis was of intent to treat group. Their study was an open labeled, randomized, comparative clinical trial in the department of rheumatology and immunology, at a tertiary care center in Bangalore. Patients who have diagnosed with rheumatoid arthritis as per American College of Rheumatology atged between 18 and 60 years were recruited and randomized to receive leflunomide (10mg/day p.o.) or a combination of methotrexate and folate supplementation for 12 weeks. The European League Against Rheumatism criteria of improvement according to disease activity score 28 was considered as the primary efficacy variable. Baseline and end of study values were evaluated. The duration of the study period was 1 year. After 12 weeks, improvement noted in patients treated with leflunomide was similar to those treated with a combination of methotexate and hydroxycholoroquine. There was no statistical significance in improvement in disease activity between the two groups (P=0.377). Combination of methotrexate and hydroxychloroquine is equivalent to leflunomide in terms of efficacy in reducing disease activity in the initial treatment of severe rheumatoid arthritis.

To compare efficacy, toxicity, and the pharmacokinetics of the combination of SSZ and MTX vs MTX alone in the treatment of SSZ-resistant RA, conducted a controlled open clinical trial[13]. Forty RA patients with active arthritis despite adequate SSZ therapy were allocated randomly to regimes of either SSZ+MTX or MTX alone. The patients were evaluated openly by a single observer for 24 weeks. In the first 115 patients using the combination, pharmacokinetics of MTX without and with SSZ were studied. Thirty-eight patients completed the trial. The mean decrease in the disease activity score in the group of patients receiving the combination was significantly greater than in the MTX group (-2.6vs-1.3 respectively). The same pattern was seen concerning the other efficacy variables. There was no difference in the occurrence of toxicity. SSZ had no influence on the pharmacokinetics of MTX. This open study the efficacy of combination of MTX and SSZ seems to be superior to MTX alone, the toxicity of both therapies was similar. This effect was not explained by the pharmacokinetics of MTX which were not altered by concomitant SSZ administration.

Early aggressive treatment of rheumatoid arthritis is associated with improved disease control, slower radiological progression and improved functional outcomes[14].

The results of randomized controlled trials (RCTs) on the combination of MTX and SSZ in naive patients and in patients with an insufficient response to SSZ[15].

The diagnosis of rheumatoid arthritis was concluded on diagnostic criteria of American Rheumatism Association (ARA)[16] compared 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 the investigators were based on principals of drug applications. 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 09 vs. 14). The positive rheumatoid factor was found to (55 vs. 17 patients).

Therefore, at some stage during the lengthy course of RA, institution of traditional DMARDs that have previously been applied may have to be reconsidered. In a investigation the effectiveness of re-employed methotrexate in patients with a history of previous methotrexate failure (original course)[17]. A total of 1,490 RA patients (80% female, 59% rheumatoid factor positive) were followed from their first presentation, yielding a total of 6,470 patient-years of observation. The investigators identified patients in whom methotrexate was re-employed after at least one intermittent course of a different DMARD. The investigators compared reasons for discontinuation, improvement in acute phase reactants, and cumulative retention rates of methotrexate therapy between the original course of methotrexate and its re-employment. Similar analyses were performed for other DMARDs. Methotrexate was re-employed in 86 patients. Compared with the original courses, re-employment was associated with a reduced risk for treatment termination because of ineffectiveness ($P = 0.02$, by McNemar test), especially if the maximum methotrexate dose of the original course had been low (<12.5 mg/week; $P= 0.02$, by logistic regression). In a Cox regression model, re-employed MTX was associated with a significantly reduced hazard of treatment termination compared with the original course of methotrexate, adjusting for dose and year of employment (hazard ratio 0.64, 95% confidence interval 0.42-0.97; $P= 0.04$).

In a assessment the impact of these therapies on the cytokine cascade, the in vitro production and circulating concentrations of several cytokines and endogenous cytokine antagonists were measured in 30 healthy controls and longitudinally in a subset of 26 patients enrolled in this study[18]. Compared to controls, RA patients had significantly higher circulating concentrations of interleukin-6 (IL-6), soluble receptors for tumour necrosis factor (sTNFR), soluble receptors for interleukin-2 (sIL-2R) and interleukin-1 receptor antagonists (IL-1RA), and their peripheral blood mononuclear cells (PBMNC) showed a higher spontaneous production of interleukin-1 beta (IL-1 beta), tumour necrosis factor alpha (TNF alpha) and IL-1RA (both secreted and cell-associated) and a higher stimulated production of cell-associated TNF alpha, IL-1RA and (to a lesser extent) IL-1 beta. Treatment with MTX alone ($n = 12$) or combined with SSZ ($n = 14$), resulted in significant reductions of circulating IL-6 and sIL-2R but did not alter IL-1 beta, TNF alpha or IL-1 RA concentrations. Decreases in circulating levels of sTNFR and in the in vitro production of cell-associated IL-1 beta and IL-1RA after stimulation were only observed in patients treated with MTX + SSZ. The concentrations of IL-1 RA and sTNFR in the circulation exceeded moderately those of IL-1 beta and TNF alpha but this is probably insufficient to block IL-1 and TNF alpha activity.

For pharmacological reasons, the effect of the combination of MTX and SSZ may be different in RA patients who are naive to these drugs compared to patients with an insufficient response to one of them. Therefore, compared the results of randomized controlled trials (RCTs) on the combination of MTX and SSZ in naive patients and in patients with an insufficient response to SSZ[19]. A systematic literature search was performed to identify RCTs that compared the MTX-SSZ combination to either drug alone. The databases MEDLINE and the Cochrane Clinical Trials registry were searched from 1966 up to April 2007. The efficacy of the single therapeutic agents or their combination was assessed using the mean change in the disease activity score (DAS) and the ACR improvement criteria. Four RCTs were identified to compare the efficacy of the combination MTX-SSZ to the efficacy of either drug alone. Two parallel trials were performed with patient's naive to both drugs and two add-on trials were performed in SSZ failures. In the trials with naive patients, the mean DAS changes for the combination MTX and SSZ pointed to a sub-additive efficacy. In the trials with patients who previously failed to SSZ, the mean DAS changes for the combination MTX and SSZ indicated additive efficacy. In RA, addition of MTX to SSZ is a therapeutic option in SSZ failures, whereas combination of MTX and SSZ in DMARD-naïve patients has no added value.

Conclusion

This suggests that the mean changes in the DAS28 score significantly lower in those who received combination

therapy compared with those who received either MTX or SSZ alone. Combination showed no drug toxicity or had not been stopped in any patients due to side effects. The combination of MTX and SSZ, is relatively inexpensive. Combination of MTX & SSZ proved more effective than monotherapy in patients of Rheumatoid arthritis.

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References

1. Graudal NA, Jurik A.G, De Carvalho A, Graudal HK. Radiographic progression in rheumatoid arthritis: a long-term prospective study of 109 patients. Arthritis Rheum. 1998; 41: 1470-1480.

2. O'Dell JR, Leff R, Paulsen G, Haire C, Mallek J, Eckhoff PJ, et al. Treatment of rheumatoid arthritis with methotrexate and Hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002; 46(5): 1164-70.

3. Fries JF. Effectiveness and toxicity considerations in outcome directed therapy in rheumatoid arthritis. J Rheumatol Suppl. 1996; 44: 102-106.

4. Therapeutic strategies in early rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2005; 19: 163-77.

5. Schipper L.G, Fransen J, Barrera P, Piet LCM, Riel V. Methotrexate in combination with sulfasalazine is more effective in rheumatoid arthritis patients who failed sulfasalazine than in patients naive to both drugs. Rheumatology. 2009; 48: 828-833.

6. Barrera P, Haagsma CJ, Boerbooms AMTH, Van Riel PLCM, Borm GF, Van De, et al. Effect of Methotrexate alone or in combination with sulfasalazine on the production and circulating concentrations of cytokines and their antagonists: longitudinal evaluation in patients with rheumatoid arthritis. Br J Rheumatol. 1995; 34: 747-755.

7. Haagsma CJ, Van Reil PLCM, De Rooij DJRA, Vree TB, Russel FJM, Vant's Hof MA, et al. Combination of methotrexate and sulphasalazine vs methotrexate alone: a randomised open clinical trial in rheumatoid arthritis patients resistance to sulphasalazine therapy. Br J Rheumatol. 1994; 33: 1049-55.

8. Haagsma CJ, Van Reil PLCM, De Jang AJL, Van De Putte LBA. Combination of methotrexate and sulphasalazine versus the single components in early rheumatoid arthritis: a randomized, controlled, double-blind, 52 week clinical trial. Br J Rheumatol. 1997; 36: 1982-8.

9. Dohertly H., Ralston S.H. Musculoskeletal disease. In: Colledge NR., Walker BR., Ralston HS., Editors. Davidsons Principles and Practice of Medicine. 21th ed. Churchill Living stone: Edinburg; 2010: 1089-91.

10. Shah A, William E st. Clair. Rheumatoid Arthritis. In: Kasper DL, Fauci AS, Longo DL, Braunwald E, Hauser SL, Jameson Jl, et al, editors. Harrisons Principles of Internal Medicine. 18th ed. USA: McGraw Hill; 2012: 2741-46.

11. Anuner K, Melnizky P, Rathkolb O. HAQ (Health Assessment Questionnaire) Scores of Out-Patients in a Clinic for Physical Medicine; 2002.

12. Shashikumar N.S., Shivamurthy MC, Chandrashekara S. Evaluation of efficacy of combination of methotrexate and hydroxychloroquine with leflunomide in active rheumatoid arthritis. Indian Journal of Pharmacology. 2010; 42(6): 35-361.

13. Haagsma CJ, Russel FG, Vree TB, Van Riel PL, Van De Putte LB. Combination of methotrexate and sulphasalazine in patients with rheumatoid arthritis: pharmacokinetic analysis and relationship to clinical response. Br J Clin Pharmacol. 1996; 42: 195-200.

14. Dale J, Alcorn N, Capell H, Madhol R. Combination therapy for rheumatoid arthritis: methotrexate and sulfasalazine together or with other DMARDs. Nature Clinical Practice Rheumatology. 2007; 3: 450-458.

15. Ringold S, Singer NG. Measures of Disease Activity in Rheumatoid Arthritis: A Clinician's Guide. Current Rheumatology Reviews. 2008; 4: 259-265.

16. Rexhepi S, Dragusha G, Rexhepi M, Pllana E, Sahatciu-Meka V, Gashi M, et al. Treatment of Rheumatoid Arthritis in Combined Therapy with Methotrexate; 2010.

17. Kapral T, Stamm T, Machold KP, Montag K, Smolen J, Aletaha D. Methotrexate in rheumatoid arthritis is frequently effective, even if re-employed after a previous failure. Arthritis Research & Therapy. 2006; 8: 46.

18. Barrera P, Haagsma CJ, Boerbooms AMTH, Van Riel PLCM, Borm GF, Van De, et al. Effect of Methotrexate alone or in combination with sulfasalazine on the production and circulating concentrations of cytokines and their antagonists: longitudinal evaluation in patients with rheumatoid arthritis. Br J Rheumatol. 1995; 34: 747-755.

19. Katchamart W, Trudeau J, Phumethum V, Bombardier C. Efficacy and toxicity of methotrexate (MTX) monotherapy versus MTX combination therapy with non-biological disease-modifying antirheumatic drugs in rheumatoid arthritis: a systematic review and meta-analysis. Ann Rheum Dis. 2009; 68: 1105-1112.