COVERING LETTER

From:
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23.02.2021

To,
Clinicaltrial.gov.

Subject : Submission of Study protocol, Statistical analysis plan (SAP) and informed consent form (ICF) .

Dear Sir// Madam,
I, Pooja Belani, am hereby submitting study protocol, statistical analysis plan (SAP) and informed consent form (ICF) for the following clinical study (details):

Study Title : Comparison of Sulfasalazine versus Leflunomide based combination disease modifying anti-rheumatic drug therapy (DMARD) in patients with Rheumatoid arthritis failing Methotrexate monotherapy : A randomized control trial

NCT number : NCT02930343

Document date : 02.05.2016

Kindly find appropriate documents hereby .
Thanking you.
Best regards.

STUDY PROTOCOL

Background

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammatory polyarthritis. The hallmark of RA is symmetric synovial proliferation and inflammation of joints that leads to erosions and progressive destruction of joints leading to disability. Disease modifying anti rheumatic drugs (DMARDS) form the mainstay for RA treatment. Early aggressive treatment of RA can halt or slow down the disease progression and disease, thus decreasing disease related disability and improving the quality of life significantly.

The current strategy for treatment of RA is “treat – to- target” approach (1) to achieve early and sustained remission. Methotrexate is the initial drug of choice for early DMARD naïve patients. Patients not achieving the target for disease control, can be started either on combination of conventional DMARDS therapy or biologic agents (TNF inhibitors) (1)(2). According to the latest EULAR recommendations, addition of a biological DMARD, especially a Tumor Necrosis Factor (TNF) inhibitor, should be considered when poor prognostic factors are present; in the absence of poor prognostic factors, a combination therapy should be considered. (2).

The main hurdle for the use of TNF inhibitors or other biologicals for management of RA in Indian as well as western setting is high cost of therapy. The annual cost for biologic treatment for RA ranges from Rs. 3 lacs (for Rituximab) to Rs. 44 lacs (for Adalimumab), whereas that for combination therapy with Methotrexate (MTX) + Sulfasalazine (SSZ) + Hydroxychloroquine (HCQ) is Rs.15,000 and that of MTX+ Leflunomide (LEF)+HCQ is Rs. 30,000. Also the rate of infections with Biologics is higher especially Tuberculosis in Indian setting. The combination non-biological DMARDs are not only cheaper but also safer alternatives to the biological agents.

However, there are no guidelines to direct the treating physician regarding the choice of combination conventional DMARDs as there are no head to head trials comparing the efficacy, safety and cost effectiveness of various combination DMARDs.

Rationale

Inspite of various advances in field of early diagnosis of RA, there is still a need for better understanding of the efficacy and safety of various combinations of conventional DMARDS, and to rank them in order accordingly, so as to give a clearer vision for further management of RA once MTX monotherapy fails, and to achieve remission as soon as possible.

Novelty

This study will attempt to compare 2 different DMARD combinations (MTX+SSZ+HCQ versus MTX+LEF+HCQ) in terms of its efficacy and safety in the treatment of RA.. Both these regimes are approved and used for the treatment of RA but head to head comparison data is not available.

Expected outcome and application

The results of the study may help to rationalize treatment of patients with RA especially in countries like India where resources are limited and cost is a constraint. The result of the study may also provide evidence for better and prompt management of the disease with appropriate combination therapy once MTX monotherapy fails.

Research Question: which combination of conventional DMARD is better and should be recommended, in terms of efficacy and safety for the treatment of early RA, in patients who fail to respond to Methotrexate monotherapy?

Research Hypothesis: LEF based combination DMARD regimes is inferior to SSZ based combination DMARD therapy in safety and efficacy in patients with RA who fail initial MTX monotherapy.

Aims and Objectives: (PICO format)

Aim : To compare 2 combination DMARD therapies (MTX+SSZ+HCQ versus MTX+LEF+HCQ) in patient with early RA who have failed MTX monotherapy

Objectives :

1. To assess safety and efficacy of MTX+LEF+HCQ based combination DMARD therapy in patients with early RA failing MTX monotherapy
2. To assess safety and efficacy of MTX+SSZ+HCQ based combination DMARD therapy in patients with early RA failing MTX monotherapy
3. To compare the safety and efficacy profile of 2 combination DMARD therapy (MTX+LEF+HCQ and MTX+SSZ+HCQ)

Methodology

A. **Study design/type**: Randomized parallel group non-inferiority trial, pragmatic design
B. **Study participants**: Humans

For Participants

a. Inclusion criteria :

Age >18 years satisfying ACR-EULAR criteria for RA

1. Polyarthritis (>4 joints)
2. Disease duration of less than 2 years
3. Patients with moderate to severe disease activity (DAS28≥3.2)
4. Patients who have failed to respond to initial Methotrexate monotherapy

b. Exclusion criteria :

1. End stage disease (deformed fixed joints)
2. Patients with vasculitis, extra-articular features like interstitial lung disease
3. Contraindications to DMARD therapy (Chronic Alcoholism, Chronic liver disease, Evidence of acute/chronic infection, Chronic kidney disease, Patients with leucopenia (<3.0×109/l), thrombocytopenia (<150×109/l), AST/ALT>2× upper normal value and creatinine clearance <30ml/minute)
4. Pregnant, lactating women ; patients (both men and women) of reproductive age group unwilling for contraceptive use who have not completed the family
5. Patients unable to come for regular follow up

c. **Number of groups to be studied, their names and definitions**:

Group 1: MTX+LEF+HCQ

Group 2: MTX+SSZ+HCQ

C. Sampling

a. Sampling Population : Patients >18 years of age diagnosed with RA, attending OPD services of the Department of Clinical Immunology

b. Sample size calculation : (calculated for non inferiority trial)

Sample size has been estimated as 70 patients in each group using the N master software considering success rate as 75 % in both groups (calculated from FIN-RACo trial group, Lancet 1999 (13)) and non inferiority limit as 20% with 5 % alpha error ,statistical power of 80 % and dropout rate as 20%

c. Sampling technique: block randomization

D. Randomization details: block of 10, 1:1 random allocation.

E. Study Procedure

A. Selection of participants: All consecutive patients of RA attending the OPD services of the department of Clinical Immunology will be included to reach a minimum sample size of in each group.

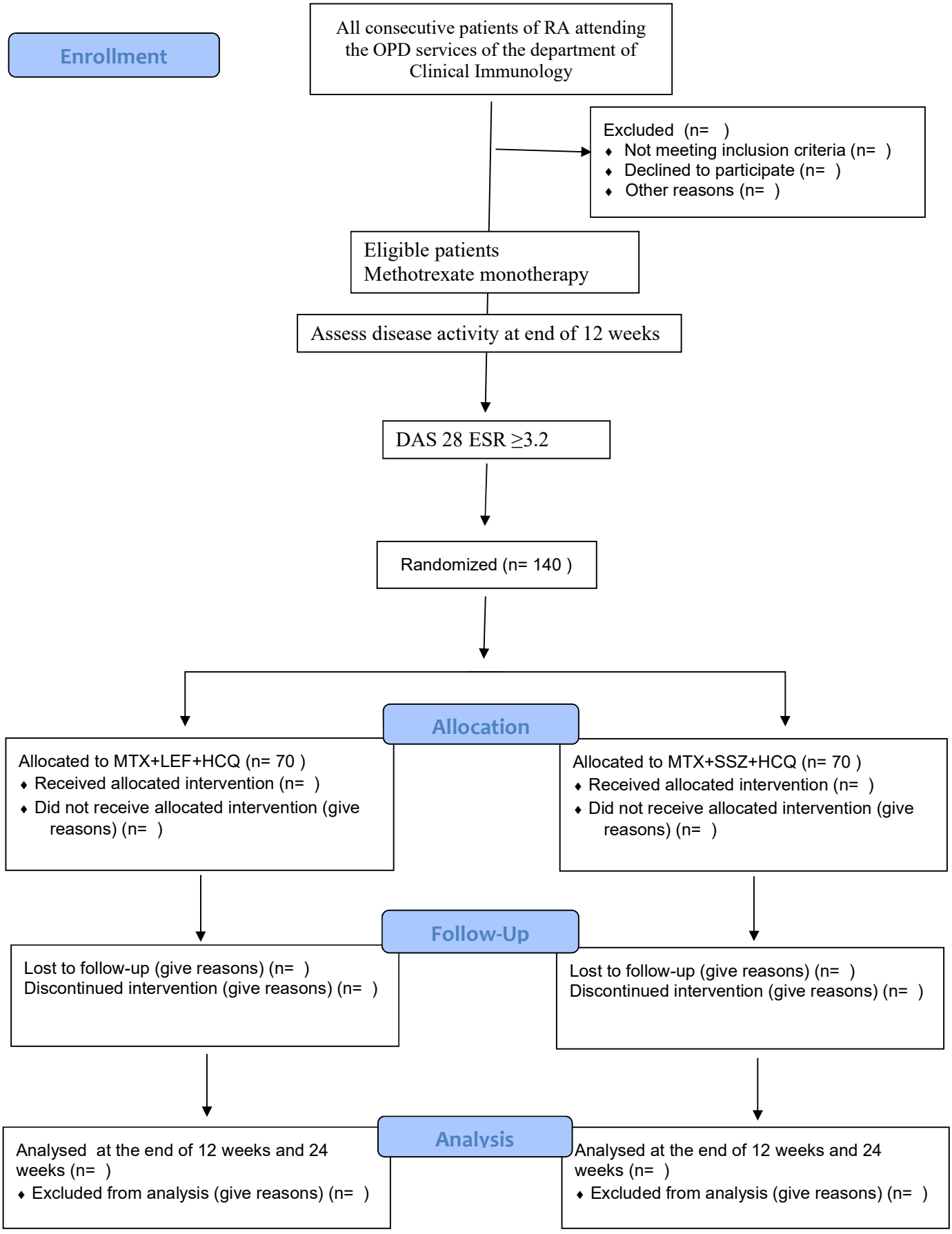
B. Patients will be assessed for eligibility and will be started on Methotrexate monotherapy initially and then only patients, who have moderate to severe disease activity inspite of 12 weeks of Methotrexate monotherapy, will be randomized to either of the 2 groups of DMARDs.

C. Allocation to groups:

Allocation concealment will be done by : Sequentially numbered, opaque, sealed envelopes (SNOSE) method

Group 1: MTX+LEF+HCQ

Group 2: MTX+SSZ+HCQ


Enrollment
All consecutive patients of RA attending the OPD services of the department of Clinical Immunology
Excluded (n=)
♦ Not meeting inclusion criteria (n=)
♦ Declined to participate (n=)
♦ Other reasons (n=)
Eligible patients
Methotrexate monotherapy
Assess disease activity at end of 12 weeks
DAS 28 ESR ≥3.2
Randomized (n= 140)
Allocation
Allocated to MTX+LEF+HCQ (n= 70)
♦ Received allocated intervention (n=)
♦ Did not receive allocated intervention (give reasons) (n=)
Allocated to MTX+SSZ+HCQ (n= 70)
♦ Received allocated intervention (n=)
♦ Did not receive allocated intervention (give reasons) (n=)
Follow-Up
Lost to follow-up (give reasons) (n=)
Discontinued intervention (give reasons) (n=)
Lost to follow-up (give reasons) (n=)
Discontinued intervention (give reasons) (n=)
Analysis
Analysed at the end of 12 weeks and 24 weeks (n=)
♦ Excluded from analysis (give reasons) (n=)
Analysed at the end of 12 weeks and 24 weeks (n=)
♦ Excluded from analysis (give reasons) (n=)

F. Data Collection method including settings and periodicity: Patients aged above 18 years diagnosed as RA according to the 2010ACR-EULAR criteria will be screened and evaluated for inclusion in the study. The patients will be examined every 2 week interval during DMARD dose escalation & then every month for next 6 weeks of MTX and for 24 weeks for either groups.

a. Clinical evaluation:

i. Adverse drug reactions (ADRs) – each visit

ii. IHAQ, DAS28 - once at baseline and then at 12 weeks of MTX monotherapy and then at the end of 24 weeks treatment with either of Group 1 or group 2 drug.

b. Laboratory:

i. Routine CBC/RFT/LFT: every 2 week interval during dose escalation & then every month for 12 weeks after starting the drug

ii. ESR & hsCRP for disease activity evaluation: every month.

iii. **USG** wrist, hand and feet (US-7 score)- at baseline and at 12 weeks of Group 1 or group 2 drug

G. List of variables and their measurement methods with standardization techniques:

a. (i) Independent variables

Socio-demographic profile:

- Age
- Gender

b. Outcome Variables:

Disease-related parameters –

Primary outcome measures:

a. Disease activity (state) - DAS28

Secondary outcome measures:

a. Functional ability – iHAQ

b. Mean changes over time in:

i. Inflammatory parameters: ESR, hs-CRP

ii. Disease activity as per US-7 score

c. Adverse drug reactions

Primary endpoint:

Proportion of patients in both groups achieving good response according to European League Against Rheumatism (EULAR) response criteria at the end of 12 weeks of combination therapy

Secondary endpoint:

1. Change in functional ability (Indian Health Assessment Questionnaire; iHAQ) at the end of 12 weeks of combination therapy
2. disease activity by US7 score at 12 weeks
3. Safety of study medications (adverse drug reactions) during study period (till 24 weeks)
4. Proportion of patients achieving good EULAR response at the end of 24 weeks of combination therapy

Assessment of treatment response

The disease activity will be reassessed at the end of 12 and 24 weeks of random group allocation. The treatment response will be graded according to EULAR response criteria

Radiological assessment of disease activity

Musculoskeletal Ultrasound (**US-7 score**) will be performed in all patients in non blinded manner by the researcher

Clinical Evaluation :

a. Demography: Age/Sex, ethnicity
b. Detailed history and examination will be done for all patients
c. Baseline evaluation of patient

   Disease Activity: Indian Health associated questionnaire (IHAQ), Disease Activity Score-28 (DAS28)

   Damage: Joint: Loss of motion, Deformity, Mal-alignment

d. Extra-articular: Sicca symptoms & signs, sub cutaneous nodules, evidence of Interstitial Lung Disease (ILD), peripheral neuropathy, scleritis/episcleritis

Laboratory investigations

i. **Routine**: Complete blood count (CBC), Erythrocyte Sedimentation Rate (ESR), Sugar (FBS/PP2BS), Liver Function Test (LFT), Renal function test (RFT), Mantoux Test, Viral markers (HIV, HBsAg, Anti HCV), urine analysis, Thyroid function test (TFT)

ii. **Ultrasound (USG)** wrist, hand and feet (US-7 score)

Immunological: High sensitivity C-reactive protein (hsCRP), Rheumatoid Factor (RF), Anti-CCP antibody (ACPA) in all participants .

After baseline evaluation, all consecutive patients with RA will be started on MTX monotherapy unless contraindicated. Patients not responding adequately to MTX monotherapy (DAS28≥3.2) at the end of 12 weeks will be randomized to either of the 2 groups by block randomization after written informed consent.

- MTX+LEF+HCQ- Group 1
- MTX+SSZ+HCQ- Group 2

Concurrent treatment with the following drugs will be allowed during the study as per severity of symptoms and in cases of breakthrough pain:

1. Non-steroidal anti-inflammatory drugs (NSAIDs) - Tablet Diclofenac sodium 50mg twice a day (will be given for minimum duration) and if given on "as and when required" basis, patient will be asked to maintain an NSAID dairy so as to know their requirement.
2. Oral low dose Glucocorticoids (GC) - 7.5 mg/d for 4 weeks followed by 5 mg/day for 2 weeks followed by 5mg on alternate day for 2 weeks – as a bridge therapy. Thereafter, it can be given if disease flares (patient being symptomatic with continued DMARD therapy), with the maximum dose being 7.5mg/day.
3. Intra articular steroids-will be allowed during the study, as per severity of patient's symptoms. The number of intraarticular injections required in each group will be calculated.

DMARD dosages used are:

For all patients as a standard protocol for management of all patients with RA :

1. **MTX** – starting dose 10 mg/week orally for 2 weeks ⟶ 15mg / week for 2 weeks 20 mg/ week for 2 weeks ⟶ 25mg/ week ⟶ assessment of response to MTX after 6 weeks (at the end of 12 weeks after starting MTX)
2. In patients , not tolerating adequate doses of oral MTX in the form of nausea, vomiting, the following strategies will be adopted- 1) dose will be split into two 2) oral MTX will be converted to im formulation.
3. T. Ondansetron 4mg twice a day for 2 days a week will be allowed in the study if patient has nausea or vomiting with MTX.
4. T. Folic acid 5 mg twice a week

Those not achieving adequate response to a maximum permissible dose of MTX (25 mg / week) ie. DAS28ESR >3.2 will be enrolled in the study after randomization:

For **Group 1**

1. T. MTX will be continued at 25mg/week
2. T. folic acid 5 mg twice per week
3. T. LEF -10 mg/day starting dose for 2 weeks ⟶ 20mg /day
4. T. HCQ 200 mg/day at night

For **Group 2**

1. T.MTX will be continued at 25mg/week
2. T. Folic acid 5 mg twice a week
3. T.SSZ 500mg once a day for 7 days ⟶ 500mg twice a day for 7 days ⟶ 500mg thrice a day for 7 days ⟶ 1gram twice a day
4. T. HCQ 200mg/day at night

Note: During the course of the study any patients developing extra-articular manifestations requiring different mode of therapy will be excluded from study (but intention to treat analysis will be used for analysis of results).

STATISTICAL ANALYSIS PLAN (SAP)

The trial is designed as a non-inferiority pragmatic trial trial. The assessment will be done in unblinded fashion by the researcher. Arbitrarily considering EULAR good response rate (primary endpoint) of 75% with SSZ based triple regimen (tREACH and TICORA study) and non-inferiority margin of Δ=(-20%) for LEF, a sample size of 140 (70 in each group) was determined using nMaster sample size calculator (version2 software) using 2-sided confidence levels (CI) of 95%, power of 80% and dropout rate of 20%.

Data will be analyzed using SPSS (IBM pasw statistics, version 19.0) for windows. For quantitative data [DAS28ESR, iHAQ], normality of distribution will be checked by Shapiro-Wilks W test. Continuous data was presented as median and interquartile range (IQR25-75) / mean with SD as appropriate . Mann-Whitney U test / Students t test will be used for comparison between median/ mean of 2 groups respectively. Qualitative or categorical variables (such as EULAR good response) will be described as proportions and will be tested using Chi-square. Odds ratio (OR) – odds of achieving the outcome (treatment response) in patients exposed to LEF in comparison to patients not exposed to LEF (SSZ group) along with 95% confidence interval and p-value will be used to study the statistically significant difference in treatment outcome between 2 groups. P-value of <0.05 was considered as significant.

The primary endpoint will be analyzed by both intention-to-treat (ITT) and per-protocol (PP) analysis. The rest of the parameters will be analyzed by ITT analysis only. Patients who do not complete the study, the last observation will be taken as their outcome for ITT analysis. For missing data, the last available readings will be carried forward in case of patients who are not available for the endpoint assessment. Non-inferiority testing will be done by using a 95% confidence interval (CI) of the difference between the proportions of patients achieving the primary endpoint between 2 groups. Extension of CONSORT 2010 statement will be used for reporting of non-inferiority of the LEF group.

INFORMED CONSENT FORM

(ICF)

Patient / Participant information sheet

INFORMATION FOR PARTICIPANTS OF THE STUDY

Title of the project: Comparison of Sulfasalazine versus Leflunomide based combination Disease modifying anti rheumatic drug (DMARD) therapy in patients with Rheumatoid arthritis failing Methotrexate monotherapy : A randomized control trial

Purpose of this project/study

This comparative study will help us determine which combination of drugs used for the treatment of rheumatoid arthritis called as DMARDs is safer and more effective in patients who have failed to respond adequately to treatment with a single drug methotrexate.

Procedure/methods of the study

The study will be conducted at the Department of Clinical Immunology, JIPMER. Once you are diagnosed to have RA with the disease duration of less than 2 years, you will be evaluated for disease activity and severity, socio-demographic features, extra-articular manifestations. You will be evaluated for your suitability to be treated DMARDs by a battery of blood and radiological tests. All testing will be done inside hospital, free of cost. The results of the investigation will be made available and discussed with you. You will be informed about the nature and severity of the disease and about the various treatment options and the duration of treatment. During the course of treatment you will be regularly evaluated for beneficial as well as adverse effect of the drugs. On completion of the study if you have satisfactory response, you will continue to receive the drugs. Otherwise other suitable modality of treatment as per standard guidelines will be offered.

Expected duration of the subject participation:

24 weeks

The benefits to be expected from the research to the participant or to others and the post trial responsibilities of the investigator

In early RA, once patient fails the initial 12 weeks trial of MTX monotherapy, the patient is at a very high risk of joint deformities and disability. At present there is no consensus or any definite guidelines to guide the treating physician for the next step of management. Combination drugs (DMARDs) or Biologics are recommended as the next line of management. However, biologics are very costly (more than 100 times the cost of combination drugs) and out of the reach of most of Indian population. Therefore the most suitable option is combination DMARD therapy.

However, as of now we do not know which combination is better for the management of severe RA nonresponsive to methotrexate. This study takes that initiative to compare the efficacy and safety of the two easily available and cheap combination DMARDs for the treatment of rheumatoid arthritis. Thus, the results of the study may be beneficial to the participant as well as other patients of rheumatoid arthritis.

Any risks expected from the study to the participant

The study is trying to find out the best combinations of drugs for the treatment of patients with severe rheumatoid arthritis who do not respond to methotrexate. The drugs used for the treatment are the approved ones for the treatment of this condition and will be used according to standard guidelines for treatment of RA. Rarely these drugs may be associated with side effects which in most cases are minor and can be prevented from happening by your regular follow up clinical and laboratory evaluation. The treatment does not contain any additional procedure or treatment other than the standard of care practice for the management of RA. Therefore there are no additional risks to the patient other than expected during the normal course of treatment of patients with RA.

Maintenance of confidentiality of records

Yes. The information obtained from you will be maintained confidential. In case of publication of data the individual identities of the study participants will not be disclosed. Your identity will be maintained confidential during all the steps of the study i.e. data collection, analysis and publication.

Provision of free treatment for research related injury

The study procedure carries more than minimal risk. In the case of research related injury free treatment will be provided as per JIPMER guidelines.

Compensation for participating in the study

Participation in the study is voluntary without any financial incentives

Compensation to the participants for foreseeable risks and unforeseeable risks related to research study leading to disability or death.

Compensation for any unforeseeable events, disability and death will be paid as per JIPMER guidelines.

Freedom to withdraw from the study at any time during the study period without the loss of benefits that the participant would otherwise be entitled9

Yes, you can, at your own discretion, withdraw from the study at any time without assigning

any reasons and without loss of benefits. Withdrawal from the study will not affect your regular treatment in the hospital in any way.

Possible current and future uses of the biological material and of the data to be generated from the research and if the material is likely to be used for secondary purposes or would be shared with others

Biologic materials (serum) will be used for patient investigations only and will not be used for any other purposes. Records will be preserved for a period of 3 years. Data emerging from this study may be published as a research article in medical research journals without divulging individual identities of the study participants. Biological materials will not be shared with others.

Address and telephone number of the investigator and co-investigator/guide

Signature of the investigator:

Signature and thumb imprint of participant :

Signature and thumb imprint of witness :

Date: _____

CONSENT FORM

Title of the project: Comparison of Sulfasalazine versus Leflunomide based combination disease modifying anti rheumatic drug (DMARD) therapy in patients with Rheumatoid arthritis failing Methotrexate monotherapy: A randomized control trial

Participant's name: Address:

The details of the study have been provided to me in writing and explained to me in my own language. I confirm that I have understood the above study and had the opportunity to ask questions. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without the medical care that will normally be provided by the hospital being affected. Risk-benefit of the study has been explained to me. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). I have been given an information sheet giving details of the study. I fully consent to participate in the above study.

Signature of the participant: _____ Date: _____

Signature of the witness: _____ Date: _____

Name:
Address:

Signature of the investigator: _____ Date: _____

DATA COLLECTION PROFORMA

CODE NO: **Date of enrollment:**

Name/ age/ sex/ CCR no : Contact number

Disease duration:

Co-morbid conditions (with duration):

Personal history (habits/addictions):

Treatment history:

Family history:

Baseline Investigations:

RF: **HIV:** **HBsAg:** **HCV:**

Anti-CCP: **Mantoux test:**

Drug	**Dose**	**since when**	**Side effects**
1			
2			
3			

	Baseline	**4mo**	**5mo**	**6mo**
IA Steroids				
Oral steroids				

	Baseline	**4 week**	**8 week**	**12 week**	**16 week**	**20 week**	**24 week**
TJ28							
SJ28							
VAS							
ESR							
hsCRP							
DAS28							
iHAQ							
Morning stiffness							

Extraarticular features							
Adverse drug reactions							

FOLLOW UP INVESTIGATIONS

Investigations	**Baseline**	**4W**	**8W**	**12W**	**16W**	**20W**	**24W**
Hb							
TLC							
DLC							
MCV							
Platelets							
Peripheral smear							
Urine albumin							
Microscopy							
Blood urea							
Sr. Creatinine							
Bilirubin (T/D)							
AST/ ALT							
ALP/GGT							
Total protein /Alb							
CPK / LDH							
Sugar (AC/PC)							
CH/TG/HDL/LDL							
CT/USG/MRI							
ECG/ECHO							

US7 Score		Baseline	12 week	24 week
Synovitis	GS			
	PD			
TS	GS			
	PD			
Erosion	GS			