ISRCTN18445519 https://doi.org/10.1186/ISRCTN18445519

Combination therapy in rheumatoid arthritis

Submission date 13/11/2009	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 27/11/2009	**Overall study status** Completed	
Last Edited 27/11/2009	**Condition category** Musculoskeletal Diseases	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

Contact name
Prof Timo Möttönen

Contact details
TYKS, Paimio Hospital
Alvar aalto way 275
Paimio
Finland
21540

Additional identifiers

Protocol serial number
31.1.1993

Study information

Scientific Title
Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a multicentre randomised open parallel-group treatment strategy trial

Acronym
FIN-RACo trial

Study objectives

Using the combination of disease modifying anti-rheumatic drugs (DMARDs) (sulphasalazine, hydroxychloroquine, and methotrexate) with low dose prednisolone at very early stage of rheumatoid arthritis may be the better treatment strategy in the induction of remission and improvement of disease clinical activity than single-drug treatment stategy of rheumatoid arthritis.

Ethics approval required
Old ethics approval format

Ethics approval(s)
The Joint Commission on Ethics of the Turku University and the Turku University Central Hospital approved on the 2nd March 1993 (ref: supp 1 § 34)

Study design
Multicentre randomised open parallel-group treatment strategy trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Rheumatoid arthritis

Interventions
Combination therapy started with sulphasalazine 500 mg twice daily, methotrexate 7.5 mg weekly, and hydroxichloroquine 300 mg daily, and prednisolone 5 mg daily. This initial combination, if tolerated, was continued for 3 months. If the clinical improvement at 3 months was under 50% in at least two of the three criteria (swollen joints, tender joints, and ESR or CRP), the respective doses of methotrexate and prednisolone were increased to 10 mg weekly and 7.5 mg daily. The protocol allowed flexible subsequent dose adjustment to mimic clinical practice. Thus, the highest dose at 9 months and thereafter was 2 g daily for sulphasalazine, 15 mg weekly for methotrexate, 300 mg daily for hydroxychloroquine, and 10 mg daily for prednisolone. If a patient reached remission during the first year with initial combination, the drug doses were tapered, and prednisolone and methotrexate could even be discontinued at 9 months and 18 months, respectively. Sulphasalazine (1 g daily), and hydroxychloroquine (300 mg daily) had to be continued for 2 years. In the patients who reached remission during the first year, but not with the initial combination, the drug doses were gradually tapered to those of the second year. If the induced remission was lost, the DMARD doses were increased with the intention of reaching remission. If one or several components of the combination had to be discontinued for any reason, a combination of three DMARDs was restarted by replacing sulphasalazine and hydroxychloroquine with auranofin (3 - 6 mg daily), and methotrexate with azathioprine (2 mg/kg daily). Other DMARDs could also be used as substitutes.

The single-treatment strategy was also targeted to achieve remission. The simultaneous use of oral prednisolone up to 10 mg was allowed in patients with continuously active disease, but simultaneous use of multiple DMARDs was not allowed. The decision to use prednisolone was made by the treating physician. The patients were treated continuously with one DMARD alone, with or without prednisolone. If a more beneficial effect was needed, the dose was increased or the DMARD was changed. Sulphasalazine (2 g daily) was used as the initial drug in all patients,

and the dose was increase to 3 g daily at 3 months, if clinically indicated. If an adverse event occurred, or if the clinical response was less than 25% at 6 months, the protocol required that sulphasalazine was replaced with methotrexate 87.5 mg - 15 mg weekly).

Intraarticular injections of glucocorticoids into inflamed joints were allowed in both treatment arms.

All the patients were clinically assessed at baseline and at months 1, 3, 4, 5, 6, 9, 12, and 24 and the adjusments of drug doses were performed.

After two years, treatment was still aimed at achieving or maintaining remissions, but the choise and use of DMARDs was unrestricted. Thus, regardless of the original randomisation group, patients who had an insufficient response could be treated liberally with increased dosages of DMARDs (methotrexate up to 25 mg/week) and with DMARD combination when clinically indicated and tolerated.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Sulphasalazine, hydroxychloroquine, methotrexate, prednisolone

Primary outcome(s)
Induction of remission: American College of Rheumatology (ACR) preliminary criteria for remission were used. However, the patient might or might not be using any drug treatment, and fatigue and duration definition were excluded. The patient with remission was not, by definition, one with any swollen or tender joints. Assessed at 6 months, 12 months and thereafter annually for 11 years.

Key secondary outcome(s))
Assessed at 1, 3, 4, 5, 6, 9, 12 months and thereafter annually for 11 years:
1. Proportion of patients achieving a meaningful clinical response (ACR50% response)
2. Development of radiographic joint damage
3. Frequency of adverse effects
4. Physical function (HAQ)
5. Work capacity

Completion date
28/03/2007

Eligibility

Key inclusion criteria
1. American Rheumatism Association criteria for rheumatoid arthritis
2. Aged between 18 and 65 years, either sex
3. Duration of symptoms of less than 2 years
4. Active disease with three or more swollen joints and at least three of the following:
4.1. Erythrocyte sedimentation rate (ESR) at least 28 mm/h

4.2. C-reactive protein (CRP) above 19 mg/l
4.3. Morning stiffness of 29 minutes or more
4.4. More than five swollen joints
4.5. More than ten tender joints

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Patients who had used DMARDs in the past
2. Had undergone glucocorticoid therapy within the previous 2 weeks
3. Patients with serious comorbidity
4. Suspected inability to comply with the protocol
5. Hypersensitivity to any study medication
6. A history of cancer
7. Pregnant women
8. Women of childbearing age who were not using reliable methods of contraception

Date of first enrolment
30/04/1993

Date of final enrolment
28/03/2007

Locations

Countries of recruitment
Finland

Study participating centre
TYKS, Paimio Hospital
Paimio
Finland
21540

Sponsor information

Organisation
Turku University Hospital (Finland)

ROR
https://ror.org/05dbzj528

Funder(s)

Funder type
Government

Funder Name
All costs are classed as usual treatment and are therefore covered under the Finnish National Health Insurance (NHI) scheme (Finland)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	08/05/1999		Yes	No
Results article	results	01/11/2000		Yes	No
Results article	results	01/04/2002		Yes	No
Results article	results	01/07/2004		Yes	No
Results article	results	01/01/2005		Yes	No
Results article	results	01/05/2009		Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes