Renal safety of initial combination versus single DMARD therapy in patients with early rheumatoid arthritis: an 11-year experience from the FIN-RACo Trial

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Abstract

Objective

To evaluate the renal safety of traditional disease-modifying antirheumatic drugs (DMARDs) in early rheumatoid arthritis (RA).

Methods

One hundred and ninety-five DMARD-naïve patients with recent-onset RA were randomised to receive combination DMARD therapy (n=97) starting with sulfasalazine, methotrexate, hydroxychloroquine, and prednisolone (COMBI) or monotherapy (n=98), initially with sulfasalazine, with or without prednisolone (SINGLE). After two years, the choice and dosing of DMARDs and prednisolone were not restricted, but the treatment was still targeted to achieve or maintain remission. Urinalysis, serum creatinine and glomerular filtration rate (GFR; estimated according to the Cockcroft-Gault formula [$eGFR_{CG}$]) were analysed at baseline and at months 6, 9, 12, 18, 24 and thereafter yearly up to 11 years.

Results

The cumulative incidence of repeated (≥3 times) abnormal renal findings during the 11-year follow-up period were as follows (COMBI versus SINGLE; p-values adjusted for age and sex): proteinuria (dipstick positive) 4.8% (95%CI 1.8-12.2) vs. 5.3% (95%CI 2.0-13.7, p=0.93), haematuria (dipstick positive) 14.1% (95%CI 8.0-24.2) vs. 22.1 % (95%CI 14.5-33.0, p=0.14), raised serum creatinine (≥100 µmol/l in females and ≥115 µmol/l in males) 4.4% (95%CI 1.7-11.4) vs. 6.7% (3.0-14.3, p=0.87) and $eGFR_{GC}$ <60 ml/min/1,73m^2 11.9% (95%CI 6.8-20.5) vs. 10.5% (95%CI 5.8-18.7, p=0.85).

Conclusion

Initial remission targeted therapy with the FIN-RACo DMARD combination in early RA is safe for kidneys and does not induce more short- or long-term renal complications compared to traditional therapy with a single DMARD.

Key words

Chronic kidney failure, combination drug therapy, DMARD, haematuria, proteinuria, rheumatoid arthritis.

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Introduction

Accumulating data indicate that induction of remission and prevention of structural joint damage in rheumatoid arthritis (RA) require intensive use of traditional DMARDs and "tight" control of the patients (1-5). Good treatment-response is also related to improved quality of life (6). Still, there is a shortage of knowledge regarding the influence of modern intensive DMARD treatment strategies on kidney functions compared to the traditional one using a single DMARD on a time.

Clinical nephropathy findings (haematuria, proteinuria and raised serum creatinine) are common in patients with RA (7-11), but knowledge about the occurrence of these findings and their relationship to different treatment strategies in early RA population is scant (12). In a cross-sectional study of RA patients with on an average of 15 years of disease duration the respective prevalences of proteinuria, haematuria and chronic renal failure were 6%, 9% and 6% (11). The study was conducted twenty years ago and the treatment strategies of RA have changed essentially since then. As far as we know, only Koseki and associates (12) have reported the incidences of persistent renal function impairments in an early RA population (duration of RA <1 year). According to their study the occurrence of persistent clinical renal findings was considerable (7% for proteinuria, 18% for haematuria and 6% for raised serum creatinine concentration).

The aim of our study was to establish whether the selected treatment strategy (combination or single DMARD strategy) has an influence on the appearance and persistence of clinical renal findings in patients with early RA during the 11-year follow-up period.

Materials and methods

Patients and study design

From April 1993 to May 1995, 195 DMARD-naïve patients with recent-onset RA (duration of symptoms <2 years) were enrolled in the Finnish RA Combination study (FIN-RACo) (2). This multicenter, randomised, open parallel-group trial was designed to compare two different DMARD treatment strategies. Patients were randomised to receive either combination DMARD therapy (COMBI, n=97) including sulfasalazine, methotrexate, hydroxychloroquine, and prednisolone or single DMARD therapy (SINGLE, n=98), initially with sulfasalazine, with or without prednisolone. Non-steroidal anti-inflammatory drugs (NSAIDs) were used as clinically needed. Oral prednisolone was prescribed for 63 patients in the SINGLE group (according to treating clinicians' decisions). The treatment was targeted to remission in all patients. The study has been described in detail previously (2). After two years, the choice and dosing of DMARDs and prednisolone were not restricted, but the treatment was still aimed to achieve or maintain remission (4, 13). Between 2 and 11 years, combination DMARD therapy (at least two DMARDs at the same time) was used in 79% (median, IQR 43, 100) of the length of the follow-up period in the original COMBI group and in 54% (median, IQR 3, 94) in the original SINGLE group. The corresponding proportions of single DMARD therapy were 5% (median, IQR 0, 30) in the COMBI group and 35% (median, IQR 3, 67) in SINGLE (13). The clinical responses to the therapy have previously been reported by Rantalaiho *et al*. (13).

Inclusion criteria were as follows: 1) fulfilment of the American College of Rheumatology 1987 revised criteria for RA (14), 2) age 18-65 years, 3) duration of symptoms <2 years, and active disease with ≥3 swollen joints and at least 3 of the following: a) erythrocyte sedimentation rate (ESR) >28 mm/hour or C-reactive protein (CRP) >19 mg/liter, b) morning stiffness of ≥29 minutes, c) >5 swollen joints, or d) >10 tender joints. In addition, the patients should have been DMARD naïve, and not been treated with oral glucocorticoids for RA at entry.

One hundred and seventy-eight patients completed the two-year follow-up, 160 completed the 5-year follow-up and 138 participated in the 11-year check-up visit (13).

Ethical considerations

The study was carried out in compliance with the Helsinki Declaration and approval for the study was obtained

from the national health authorities and ethics committees in all 18 participating hospitals. All patients gave written informed consent.

Methods

The serum creatinine and urianalysis were analysed at baseline and at months 6, 9, 12, 18, 24 and at yearly intervals thereafter up to 11 years. Haematuria and proteinuria were defined as positive by dipstick test. Assay sensitivities were defined according to the reference values of the local hospital. Renal function was likewise assessed by measuring serum creatinine concentration according the in-house method of each hospital. A raised serum creatinine concentration was defined as ≥100 μmol/l in females and ≥115 μmol/l in males. In addition, glomerular filtration rate (GFR) was estimated according to the Cockcroft-Gault (CG) (15) formula:

$eGFR_{CG}$={(140-age) × body weight (kg)}/(plasma creatinine (μmol/l) × a) where a =0.8 if male, and 0.95 if female

A reduction in the estimated GFR below 60 ml/min/1,73m^2 was considered to be clinically significant. Renal findings were defined as repeatedly abnormal if detected ≥3 times during the follow-up and as a single abnormality when it occurred at least once. In addition to the data concerning abnormal renal findings, the details of reported serious adverse event were also collected and recorded.

Statistical analysis

All the patients who started therapy (n=195) were included in the study. Last-observation carried-forward (LOCF) analysis was used when the clinical renal findings for each patient were analysed. We used the Kaplan-Meier method to estimate the cumulative incidence of patients with clinical renal findings. Cox regression analyses were made to adjust for confounding factors (age and sex). Also the prevalences of haematuria, proteinuria and clinically significant renal functional impairments were analysed cross-sectionally at baseline and at 2, 5 and 11-year follow-up visits. Cross-sectional analyses during follow-up were based on time-by-time analysis. A time-by-time analysis of the longitudinal data consists of four separate analyses corresponding to each observation time point (baseline, 2, 5 and 11 years).

Table I. Baseline demographics and clinical renal characteristics of patients.

Characteristics	Treatment group	
	COMBI [a] (n=97)	SINGLE [b] (n=98)
Demographic		
Female no. (%)	56 (58)	65 (66)
Mean (range) age, years	47 (23-65)	48 (20-65)
Mean (range) duration of disease, months	7.3 (2-22)	8.6 (2-23)
Nephropathy findings		
Proteinuria no.	1	3
Hematuria no.	10	8
Elevated serum creatinine [c] no.	2	1
$eGFR_{CG}$ [d] < 60 ml/min/1.73m^2 no.	5	1

[a] initial combination DMARD therapy; [b] initial single DMARD therapy; [c]defined as 100 μmol/l or more in females and 115 μmol/l or more in males; [d]glomerular filtration rate estimated by Cockcroft-Gault formula.

Results

The cumulative incidences of abnormal renal findings

The baseline characteristics of the patients are shown in Table I. The cumulative incidences of various repeated nephropathy findings were comparable in the COMBI and SINGLE groups during the follow-up period (Fig. 1). The cumulative incidences of repeated proteinuria in the COMBI and SINGLE groups during the two- and 11-year follow-up periods were 3.4% (95%CI 1.1-10.1) and 4.8% (95%CI 1.8-12.2) versus 1.1% (95%CI 0.2-7.8) and 5.3% (95%CI 2.0-13.7), respectively (p=0.93, adjusted for age and sex). The corresponding cumulative incidences of repeated haematuria were 9.4% (95% CI 4.8-18.0) and 14.1% (95%CI 8.0-24.2) versus 16.4% (95% CI 10.0-26.1) and 22.1 % (95%CI 14.5-33.0), respectively (adjusted p=0.14), and those of raised serum creatinine 2.1% (95%CI 0.5-8.0) and 4.4% (95%CI 1.7-11.4) versus 4.2% (95%CI 1.6-10.7) and 6.7% (95%CI 3.0-14.3) (adjusted p= 0.87). The corresponding cumulative figures of the $eGFR_{GC}$ <60 ml/min/1,73m^2 in the COMBI and SINGLE groups were 7.3% (95%CI 3.5-14.7) and 11.9% (95%CI 6.8-20.5) versus 9.3% (95%CI 5.0-17.1) and 10.5% (95%CI 5.8-18.7), respectively (p=0.85).

If the cumulative incidences were analysed according to the first single abnormal sample, the statistical difference was seen only in the incidence of haematuria (all data not shown). The cumulative incidences of single haematuria findings in the COMBI and SINGLE groups during the two-year follow-up period were 17.7% (95%CI 15.7-20.0) and 27.0% (95%CI 24.6-29.5), while the corresponding figures during the 11-year follow-up were 38.4% (35.6-41.3) and 45.5% (42.6-48.4) (p< 0.001, adjusted for age and sex).

Cross-sectional prevalences of abnormal renal findings

Cross-sectional prevalences of all the findings are shown in Table II. The amount of the patients attending the follow-up visits fluctuated from visit to visit and the cross-sectional prevalences reflect only the situation of the attending patients. Prevalence of haematuria was fairly stable in both treatment groups throughout the 11-year follow-up (8-12%). The cross-sectional prevalence of proteinuria fluctuated from visit to visit, but no difference between treatment strategy groups could be found. The prevalence of elevated serum creatinine values was 2-4% and that of glomerular filtration rates <60 ml/min 1-7% throughout the study in both groups.

Relationship between single nephropathy findings and nephrotoxic DMARD-treatments

Especially the association of gold salts and D-penicillamine (DPA) use with proteinuria and that of cyclosporine

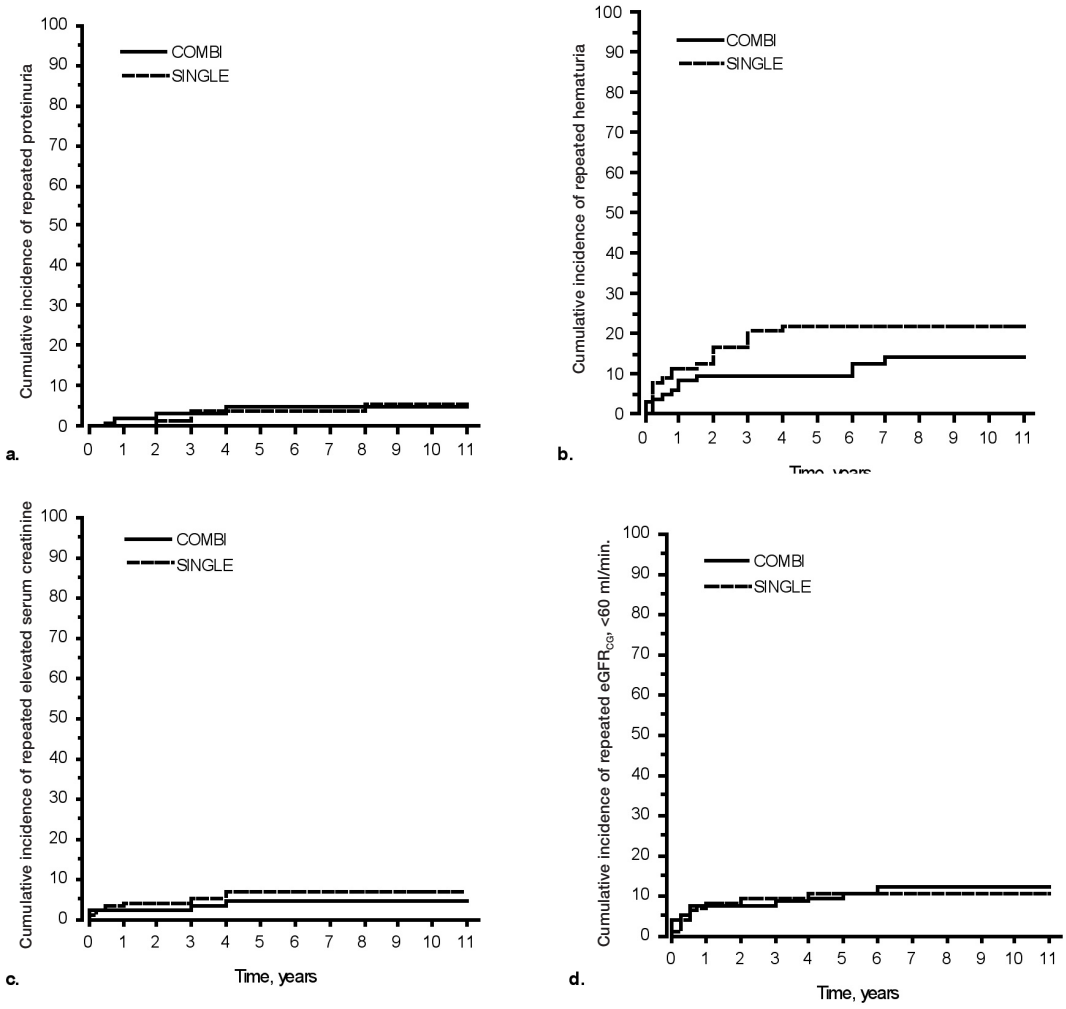

Fig. 1. Cumulative incidences of repeated a) proteinuria, b) haematuria, c) elevated serum creatinine and d) $eGFR_{CG}$ <60 ml/min/1.73m^2 in combination (COMBI) and single (SINGLE) treatment groups.

with raised serum creatinine level or decreased $eGFR_{GC}$ (below 60 ml/min/1,73m^2) was analysed. During the whole 11-year follow-up period proteinuria was detected 55 times and only one of the findings (in the SINGLE group) was related to the use of DPA. The proteinuria in the patient in question progressed to nephrotic-range proteinuria. Renal biopsy indicated a histological diagnosis of minimal-change nephropathy. Proteinuria resolved totally within a couple of months after the cessation of DPA. None of the proteinuria findings was related to the use of gold salts. Serum creatinine was raised 90 times and the finding was associated with cyclosporine use in three cases. $eGFR_{GC}$ <60 ml/min/1,73m^2 was found 272 times, but only three of the findings were related to cyclosporine use.

Discussion

The present long-term follow-up study shows that the initial therapy of RA with a combination of DMARDs including sulfasalazine, methotrexate,

Table II. Cross-sectional (time-by-time analysis) prevalences (number of patients, %) of abnormal clinical renal findings among study patients attending follow-up visits.

	Cross-sectional prevalence of the findings / all studied patients (%)							
	Baseline		2 years		5 years		11 years	
	COMBI[a]	SINGLE[b]	COMBI	SINGLE	COMBI	SINGLE	COMBI	SINGLE
Finding								
Proteinuria	1/97 (1)	3/98 (3)	7/92 (8)	3/95 (3)	1/82 (1)	0/85 (0)	3/77 (4)	4/73 (5)
Haematuria	10/97 (10)	8/98 (8)	8/92 (9)	11/95 (12)	9/82 (11)	10/85 (12)	8/77 (10)	7/73 (10)
Elevated serum creatinine [c]	2/97 (2)	1/98 (1)	2/92 (2)	0/95 (0)	3/82 (4)	3/85 (4)	2/77 (3)	1/73 (1)
$eGFR_{CG}$< 60 ml/min [d]	5/97 (5)	1/98 (1)	3/92 (3)	3/95 (3)	6/82 (7)	5/85 (6)	4/77 (5)	5/73 (7)

[a] initial combination DMARD therapy; [b] initial single DMARD therapy; [c] defined as 100 µmol/l or more in females and 115 µmol/l or more in males; [d] glomerular filtration rate estimated by Cockcroft-Gault formula.

hydroxychloroquine, and prednisolone is safe, and does not cause nephrological complications more frequently than the traditional therapy with a single DMARD. Furthermore, most of the repeated abnormal nephrological findings occurred during the first 2-4 years of DMARD therapy and thereafter the incidence of nephrological complications remained rather constant. As far as we know, our long-term follow-up study defining the influence of DMARD treatment strategies on clinical renal findings in early RA is a pioneering one.

We have previously shown that more patients on initial combination DMARD therapy reach clinical remission at two years than those on DMARD monotherapy (37% versus 18%, p=0.03) (2) and the difference sustains up to 11 years (13). Furthermore, the radiological progression of peripheral joint damage was significantly reduced in the patients treated with initial combination DMARD after both at two- (2) and five-year radiographs (4). In the present long-term follow-up study we also demonstrate that the nephrological safety profile of the initial combination DMARD therapy strategy is not inferior to that of the single DMARD strategy.

Earlier studies have shown that abnormal renal findings are common in RA patients. The data, however, have for the most part been cross-sectional and the studies have been performed in advanced RA populations (7-11). Koseki and associates (12) reported an average of 42 months follow-up results regarding early RA patients. The occurrence of persistent proteinuria of 7% was found, which is more than seen in our study. Most of the persistent proteinuria in their study was DMARD-induced and the usage of the nephrotoxic DMARDs such as gold salts, bucillamine and DPA was frequent. In the present study, proteinuria could be associated with DMARD therapy in only one patient on DPA therapy.

The incidence of haematuria, analysed according to the first single finding, was significantly more frequent in the single DMARD than in the combination DMARD strategy group. The statistical significance between the groups was lost when repeated haematuria was analysed. Earlier studies have not shown anyclinical associations between isolated haematuria findings and DMARD or non-steroidal anti-inflammatory drug (NSAID) therapies (12, 16, 17). A prevalence of 9.5 % for haematuria was stated in patients with advanced RA treated with traditional DMARDs in a population based cross-sectional study (11). Interestingly, the cross-sectional prevalences of haematuria in the present study over time were comparable (8–13%). Furthermore, the prevalences were identical even before the initiation of DMARD therapy. The result confirms earlier findings that haematuria is only remotely, if at all related to DMARD therapy in RA patients. In renal biopsy materials, mesangial glomerulonephritis has been a frequent finding in RA patients with haematuria (18-21) and it has been regarded as one of the extra-articular manifestations of seviere RA (22).

No difference in the incidence of decreased renal function between our treatment groups was found. To define the limits for raised serum creatinine we adopted the same reference values for raised serum creatinine (≥100 μmol/l in females and ≥115 μmol/l in males) as in our previous studies (11, 23, 24). Slightly higher levels for upper normal limits than in routine laboratory reference values were used to avoid false positive results. Nonetheless, reports on poor reliability of serum creatinine concentration to reflect real GFR in RA patients have been published (25-27). Due to low muscle mass in RA patients it appears to overestimate GFR (28). Cockcroft-Gault (15) formula ($eGFR_{CG}$) and creatinine clearance have been reported to perform better than plasma creatinine at identifying reduced renal function in RA patients (27). Therefore in the present study $eGFR_{CG}$ was also applied in the estimation of renal function. A threshold limit of 60 ml/min/1.73m^2 was adopted, because still lower values are regarded as a sign of significantly reduced renal function.

The observed favourable nephrological safety profile of the iniatial combination DMARD therapy strategy is probably explained by the fact that the DMARDs used in FIN-RACo-combination are not regarded as nephrotoxic drugs. However, knowledge of the renal safety of the DMARDs used as combination is scant. Clinically significant nephropathy finding (nephrotic syndrome and minimal change nephropathy) was seen only in one patient, who was on D-penicillamine therapy.

We conclude that initial combination DMARD therapy with sulfasalazine, methotrexate, hydroxychloroquine and prednisolone in early RA patients is safe for the kidneys and does not induce more nephrological complications than the traditional therapy with a single DMARD.

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