Low-dose prednisone chronotherapy for rheumatoid arthritis: A randomised clinical trial (CAPRA-2)

SUPPLEMENTARY MATERIAL

Inclusion and Exclusion criteria

Key inclusion criteria for the study were: diagnosis of RA; documented history of RA (sero-negative or sero-positive) in agreement with American College of Rheumatology (ACR) criteria, including having symptoms of morning stiffness, joint pain, tender and swollen joints, and an inflammatory state with elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP); treatment with DMARDs for RA for at least 6 months, with a stable dose for at least 6 weeks before the screening visit; duration of morning stiffness of at least 45 minutes on at least 4 days within the 7 days of screening; having a swollen joint count at least 4 out of 28 and a tender joint count of at least 4 out of 28; and age 18–80 years. In addition, female patients of childbearing potential had to be using a medically accepted contraceptive regimen.

Key exclusion criteria were: having another condition that required glucocorticoid treatment during the study period; synovectomy within 4 months before the study start; use of glucocorticoids; continued use of systemic glucocorticoids within 4 weeks before the screening visit; intermittent use of glucocorticoids (defined as a maximum of 7 days' treatment with a cumulative dose of ≤100 mg prednisone or equivalent in the 6 weeks before the screening visit) within 2 weeks before the screening visit; intra-articular glucocorticoid injections in the 6 weeks before the

screening visit; use of biological therapies such as TNFα inhibitors within 5 serum half-lives before the screening visit; clinically relevant abnormal laboratory values suggesting an unknown disease and requiring further clinical evaluation; pregnancy or nursing; alcohol or drug abuse; significant renal impairment (serum creatinine >150 µmol/L); significant hepatic impairment (as judged by the investigator).

Randomisation

Patients were assigned to treatment by giving a unique 4-digit patient number to each patient who had provided informed consent. The randomisation schedule was generated by the Contract Research Organization and linked sequential numbers to treatment codes allocated at random with a 2:1 (MR prednisone vs placebo) randomisation ratio. The randomisation numbers were blocked: within each block, patients were allocated to each of the two treatment groups. The block size was not revealed. Randomisation to study medication was balanced by investigational site. The investigational product was labelled with a three-digit randomisation number. The next patient eligible for randomisation was to receive the lowest available medication number within the study site. The investigator documented the medication number in the case report form. The randomisation schedule was kept by the randomisation code administrator who was independent of the study team. A copy of the randomisation schedule was provided to the drug supplier responsible for packaging the investigational products. Tablets were taken with or after the evening meal, at about 10:00 p.m. Both tablets were identical in appearance, and patients and investigators were blinded to treatment.

Permitted and prohibited concomitant medications

In the event of an acute exacerbation of pain, patients were permitted to take a non-anti-inflammatory pain-killing drug, preferably paracetamol, and this was to be recorded in the patient's diary. The following concomitant treatments were not permitted during the study: glucocorticoids other than the study medication, intra-articular injections, synoviorthesis, biological therapies, and initiation of DMARD or non-steroidal anti-inflammatory drug (NSAID) therapy.

Secondary endpoints

In addition to the key secondary endpoint, duration of morning stiffness, the following secondary efficacy endpoints are reported in this paper: proportions of patients with a 50% or a 70% improvement in RA signs and symptoms according to ACR criteria (i.e. ACR50 and ACR70 responses, respectively), change from baseline in the individual ACR core set measures, and change from baseline in: severity of morning stiffness, recurrence of stiffness during the day, morning and evening pain, inflammatory markers (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP] measured at each study visit and IL-6 and TNFα measured at screening and week 12), and measures of health-related quality of life. Routine clinical laboratory assessments were conducted at baseline and week 12. The following additional secondary endpoints were assessed during the study but are not reported here: time to ACR20 response, response according to the European League Against Rheumatism criteria, change from baseline in urine C-terminal cross-linked telopeptides of collagen type I, and analgesic use.

Calculation of duration of morning stiffness

Duration of morning stiffness was the difference between the time of resolution of morning stiffness and the time of waking. The latest resolution time for morning stiffness was set to noon; therefore, if the time when the morning stiffness eased was after noon, this was censored at noon, and duration of morning stiffness was noon minus the time of getting up in the morning. Duration of morning stiffness was calculated as the average of the morning stiffness duration in the 7 days before the visit (including the day of the visit). If more than four assessments were missing, the duration was set to missing. If at least four assessments were available, the 7-day average was calculated using the available values from the 7 days before the visit day for the duration of morning stiffness (LOCF).

Statistical analyses

The primary analysis of the study was according to treatment received, as specified in the statistical analysis plan. Data were analysed both according to treatment received and according to treatment assigned (intention-to-treat, ITT). Where comparison to baseline was required, data were analysed for the modified ITT (mITT) group which excluded patients without baseline data. All analyses yielded consistent results. Results of the ITT (of mITT where appropriate) analysis are reported here. Safety data were analysed according to received treatment. The last-observation-carried-forward (LOCF) method was used for patients who discontinued study treatment prematurely.

A logistic regression model with treatment as a factor was used to assess ACR50 and ACR70 response rates using a two-sided significance level of $\alpha = 0.05$. Relative

changes from baseline for all ACR core set measures except DAS28, other clinical measures (morning pain score, evening pain score, severity of morning stiffness and recurrence of stiffness) and health-related quality of life measures (FACIT-F score, SF-36 physical component score and SF-36 mental component score) were analysed using analysis of covariance (ANCOVA) with treatment and geographical region as factors. Relative change from baseline for DAS28 was analysed using a mixed model with treatment, pooled sites as a nested effect of geographical region, and the interaction between the nested effect and treatment. For assessment of the change from baseline in the inflammatory markers, CRP, IL-6 and TNFα, data were log transformed before the analysis and the estimates were back transformed as these were not normally distributed. Differences between treatment groups for these inflammatory markers were assessed using the 95% CI.

Supplementary Table 1. Patient locations.

Principal investigator	Town/City	Number of patients
USA		
Mehta	Elizabethtown	13
Huh	Los Angeles	2
Kempf	San Antonio	2
Codding	Oklahoma City	4
Cruse	Tampa	4
Kades	Los Angeles	3
Dikranian	San Diego	1
Huff	San Antonio	5
Kennedy	Vero Beach	2
Kirby	Belmont	5
Lee	Upland	6
Rapoport	Fall River	3
Raskin	Pacific Palisades	1
Fairfax	Mesa	3

Principal investigator	Town/City	Number of patients
Trapp	Springfield	4
Archuleta	Wheat Ridge	3
DeGarmao	Greer	2
Hagan	Billings	2
Khan	Bellevue	1
Kimmel	Tamarac	1
Bode	Tucson	4
Goldberger	Perrysburg	1
Lowenstein	Palm Harbour	3
		Total = 75
Canada		
Rodriguez	Windsor	11
Lee	Pickering	2
		Total = 13
Germany		
Buttgereit	Berlin	1
Alten	Berlin	1

Principal investigator	Town/City	Number of patients
Krüger	München	1
		Total = 3
Hungary		
Gal	Kecskemét	7
Náfrádi	Szombathely	6
Nékám	Budapest	6
Sámson	Szolnok	6
Surányi	Debrecen	12
Szántó	Debrecen	18
Takács	Kiskunhalas	12
Balázs	Bekescsaba	5
Szombati	Budapest	30
		Total = 102
Poland		
Szechinski	Wroclaw	27
Dudek	Warszawa	13
Jeka	Torun	19

Principal investigator	Town/City	Number of patients
Mackiewicz	Poznan	7
Majdan	Lublin	4
Sierakowski	Bialystok	16
Sochoka-Bykowska	Sopot	4
Supronik	Bialystok	30
Brzezicki	Elblag	24
Ruzga	Wroclaw	1
		Total = 145
UK		
Kirwan	Bristol	2
George	Upton	1
Szbenyi	Grimsby	9
		Total = 12

Supplementary Table 2. Concomitant DMARD and NSAID therapy at baseline and the end of the study taken by more than 2% of patients.

	Baseline			End of Study		
Concomitant medication, % (n)	MR Prednisone (N=231)	Placebo (N=119)	Total (N=350)	MR Prednisone (N=231)	Placebo (N=119)	Total (N=350)
DMARDs						
Any DMARDs medication	97.0 (224)	96.6 (115)	96.9 (339)	98.3 (227)	100.0 (119)	98.9 (346)
Methotrexate*	74.5 (172)	65.5 (78)	71.4 (250)	74.5 (172)	68.1 (81)	72.3 (253)
Sulfasalazine	15.6 (36)	12.6 (15)	14.6 (51)	15.6 (36)	12.6 (15)	14.6 (51)
Leflunomide	9.5 (22)	13.4 (16)	10.9 (38)	9.5 (22)	13.4 (16)	10.9 (38)
Hydroxychloroquine*	8.2 (19)	10.1 (12)	8.9 (31)	7.8 (18)	10.1 (12)	8.6 (30)
Analgesics						
Any concomitant analgesics medication	83.5 (193)	86.6 (103)	84.6 (296)	77.9 (180)	81.5 (97)	79.1 (277)

*A small number of patients underwent changes in DMARD therapy during the study despite this being prohibited by study protocol; however these were not uncovered until unblinding.

Supplementary Table 3. Patients achieving low disease activity/remission.

Proportion of patients achieving disease status, % (n)	**MR prednisone N = 231**	**Placebo N = 119**	**p-value**
At 2 weeks			
Low disease activity	6.5 (15)	5.9 (7)	1.0000
Remission of disease	3.0 (7)	1.7 (2)	0.7237
At 6 weeks			
Low disease activity	19.1 (44)	5.9 (7)	0.0007
Remission of disease	8.7 (20)	2.5 (3)	0.0381
At 12 weeks			
Low disease activity	27.4 (63)	15.1 (18)	0.0109
Remission of disease	11.3 (26)	6.7 (8)	0.1882

Remission of disease was defined as a 28-joint disease activity (DAS28) score < 2.6.

Low disease activity was defined as a DAS28 score < 3.2.

p-value calculated with Fisher's exact test.

Supplementary Table 4. Duration of morning stiffness relative to disease duration.

Change in morning stiffness from baseline at week 12, Median (95% CI)	**MR prednisone N = 231**	**Placebo N = 119**
< 2 years RA		
Number of patients	38	26
Duration (minutes)	-51.8 (-80.7 to -27.7)	-28.7 (-53.6 to 38.6)
Percentage change	-48.1 (-73.7 to -10.8)	-19.3 (-43.9 to 17.0)
≥ 2 years to < 5 years		
Number of patients	58	23
Duration (minutes)	-62.1 (-88.7 to -38.6)	-30.0 (-89.1 to 2.9)
Percentage change	-69.8 (-83.6 to -36.1)	-33.3 (-58.1 to 2.1)
≥ 5 years to < 10 years		
Number of patients	52	25
Duration (minutes)	-56.9 (-90.0 to -47.1)	-32.1 (-70.7 to -7.5)
Percentage change	-63.8 (-81.7 to -42.0)	-37.8 (-70.5 to -11.1)
≥ 10 years		
Number of patients	68	33
Duration (minutes)	-54.4 (-66.0 to -28.1)	-50.7 (-91.0 to -22.3)

Change in morning stiffness from baseline at week 12, Median (95% CI)	**MR prednisone N = 231**	**Placebo N = 119**
Percentage change	-54.9 (-82.1 to -34.0)	-42.1 (-72.1 to -21.1)

Patient numbers do not add up to total N value for each group as this analysis uses last observation carried forward and post-baseline data was not collected from all patients.

RA, rheumatoid arthritis; CI, confidence interval.

Supplemental Table 5. Integrated safety analysis for the first 3 months of treatment with prednisone.

Preferred Term	MR prednisone (N=375)	IR prednisone (N=144)	Placebo (N=119)
SAE (any event)	1.3%	2.1%	1.7%
Any Event			
Mild	18.4%	17.4%	29.4%
Moderate	21.1%	19.4%	15.1%
Severe	2.4%	2.8%	4.2%
AEs reported in > 2% of patients			
Aggravated RA/RA flare-up	12.8%	9.7%	26.1%
Nasopharyngitis	4.3%	5.6%	3.4%
Headache	4.0%	3.5%	4.2%
Nausea	2.1%	2.8%	0%
Abdominal pain upper	1.6%	5.6%	1.7%
Bronchitis	1.3%	3.5%	4.2%
Vertigo	1.1%	3.5%	0%
Diarrhoea	1.1%	2.8%	0.8%

Preferred Term	MR prednisone (N=375)	IR prednisone (N=144)	Placebo (N=119)
Dyspepsia	0.8%	2.1%	0%
Upper respiratory tract infection	0.5%	2.1%	0.8%
Chest pain	0.5%	2.1%	0%

Integrated safety analysis for patients receiving treatment with: 1) MR prednisone for 3 months in CAPRA-1 (n = 144) or CAPRA-2 (n = 231); IR prednisone for 3 months in CAPRA-1 (n = 144); or placebo for 3 months in CAPRA-2 (n = 119).

There were ten SAEs and one death (in the IR prednisone group) during the first 3 months of the integrated safety analysis; none were considered by the investigator to be related to study medication. SAEs recorded were tendon rupture, thumb osteoarthritis, spinaliom right cheek, Baker's cyst, myocardial infarction, disorder of consciousness, chest pain, abdominal pain exacerbation, palpitations, ischemic heart disease and abnormal cytology.

SAE, serious adverse event; MR, modified release; IR, immediate release; RA, rheumatoid arthritis; CAPRA, Circadian Administration of Prednisone in Rheumatoid Arthritis.

Safety data for CAPRA-1 have been presented previously.[1]

Supplemental Table 6. Integrated safety analysis for 12 months treatment with prednisone.

Preferred Term	MR prednisone months 1–12 (N=120)	IR prednisone months 1–3, MR prednisone months 4–12 (N=129)	All patients (N=249)
SAE (any event)	12.5%	14.7%	13.7%
Any Event			
Mild	18.3%	7.8%	12.9%
Moderate	27.5%	36.4%	32.1%
Severe	3.3%	7.0%	5.2%
AEs reported in > 2% of patients			
Aggravated RA/RA flare-up	14.2%	16.3%	15.3%
Flushing	4.2%	9.3%	6.8%
Back Pain	3.3%	2.3%	2.8%
Upper respiratory tract infection	3.3%	2.3%	2.8%

Preferred Term	MR prednisone months 1–12 (N=120)	IR prednisone months 1–3, MR prednisone months 4–12 (N=129)	All patients (N=249)
Weight increase	3.3%	2.3%	2.8%
Feeling hot	1.7%	3.9%	2.8%
Osteoarthritis	1.7%	3.1%	2.4%
Tachycardia	0.8%	2.3%	1.6%
Synovectomy	0%	2.3%	1.2%

Patients received the first 3 months treatment with either MR prednisone or IR prednisone. All patients then received a further 9 months treatment with MR prednisone. Data reported are overall safety data from months 0–12 of study.

Weight increase was self-reported by the patient.

There were 51 SAEs in 33 subjects. Of these only two were considered by the investigator as possibly related to treatment; perforation of stomach ulcer and digestive system bleeding; both occurred in the MR prednisone group. No deaths were reported.

SAE, serious adverse event; MR, modified release; IR, immediate release; RA, rheumatoid arthritis.

Safety data for the CAPRA-1 extension study have been presented previously.[2]

References

1 Buttgereit F, Doering G, Schaeffler A, et al. Efficacy of modified-release versus standard prednisone to reduce duration of morning stiffness of the joints in rheumatoid arthritis (CAPRA-1): a double-blind, randomised controlled trial. *Lancet*. 2008;**371**(9608):205-14.
2 Buttgereit F, Doering G, Schaeffler A, et al. Targeting pathophysiological rhythms: prednisone chronotherapy shows sustained efficacy in rheumatoid arthritis. *Ann Rheum Dis*. 2010;**69**(7):1275-80.