RHEUMATOLOGY

Original article

doi:10.1093/rheumatology/kex223

Similar efficacy and safety of initial COBRA-light and COBRA therapy in rheumatoid arthritis: 4-year results from the COBRA-light trial

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Abstract

Objective. To assess the efficacy and safety of initial COBRA-light *vs* COBRA therapy in RA patients after a 4-year follow-up period.

Methods. In the COBRA-light trial, 162 consecutive patients with recent-onset RA were randomized to either COBRA-light (prednisolone and MTX) or COBRA therapy (prednisolone, MTX and SSZ) for 1 year. After 1 year, treatment was continued without protocol, and adjusted by the treating physician according to clinical judgement, preferably with a treat-to-target strategy. Four years after trial initiation, all patients were invited to participate in the COBRA-light extension study, in which patients were interviewed and physically examined, patient reported outcomes were assessed, radiographs were made and clinical records were examined for comorbidities and medication use.

Results. In the extension study, 149 out of 162 (92%) original trial patients participated: 72 COBRA-light and 77 COBRA patients. Initial COBRA-light and COBRA therapy showed similar effect on disease activity, physical functioning, radiological outcome and Boolean remission over the 4-year follow-up period. In addition, both treatment groups showed similar survival and major comorbidities, although the power to detect differences was limited. Besides protocolled differences in prednisolone, MTX and SSZ use, the use of other synthetic and biologic DMARDs and intra-articular and intramuscular glucocorticoid injections was similar in both treatment groups over the 4-year period.

Conclusion. Early RA patients initially treated with COBRA-light or COBRA therapy had similar efficacy and safety outcomes over a 4-year follow-up period.

Key words: rheumatoid arthritis, early RA, combination therapy, DMARDs, long-term follow-up, efficacy, safety, comorbidities

CLINICAL SCIENCE

Rheumatology key messages

- RA patients on initial COBRA or COBRA-light therapy had favourable outcomes over 4 years.
- Both RA treatment strategies strongly improved disease activity, physical functioning and radiological outcome.
- Both RA treatment groups showed similar comorbidity profiles and patterns of DMARD use over time.

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Submitted 9 March 2017; revised version accepted 9 May 2017

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Introduction

Combination therapy is effective and safe in early RA patients with respect to clinical and radiological outcomes in the short and long term [1–17]. An early and well-known example of successful combination therapy is COBRA (Dutch acronym for COmbinatietherapie Bij Reumatoide Artritis) therapy, which combines initial high-dose prednisolone (60 mg/day), with MTX and SSZ [2–4]. However, despite confirmed clinical effectiveness, safety and cost-effectiveness in the short and long term, COBRA therapy is infrequently prescribed by rheumatologists due to concerns about the complexity of the treatment schedule, the large number of pills and the possible side effects of high-dose prednisolone use [18, 19].

Therefore, an attenuated and simplified combination therapy was designed, combining a lower initial prednisolone dose (30 mg/day), with a higher dose of MTX and without SSZ. In an open-label randomized controlled trial, COBRA-light therapy proved to be non-inferior to COBRA therapy in clinical and radiological efficacy and safety after 6 and 12 months in early RA patients [5, 6]. The majority of early RA trials monitor their patients over a 1- or 2-year period, while studies with longer observation time are scarce. Therefore, the aim of the present study was to compare efficacy and safety of initial COBRA-light *vs* COBRA therapy in RA patients after a 4-year follow-up period.

Methods

Study design and study population

This study is a follow-up of the multicentre COBRA-light trial, which assessed the non-inferiority of COBRA-light *vs* COBRA therapy on clinical and radiological outcomes in 162 early RA patients at VU University Medical Center, Reade and Westfriesgasthuis in The Netherlands (ISRCTN Clinical Trial Registration Number: 55552928) [5, 6]. In brief, COBRA-light therapy (prednisolone 30 mg/day, tapered to 7.5 mg/day in 8 weeks and MTX escalated to 25 mg/week in 8 weeks) was compared with COBRA therapy (prednisolone 60 mg/day, tapered to 7.5 mg/day in 6 weeks, MTX 7.5 mg/week and SSZ 2 g/day), with DAS < 1.6 as treatment goal. After 6 months, COBRA-light patients had received 1750 mg prednisolone and 550 mg MTX, COBRA patients 2275 mg prednisolone and 188 mg MTX.

In the period of 6 months to 1 year, treatment intensification of MTX (in COBRA) and addition of etanercept was mandated per protocol in patients who did not reach minimal disease activity (DAS < 1.6). Per protocol, 61 COBRA-light and 47 COBRA patients needed treatment intensification with etanercept. In practice, only 40 COBRA-light and 27 COBRA patients actually started etanercept, due to treatment deviations and/or protocol violations [6]. After 1 year, treatment was continued without protocol, and adjusted by the treating physician according to clinical judgement, preferably in a treat-to-target design. Intra-articular and intramuscular glucocorticoid injections were allowed. Patients were intensively monitored up to 2 years and visited their rheumatologist and research nurse 3, 6, 9, 12, 18 and 24 months after trial initiation.

In the COBRA-light extension study, all patients who had initiated therapy (n = 162), including drop-outs during the 2-year trial period (n = 11), were invited for a single assessment 4 years after trial initiation. Ethics committees at each participating centre approved the protocol; patients gave written informed consent, and the study was conducted in accordance with the Declaration of Helsinki/Good Clinical Practice.

Outcome measures

Disease activity and remission

DAS (44 joints) assessed disease activity, and was corrected for intra-articular and intramuscular glucocorticoid injections, as previously described [6]. A 100 mm visual analogue scale (VAS) recorded physician assessment of disease activity. Clinical remission was defined according to the ACR/EULAR Boolean and SDAI remission criteria [20], and minimal disease activity as DAS < 1.6.

Patient reported outcomes

Patient reported outcomes comprised physical functioning (Dutch HAQ) [21]; patient assessments of pain, disease activity and general well-being (100 mm VAS); quality of life [EuroQol (EQ-5 D-3 L) and its health status VAS] [22, 23]; impact of RA (Rheumatoid Arthritis Impact of Disease) [24, 25]; comparison of current health status with 1 year ago [one item of the Short Form questionnaire 36 (SF-36)] [26]; and fatigue (Bristol Rheumatoid Arthritis Fatigue questionnaire, both the multi-dimensional questionnaire and numerical rating scales on severity, effect on life and coping ability) [27].

Radiological outcome

Radiographs of hands and feet at 4 year were scored independently according to the Sharp–van der Heijde score (SHS) [28] by two trained assessors who also had scored all previous study radiographs. The assessors were aware of the sequence, but blinded for treatment group and study centre, as previously described [6]. In 9 out of 149 patient sets, the two assessors differed by $\geqslant 5$ points, and the score of a third assessor (D.v.S.) was applied. The intraclass correlation coefficient for agreement between the two assessors was 0.97 (95% CI: 0.95, 0.98). Results are reported as the mean of the two assessors' scores.

Survival and comorbidities

Clinical records, and information from the general practitioner or medical specialist, where necessary, were queried for survival, including information on date and cause of death. All patients were queried and clinical records were examined according to a fixed protocol to identify new comorbidities developed during the follow-up period. Serious deteriorations of comorbidities present at baseline were also noted. Only comorbidities and events that were confirmed by a clinical record were used in the

primary analysis; a sensitivity analysis was performed to evaluate the impact of including data of patient reported comorbidities and events that were not confirmed by clinical records. When a joint was replaced after a clinical fracture, only the fracture was counted as comorbidity; remaining joint replacements were thus mainly due to OA. DXA was performed at the 4-year visit to identify changes in bone mineral density to assess osteoporosis (t-score less than −2.5) in lumbar spine (L1–L4), femoral neck or total hip. X-rays of thoracic and lumbar spine were made at the 4-year visit to identify vertebral fractures according to Genant's method [29]. The X-rays were scored by two assessors (I.B., W.L.), unaware of treatment group, and compared with baseline X-rays. Chest X-rays or instant vertebral assessment were used if no or incomplete spine X-rays were available for assessment. A prevalent vertebral fracture with >10% increase in vertebral height loss after 4 years was considered as a clinically relevant 'new vertebral fracture' during the follow-up period.

Medication use

Clinical records were examined from baseline until the 4-year visit for prednisolone and MTX use (both: duration, mean and cumulative dose), and use of other synthetic and biologic DMARDs (duration only), and number of administered intra-articular and intramuscular glucocorticoid injections.

Other outcomes

Other disease-related outcomes that were assessed in this study were the following: duration of morning stiffness; life style factors such as smoking status and BMI; and ESR and CRP.

Statistical analyses

Results are presented as mean (S.D.), or as median (interquartile range) (25th percentile, 75th percentile), where appropriate. Follow-up data of deceased patients (n = 5) were included as far as possible.

Independent t-tests or Mann–Whitney U tests (continuous outcome measures), and Chi-square or Fishers exact tests (dichotomous outcome measures) evaluated differences between the groups, where appropriate.

Generalized estimating equations and mixed model analyses assessed changes in disease activity, physical functioning, radiological outcome and Boolean remission over time between treatment groups, correcting for repeated measures. Baseline measures were included in all analyses to correct for regression to the mean, except Boolean remission, absent by definition at baseline. Mixed models analysis (Gaussian distribution) was used for DAS. Tobit regression (Gaussian distribution) analysed skewed HAQ data, with 0 as lower limit. SHS data were extremely skewed and Poisson regression was not possible because of overdispersion. Therefore, SHS data were analysed as counts outcome (all scores were rounded up) with the negative binomial (log link) distribution. A sensitivity analysis was performed with scores rounded down. Logistic generalized estimating equations analysis (binomial distribution) analysed Boolean remission. The exchangeable correlation matrix was used in all analyses. All outcomes were corrected for potential confounding or effect modification through mandatory inclusion in the analysis model of the terms sex, age, baseline DAS, baseline RF, baseline ACPA, baseline erosive disease according to 2013 EULAR definition [30], baseline BMI and baseline smoking status. Sensitivity analyses were performed to evaluate the potential impact of the deceased patients (n = 5) and drop-outs (n = 8) on DAS, HAQ and SHS over time. In these 13 patients, missing values were imputed: a missing value at an in-between visit was replaced by the mean score of the visit before and after the missing visit, a missing value at 48 months or a range of missing values (in case of drop-out) was predicted per patient via the trend of simple linear regression over all earlier visits (n = 1).

In the above described longitudinal analyses, in which the primary outcomes were tested, $P < 0.05$ was considered significant. Bonferroni corrections were applied to all secondary analyses, to retain an overall alpha level of 0.05. A total of 60 secondary analyses resulted in a Bonferroni corrected alpha level of 0.05/60 = 0.0008.

All descriptive statistical analyses were performed with SPSS Statistics, version 22 (SPSS Inc, Chicago, IL, USA) and all longitudinal analyses were performed with Stata, release 12 (StataCorp LP, College Station, TX, USA).

Results

In the extension study, 149 out of 162 (92%) original trial patients participated: 72 COBRA-light and 77 COBRA patients (Fig. 1); 5 patients died during the follow-up period (3 COBRA-light, 2 COBRA) and 8 patients were not able or willing to participate (6 COBRA-light, 2 COBRA) of whom 2 patients were in drug-free remission and out of routine care. Comorbidities and medication use of one COBRA patient who dropped out the study after 3 months and died during the follow-up period was incomplete due to an undocumented hospital switch after 3 months.

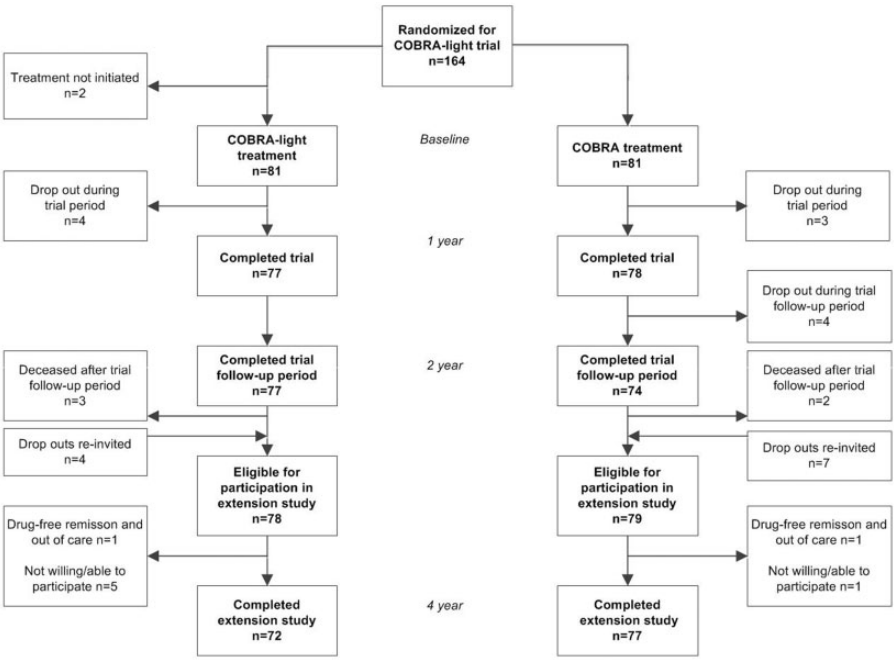
Baseline patient characteristics were extensively reported in previous COBRA-light publications [5, 6]. At the 4-year visit, the median follow-up period was 49 months (range: 34–74 months), and the median disease duration was 55 months (range: 36–85 months) in both treatment groups. Patients of the initial COBRA-light and COBRA group showed similar clinical parameters and patient reported outcomes at the 4-year visit (Table 1).

Main clinical outcomes over time

Longitudinal data analyses showed similar effects of both initial COBRA-light and COBRA therapy on DAS, HAQ, SHS and Boolean remission over time (Fig. 2). Sensitivity analyses including imputed data of deceased patients and drop-outs showed similar results for all four outcome measures. The mean changes in DAS and HAQ over time were highly similar between the treatment groups in both crude and corrected models, and no significant effect modifiers were found (Fig. 2A and B, respectively).

At 4 years, the median SHS was 0.8 (0–3) for COBRA-light and 1.5 (0–5.5) for COBRA (P = 0.06). The median increase

Fig. 1 Flow chart of the COBRA-light trial and its extension study



over 4 years was similar for both groups: 0.5 (0–2.0) for COBRA-light and 0.5 (0–2.5) for COBRA (P = 0.72). The overall mean annual progression rate was 0.16 (95% CI: 0.11, 0.21) SHS units per year. During the follow-up period, 42% COBRA-light *vs* 43% COBRA patients did not show any radiological progression; an increase in damage of $\geqslant$5 points occurred in 8% COBRA-light *vs* 15% COBRA patients (P = 0.25), and $\geqslant$10 points in 4% COBRA-light *vs* 7% COBRA patients (P = 0.53) (Fig. 3). Longitudinal analyses demonstrated that the mean change in SHS over time was highly similar between the treatment groups in both crude and corrected models (Fig. 2C). Although baseline DAS was an effect modifier in the longitudinal relationship between SHS and treatment group, there was no significant difference in the prevalence of remission between treatment groups over time when stratified for low *vs* high baseline DAS.

The mean prevalence of Boolean remission over time was similar between the treatment groups in both crude and corrected models (Fig. 2D). Although baseline BMI was an effect modifier in the longitudinal relationship between remission and treatment group, there was no significant difference in the prevalence of remission between treatment groups over time when stratified for low *vs* high baseline BMI. Age was also an effect modifier in the longitudinal relationship between remission and treatment group, and stratification for low *vs* higher age resulted in a significant difference in prevalence of remission between treatment groups in younger patients, but not in older patients.

Survival and comorbidities

After a mean follow-up period of 4 years, five patients died: three COBRA-light patients [dementia (n = 1); acute death: assumed pulmonary embolism (n = 1) and assumed cardiac cause (n = 1)] and two COBRA (both cancer). Overall, 72% of the patients developed at least one comorbidity during the 4-year follow-up period (Table 2). Cardiovascular events, hypertension, hypercholesterolaemia, diabetes mellitus (DM) type 2 and other comorbidities occurred similarly in both treatment groups. Seven patients developed cancer during the follow-up-period: five COBRA-light [lung cancer (n = 3), basal cell carcinoma (n = 1) and meningioma (n = 1)] and two COBRA (both lung cancer, both deceased during follow-up). In addition to these new cancer cases, two patients [COBRA-light (n = 1), COBRA (n = 1)] with a history of basal cell carcinoma before trial initiation suffered from a recurrent basal cell carcinoma during the follow-up period.

In addition to the new developed comorbidities, three COBRA patients with DM at baseline developed insulin-dependent DM during the follow-up period, and one COBRA patient with intermittent claudication at baseline received angioplasty and two peripheral stents in the iliac arteries during the follow-up period.

In additional sensitivity analyses, inclusion of patient-reported comorbidities and events that were not confirmed by clinical status had no effect on the main results, although the number of patients with $\geqslant$1 infection treated with antibiotic or antiviral drugs increased from 40 to 52%.

Medication use

After the 1-year trial period, 41% COBRA-light *vs* 43% COBRA patients continued prednisolone use for a consecutive period of $\geqslant$90 days (P = 0.83); 43% COBRA-light *vs* 33% COBRA patients started with $\geqslant$1 synthetic DMARD (P = 0.21); and 29% COBRA-light *vs* 39%

Table 1 Study population characteristics at the 4-year visit of the COBRA-light extension study (n = 149)

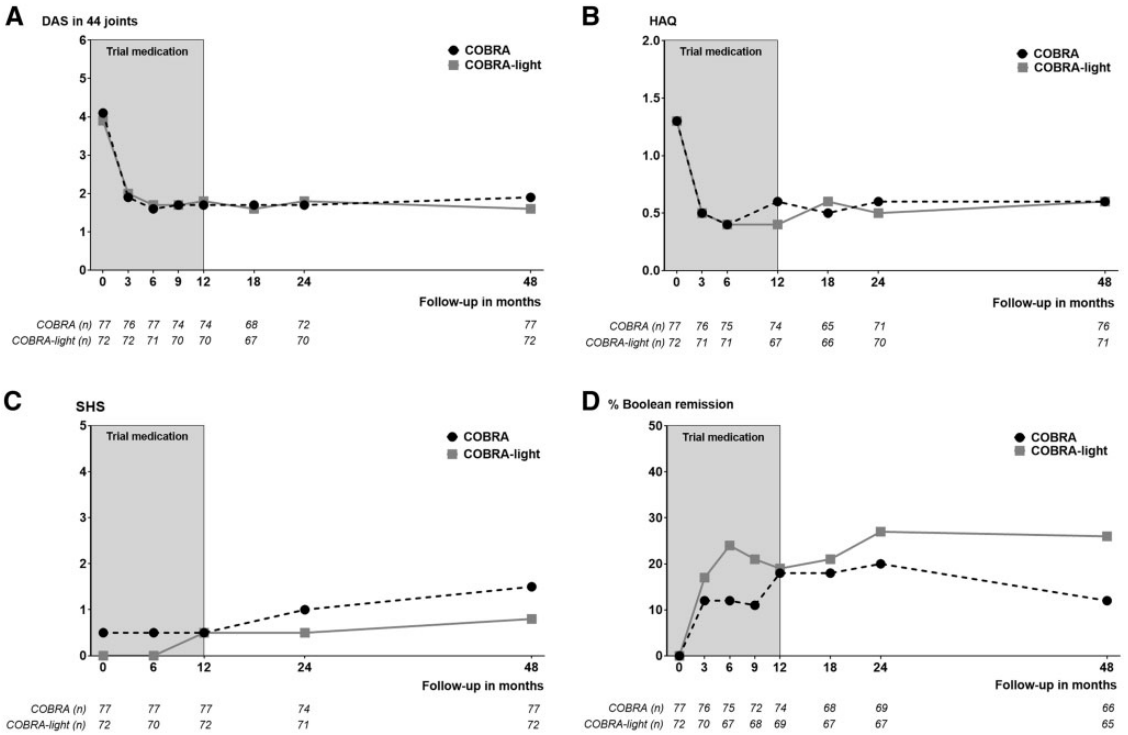
	COBRA-light (n = 72)	COBRA (n = 77)
Demographics and life style factors		
Female, n (%)	48 (67)	52 (68)
Age, mean (S.D.), years	56 (12)	58 (13)
Smoking, n (%)[a]	16 (22)	17 (22)
Alcohol use, units per week	2 (1–7)	2 (0–7)
BMI[a], kg/m^2	25.5 (23.0–29.1)	25.7 (23.2–27.4)
Clinical parameters		
Disease duration, mean (S.D.), months	55 (11)	55 (11)
DAS[a], mean (S.D.)	1.6 (0.9)	1.9 (1.2)
Tender joint count in 53 joints	2 (0–6)	2 (0–8)
Swollen joint count in 44 joints	0 (0–2)	1 (0–3)
DAS28	2.2 (1.5–3.2)	2.5 (1.6–3.2)
Physician assessment of disease activity[a]	13 (4–30)	20 (10–35)
SHS[a]	0.8 (0–3.0)	1.5 (0–5.5)
ESR, mm/h	8 (3–17)	8 (3–15)
CRP, mg/l[a]	2 (2–3)	3 (2–6)
Duration of morning stiffness in minutes	10 (1–41)	15 (2–60)
Patient reported outcomes		
HAQ[a]	0.6 (0–1.1)	0.6 (0.1–1.3)
RAID[a]	2.4 (0.4–4.5)	2.7 (1.1–4.5)
EQ-5D-3L[a]	0.81 (0.69–1.00)	0.81 (0.69–0.97)
EQ VAS health state	75 (58–90)	75 (61–85)
SF36 health status		
Better than last year, n (%)	19 (26)	21 (27)
Same as last year, n (%)	41 (59)	44 (60)
Worse than last year, n (%)	9 (13)	9 (12)
Patient global assessment	19 (5–45)	30 (10–56)
Patient assessment of disease activity[a]	14 (3–32)	15 (7–50)
Patient assessment of pain[a]	17 (3–37)	21 (9–50)
BRAF		
Multi-dimensional questionnaire[a]	19 (5–31)	20 (10–26)
NRS severity[a]	4 (1–7)	5 (3–7)
NRS effect on life[a]	4 (1–7)	5 (2–7)
NRS coping ability[a]	7 (5–9)	7 (5–8)
Minimal disease activity and remission		
Minimal disease activity		
DAS < 1.6, n (%)[a]	34 (47)	38 (49)
ACR/EULAR remission		
Boolean-based definition, n (%)[a]	17 (26)	8 (12)
Index-based definition: SDAI $\leqslant 3.3$, n (%)[a]	22 (34)	14 (21)

Results are presented as median (IQR), unless indicated otherwise. There were no significant differences between the treatment groups after application of the Bonferroni correction for secondary analyses ($P < 0.0008$ is considered significant). [a]Only these main variables were tested for significance; patient and physician assessments by visual analogue scale (VAS) in millimetre. BRAF: Bristol RA Fatigue; EQ-5 D-3 L: EuroQol version 5 D 3 L; EQ VAS health state: EuroQol visual analogue scale health state; NRS: Numerical Rating Scale; RAID: RA Impact of Disease; SDAI: Simplified Disease Activity Index; SF36 Health status: health status assessed by one item of the Short Form 36 Health Survey (SF36); SHS: Sharp–van der Heijde score.

COBRA patients started with $\geqslant 1$ biologic DMARD (P = 0.20).

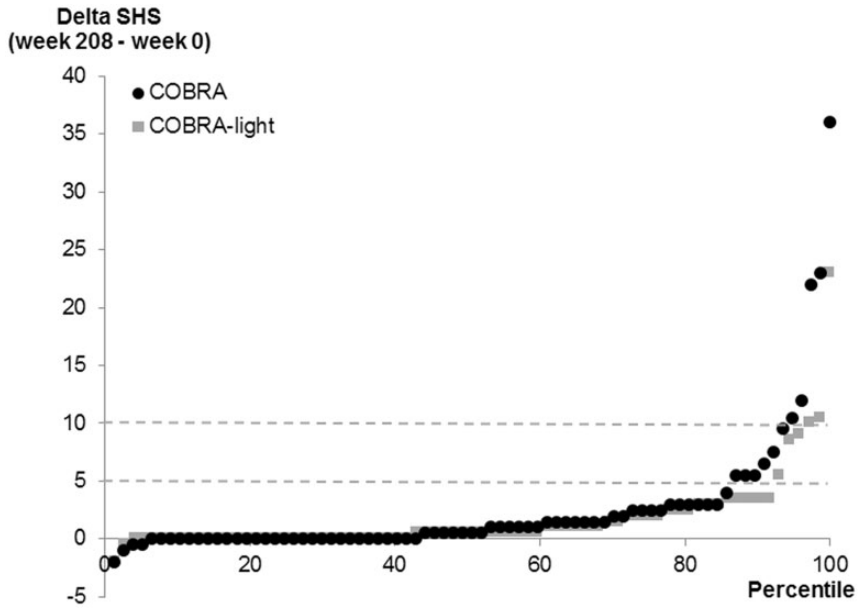
At the 4-year visit, 14% COBRA-light *vs* 17% COBRA patients were drug free (no prednisolone or DMARD use) (P = 0.61), 11% COBRA-light *vs* 8% COBRA patients were in drug-free minimal disease activity (P = 0.49) and 11% COBRA-light *vs* 2% COBRA patients were in drug free ACR/EULAR Boolean remission (P = 0.03). In addition, 19% COBRA-light *vs* 22% COBRA patients used prednisolone (P = 0.69), 72% COBRA-light *vs* 68% COBRA patients used MTX (P = 0.53), 19% COBRA-light *vs* 27% COBRA patients used another synthetic DMARD (P = 0.26) and 18% COBRA-light *vs* 22% COBRA patients used a biologic DMARD at the 4-year visit (P = 0.54). These drugs were in 55% COBRA-light *vs* 39% COBRA patients prescribed in the form of monotherapy, and thus in 45% COBRA-light *vs* 61% COBRA patients as combination therapy. At the 4-year visit, 5% COBRA-light *vs* 7% COBRA patients used etanercept.

Fig. 2 Main clinical outcomes during the 4-year follow-up period of the COBRA-light extension study (n = 149)



(**A**) Disease activity. (**B**) Physical functioning. (**C**) Radiological outcome. (**D**) Boolean remission.
SHS: Sharp–van der Heijde score.

Fig. 3 Radiographic progression during the 4-year follow-up period of the COBRA-light extension study (n = 149)



SHS: Sharp–van der Heijde score.

TABLE 2 Overview of comorbidities developed during the 4-year follow-up period of the COBRA-light extension study (n = 154)

	COBRA-light (n = 75)	COBRA (n = 79)
Any comorbidity	55 (73)	56 (71)
Any cardiovascular event[a]	7 (9)	6 (8)
Myocardial infarction	1 (1)	2 (3)
Stroke	5 (7)	2 (3)
CVA	0 (0)	0 (0)
TIA	3 (4)	2 (3)
Other[b]	2 (3)	0 (0)
Angina pectoris	0 (0)	0 (0)
Heart failure	0 (0)	0 (0)
Arrhythmia	1 (1)	3 (4)
Peripheral vascular disease	1 (1)	0 (0)
Hypertension[a]	5 (7)	7 (9)
Hypercholesterolaemia[a]	7 (9)	5 (6)
Diabetes mellitus[a]	3 (4)	1 (1)
Any joint surgery[a]	10 (13)	5 (6)
Replacement	5 (6)	1 (1)
Synovectomy	1 (1)	0 (0)
Arthroscopy	1 (1)	1 (1)
Other joint surgery	3 (4)	3 (4)
Any clinical fracture[a]	13 (17)	6 (8)
Hip	2 (3)	0 (0)
Vertebra	3 (4)	0 (0)
Other	10 (13)	6 (8)
Osteoporosis at 4-year DXA[a,c]	4 (6)	1 (1)
Vertebral facture at 4-year spine X-ray[a,d]	8 (13)	8 (11)
Bone necrosis[a]	1 (1)	0 (0)
Any infection[a,e]	30 (40)	31 (39)
Treated with antibiotics	30 (40)	26 (33)
Treated with antibiotics during hospital admission	1 (1)	4 (5)
Treated with antiviral drugs	2 (3)	2 (3)
Tuberculosis	0 (0)	0 (0)
Any gastrointestinal event[a]	3 (4)	1 (1)
Duodenal ulcer	1 (1)	0 (0)
Cholelithiasis	2 (3)	0 (0)
Intestinal perforation (colon)	0 (0)	1 (1)
Glaucoma[a]	1 (1)	0 (0)
Cataract[a]	3 (4)	5 (6)
Cancer[a]	5 (7)	2 (3)
Lung	3 (4)	2 (3)
Basal cell carcinoma	1 (1)	0 (0)
Meningioma	1 (1)	0 (0)
Other disease(s)[a]	19 (25)	20 (25)
Pulmonary embolism and thrombosis	2 (3)	1 (1)
Dementia	0 (0)	2 (3)
Depression	1 (1)	2 (3)
Deceased[a]	3 (4)	2 (3)

Results are reported as frequencies (%). There were no significant differences between the treatment groups after application of the Bonferroni correction for secondary analyses ($P < 0.0008$ is considered significant). [a]Only these main categories were tested for significance. [b]Other = eye infarct and venous occlusion left eye. [c]T score less than −2.5 at spine and/or hip, results based on DXAs of 135 patients (66 COBRA-light and 69 COBRA). [d]Results based on spine X-rays of 134 patients (63 COBRA-light and 71 COBRA), of which 19 baseline and 11 follow-up assessments were (partially) based on chest X-rays or IVA instead of spine X-rays. [e]Any infection treated with at least antibiotics or antiviral drugs. CVA: cerebrovascular accident; DXA: dual-energy X-ray absorptiometry; TIA: transient ischaemic attack.

After the 4-year follow-up period, cumulative and mean weekly MTX dose were significantly higher in initial COBRA-light group, whereas mean daily prednisolone dose was significantly higher in the initial COBRA group, but similar after correction for initial dosing per protocol (Table 3). Use of intramuscular and intra-articular glucocorticoid injections and biologic DMARDs was similar in both groups. With respect to etanercept use, 48% COBRA-light patients *vs* 34%

Table 3 Overview of medication use from baseline until the 4-year visit of the COBRA-light extension study (n = 154)

	COBRA-light (n = 75)	COBRA (n = 79)
Glucocorticoids		
Prednisolone (oral)		
Cumulative dose, mg[a]	2618 (1943–5903)	3158 (2468–6155)
Duration of use, days	324 (239–899)	348 (239–738)
Mean daily dose, mg[a]	8.1 (7.4–8.1)	9.6 (8.0–10.4)*
Injections, n (%)[a]	29 (39)	34 (43)
Intramuscular, n (%)	20 (27)	23 (29)
Intra-articular, n (%)	16 (21)	18 (23)
Synthetic DMARDs		
MTX		
Cumulative dose, mg[a]	3828 (2584–4550)	2525 (1524–3639)*.
Duration of use, weeks	189 (149–230)	188 (143–245)
Mean weekly dose, mg[a]	20.4 (17.0–23.3)	13.7 (9.6–19.6)*
SSZ		
Ever used, n (%)[a]	9 (12)	79 (100)*
Duration of use, days	273 (28–953)	799 (392–1178)
HCQ		
Ever used, n (%)[a]	26 (35)	18 (23)
Duration of use, days	281 (93–912)	151 (42–669)
LEF		
Ever used, n (%)[a]	7 (9)	2 (3)
Duration of use, days	117 (59–356)	184 (43–324)
Biologic DMARDs		
Etanercept		
Ever used, n (%)[a]	39 (52)	38 (48)
Protocolled start during 1-year trial period[b]	36 (48) [¤]	27 (34)
Non-protocolled re-start after 1-year trial period[c]	5 (7)	6 (8)
First use after 1-year protocolled trial period[d]	3 (4)	11 (14)
Duration of use, days	169 (98–464)	186 (87–599)
Other TNF-α inhibitors[e]		
Ever used, n (%)[a]	9 (12)	10 (13)
Total duration of use, days	403 (173–997)	243 (122–628)
Interleukin inhibitors[f]		
Ever used, n (%)[a]	0 (0)	3 (4)
Total duration of use, days	–	301 (241–348)
B- and T-cell inhibitors[g]		
Ever used, n (%)[a]	3 (4)	5 (6)
Duration of use, days	610 (363–723)	562 (396–1018)

Results are reported as median (IQR) unless indicated otherwise. [a]Only these main categories were tested for significance. [b]Protocolled start of etanercept during the 1-year trial period (these numbers are different from the published 52 weeks results by Ter Wee *et al.* because not all patients who started with etanercept in the trial did participate in the extension study). [c]Non-protocolled re-start of etanercept after the 1-year protocolled trial period, at the discretion of the treating physician (after $\geqslant$3 months stop). [d]First use of etanercept after the 1-year protocolled trial period, at the discretion of the treating physician. [e]Other TNF-α inhibitors = infliximab, adalumimab, golimumab and certolizumab pegol, but not etanercept. [f]Interleukin inhibitors = tocilizumab and anakinra; [g]B- and T cell inhibitors = abatacept and rituximab. *Significant difference between the treatment groups after application of the Bonferroni correction for secondary analyses ($P < 0.0008$ is considered significant).

COBRA patients started etanercept per protocol during the 1-year trial period. Of these patients, 7% COBRA-light *vs* 8% COBRA patients stopped etanercept after the 1-year trial period, but re-started etanercept use at some point in time during the 4-year follow-up period (the stop period with etanercept was at least 3 months), at the discretion of their treating physician. Furthermore, 4% COBRA-light *vs* 14% COBRA patients did not use etanercept during the 1-year trial period, but did start etanercept after the first treatment year, at the discretion of their treating physician. Overall, 52% COBRA-light *vs* 48% COBRA patients have used etanercept at some point in time during the 4-year follow-up period of the COBRA-light study, with a median duration of 6 months.

Discussion

This study demonstrates that early RA patients initially treated with COBRA-light or COBRA combination therapy had similar efficacy and safety outcomes over a 4-year follow-up period, with strong and sustained improvements in disease activity and physical functioning and good

suppression of radiological progression. Both groups showed similar patterns of synthetic and biologic DMARD use in the 3 years following the trial period, and overall use of the biologic DMARDs was low: 20% on current treatment at 4 years. As a whole, these results confirm the long-term efficacy of starting with induction therapy with combination therapy including glucocorticoids, followed by a maintenance therapy based on a treat-to-target strategy in early RA patients [31, 32].

Comparisons with results of other trials is highly speculative because of differences in study design and study populations; nevertheless, our data on physical function seem comparable to the 4- and 5-year results of the BeSt trial [12, 13], and slightly better than the 5-year results of the PREMIER trial [16]. The NEO-RACo [10] and CIMESTRA [33] trial reported a lower median HAQ at their 5-year visits compared with our 4-year visit (0 and 0.1 *vs* 0.6, respectively). Furthermore, 42% of the COBRA-light trial patients showed no radiographic progression (change in SHS $\leqslant 0$ from baseline) during the follow-up period, which is lower than the combination therapy group of the PREMIER trial (53%) [16] and the infliximab group of the NEO-RACo trial (64%) [10], but comparable to the NEO-RACo placebo group (43%) [10] and CIMESTRA (47%) [33], and better than the two monotherapy groups of the PREMIER trial (34 and 33%, respectively) [16], although different definitions were used across trials. Moreover, our mean annual progression rate of 0.16 SHS units per year is smaller than the 0.32 and 0.73 U reported for the NEO-RACo treatment groups [10] and 0.90 reported for CIMESTRA [33], and clearly below the progression rates reported for the four treatment groups of the BeSt-trial, which were all >1.1 [13].

A combination of success factors may be attributable to our good results: effective combination therapy [2, 5, 6]; intensive monitoring, especially in the first year of the trial; and the treat-to-target treatment strategy that aimed at minimal disease activity. The NEO-RACo trial [10] reported excellent 5-year follow-up results that might be even better than ours; this difference is probably caused by their intense treatment strategy (three traditional DMARDs, prednisolone and infliximab or placebo), and could be related to the 3-monthy follow-up up to 5 years. However, their slightly different study population of younger patients with shorter disease duration and a lower baseline HAQ gave this trial a different, more favourable, start position too.

Our treatment groups showed a similar safety profile after 4 years. No significant differences were found in commonly reported side effects of prednisolone, such as cardiovascular events, hypertension and DM type 2, despite a higher daily prednisolone dose in the COBRA group. The count of malignancies and deaths was comparable to that of the BeSt [12, 13], PREMIER [15, 16] and CIMESTRA trial [33], whereas no malignancies and only one death were reported in the NEO-RACo trial [9, 10]. Again, comorbidity results are very difficult to compare between studies, because of the strictness of definitions (e.g. with respect to seriousness), the method used to examine comorbidities, the classification/categories and study population characteristics (age, ethnicities, in- and exclusion criteria of original trial).

Strengths of our study include the high percentage of patients with at least partial follow-up—92% of the original trial population participated—and the 4-year follow-up period. In addition, we used a specific long-term analysis method for each of the main outcome measures. Other strengths of this study include a detailed calculation of medication use, and the protocolled examination of all clinical files to detect comorbidities. Nevertheless, detection of signals in medical records were dependent on availability, and the comprehensiveness and accuracy of recording; patient reported outcome dependent on memory, with risk of recall bias, resulting in relative over-reporting in more intensively treated patients.

A limitation of our study is that the initial power calculation was based on the short- rather than the long-term outcome of the COBRA-light trial. Consequently, the power to detect subtle differences in comorbidity patterns is low, especially when correction for multiple comparisons is applied. A longer follow-up period (e.g. 10 or 15 years) is needed to study survival and long-term effects on major comorbidities.

Practical implications of our findings include a free choice for both physicians and patients to either start their treatment with COBRA-light or COBRA therapy; and assuming that barriers towards the use of COBRA therapy continue to exist, COBRA-light is an equally effective and safe therapy to use in early active RA.

In summary, both COBRA-light and COBRA therapy are effective and safe treatment strategies for early RA patients in the short and long term. Our study confirms the importance and beneficial effects of early, treat-to-target combination therapy with traditional DMARDs and glucocorticoids in recent-onset RA patients over a 4-year period.

Acknowledgements

We would like to thank all patients for their participation, as well as all physicians who enrolled patients in this study, and all research nurses who were involved in patient management. In addition, we would like to thank B. Blomjous and E. Kooijmans for entering all data into the COBRA-light therapy database over the past few years, and K. Britsemmer and Dr J. van Nies for scoring all radiographs of this study. Finally, we would like to thank Prof. Dr J. Twisk for his epidemiological and statistical advice.

Funding: This work was supported by an unrestricted grant from Pfizer [grant number: WS905749].

Disclosure statement: I.B. has received speaker fees from Lilly Netherlands, MSD, Amgen and USB. M.N. has received speaker fees and advisory board fees from Janssen, Roche, MSD, Pfizer, Eli Lilly, BMS and Abbvie. M.B. has received consultancy fees from Pfizer, UCB and Teva. W.L. has received speaker's fee from Pfizer, Abbvie and Roche and educational grant from Pfizer. All other authors have declared no conflicts of interest.

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