A randomised trial evaluating anakinra in early active rheumatoid arthritis

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Abstract

Objective

The effectiveness of anakinra (interleukin-1 receptor antagonist) in early rheumatoid arthritis (RA) is unknown. We evaluated the efficacy of anakinra (combined with methotrexate) in a randomised clinical trial of early active RA patients.

Methods

The Combination Anti-Rheumatic Drugs in Early RA-2 (CARDERA-2) trial was a randomised trial of early (duration <1 year) active RA. Patients were randomised to 12 months of: (1) methotrexate or (2) anakinra-methotrexate. Follow-up lasted 2 years. The primary outcome was erosive progression (changes from baseline in modified Larsen scores). Secondary outcomes were changes from baseline in disease activity score on a 28-joint count (DAS28), health assessment questionnaire (HAQ), and quality of life (EQ-5D) scores alongside ACR responder rates.

Results

154 patients received the allocated intervention (from 259 screened). Similar Larsen score progression was seen at 12 and 24 months in patients receiving anakinra-methotrexate (mean changes from baseline of 2.50 and 5.10, respectively) and methotrexate monotherapy (mean changes from baseline of 4.16 and 5.20, respectively). Lower improvements in DAS28 and HAQ scores were seen at all time-points in anakinra-methotrexate treated patients; these were significantly less at 24 months (DAS28 p=0.04; HAQ P=0.02). Significantly lower EQ-5D score increases were seen at 12 months with anakinra-methotrexate (p=0.03). Anakinra-methotrexate was associated with more serious adverse events compared with methotrexate monotherapy (11 vs. 6 patients), although this was not significant (p=0.59).

Conclusion

Anakinra (combined with methotrexate) is not effective in early, active RA. It provided no clinical benefits beyond methotrexate monotherapy.

Key words

rheumatoid arthritis, interleukin 1 receptor antagonist protein, clinical trial

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Received on March 25, 2015; accepted in revised form on September 2, 2015.

Registration: CARDERA-2 was registered at the ISRCTN registry (http://www.isrctn.com) using the identification number ISRCTN15819795.

Funding: CARDERA-2 was funded by Amgen Ltd. I.C. Scott, receives funding from Arthritis Research UK (grant ref. no. 19739), the National Institute for Health Research (NIHR) (Clinical Lectureship).

Competing interests: none declared.

Introduction

Current rheumatoid arthritis (RA) management focuses on early intensive treatment with disease-modifying antirheumatic drugs (DMARDs) escalated to biologics in refractory cases (1). First-line biologics like tumour necrosis factor (TNF)-inhibitors are effective in early and established RA (2). Anakinra, an interleukin-1 receptor antagonist (IL-1ra), is approved for DMARD refractory moderate-severe RA (3). Its efficacy in established RA is less than TNF-inhibitors (4); consequently it is infrequently used in RA management. Its efficacy in early RA is unknown.

Treatments are usually most effective if instituted promptly after RA onset (5). We therefore evaluated the efficacy of anakinra in a randomised clinical trial of early active RA patients. Our primary hypothesis was that in early active RA, anakinra-methotrexate combination therapy is superior to methotrexate monotherapy in reducing erosive progression.

Materials and methods

Trial design

The Combination Anti-Rheumatic Drugs in Early RA-2 (CARDERA-2) trial was an open-label, multicentre, two-armed trial. Patients were randomised equally to methotrexate monotherapy or anakinra-methotrexate combination therapy. Active treatment was given for 12 months; follow-up lasted 24 months.

Centres

Routine rheumatology clinics at 11 English centres.

Inclusion/exclusion criteria

Included patients met the 1987 American College of Rheumatology (ACR) classification criteria, had early (duration <12 months), active disease (three from: ≥3 swollen joints, ≥6 tender joints, ≥45 minutes morning stiffness, erythrocyte sedimentation rate (ESR) ≥28mm/hr), were aged ≥18 years and could give informed consent.

Excluded patients had other inflammatory arthropathies, previous methotrexate treatment, contraindications/intolerance to the trial drugs, other serious medical disorders or were using oral steroids.

Interventions

Open-label methotrexate started at 7.5 mg/week, and increased two weekly by 2.5 mg to 15 mg/week. Further increases to 25 mg/week occurred if clinically needed. Other DMARD monotherapies were started for significant side-effects or inadequate responses.

Open-label anakinra (100 mg/day by subcutaneous injection) was given with methotrexate (as outlined above).

Study treatments were given for 12 months. Subsequent treatment was decided by patients' rheumatologists.

Outcomes

• *Primary outcome*

Erosive progression, captured by changes from baseline in modified Larsen scores, was chosen as the primary outcome due to its prognostic importance (reflecting cumulative disease activity and predicting longer-term disability (6)) and its frequent use as an outcome measure in trials of biologics in RA (7).

• *Secondary outcomes*

Changes from baseline in disease activity score for 28-joint counts (DAS28), health assessment questionnaire (HAQ) and quality of life (EQ-5D) scores alongside ACR-20, 50 and 70 responder rates.

• *Assessments*

Hand and feet x-rays were taken at 0, 12 and 24 months. Other outcomes were additionally assessed at 6 months. Assessors (of all outcome measures) were independent to the supervising clinician. Radiographs were read chronologically by one rheumatologist (DLS) experienced in radiological scoring. All assessors were blinded to treatment.

Adverse events

These were captured, irrespective of their relation to treatment.

Sample size

CARDERA-2 tested the hypothesis that anakinra-methotrexate would reduce the number of patients developing new erosions by 40% over 12 months compared with methotrexate monotherapy. Existing data suggested

71% of patients receiving methotrexate would develop new erosions over 12 months. Showing a 40% reduction with 5% significance and 90% power required 66 patients per group. Allowing for 20% dropouts the sample size was 158 patients.

Randomisation

Patients were randomly allocated to one group. The trial statistician generated the allocation sequence using random number tables. Randomisation (stratified by region) used 6 random treatment assignments in blocks of 4. Randomisation numbers were assigned chronologically at screening visits. Metrologists and the trial co-ordinator were unaware of the allocation sequence. Treatment assignments were in a locked cabinet in the co-ordinating centre pharmacy for emergency access.

Statistical analysis

Intention-to-treat (ITT) analyses evaluated treatment effects on changes from baseline in Larsen scores (primary outcome) and DAS28, HAQ and EQ-5D scores (secondary outcomes) at 12 and 24 months using linear regression. Univariate analyses used relevant outcomes as response variables and treatment as the explanatory variable. Multivariate analyses added demographic variables (gender, age, ethnicity, disease duration) as covariates. Robust standard errors (SE) were used. ACR responder rates were evaluated using logistic regression, accounting for demographic variables. Statistical significance was 5% using a 2-sided *p*-value. As 12-month Larsen scores were only missing in 10 patients (4 methotrexate; 6 anakinra-methotrexate) and DAS28/HAQ/EQ-5D in 5 patients (2 methotrexate; 3 anakinra-methotrexate) missing data were not imputed. Data management and analyses were performed using Stata, version 12.0 (Stata Corp, College Station, TX).

Ethical review

CARDERA-2 was approved by the South East Research Ethics Committee (REC reference number MREC 02/1/089). All participants provided informed consent.

Table I. Baseline patient characteristics by treatment group.

Patient characteristics	Methotrexate Monotherapy (n=75)	Anakinra Methotrexate (n=79)
Mean age in years (SD)	54 (13)	56 (12)
Female, n (%)	54 (72)	54 (68)
Caucasian, n (%)	67 (89)	65 (82)
Mean disease duration, months (SD)	0.14 (0.19)	0.13 (0.15)
Mean Larsen (SD)	7.0 (10.5)	15.3 (18.7)
RF-Positive, n (%)	54 (72)	53 (67.1)
Mean DAS28 (SD)	6.45 (1.22)	6.37 (1.19)
Mean HAQ (SD)	1.58 (0.79)	1.49 (0.71)
Mean EQ-5D (SD)	0.39 (0.34)	0.40 (0.34)

n: number; SD: standard deviation; RF: Rheumatoid Factor; DAS28: Disease Activity Score on a 28-joint count; HAQ: Health Assessment Questionnaire.

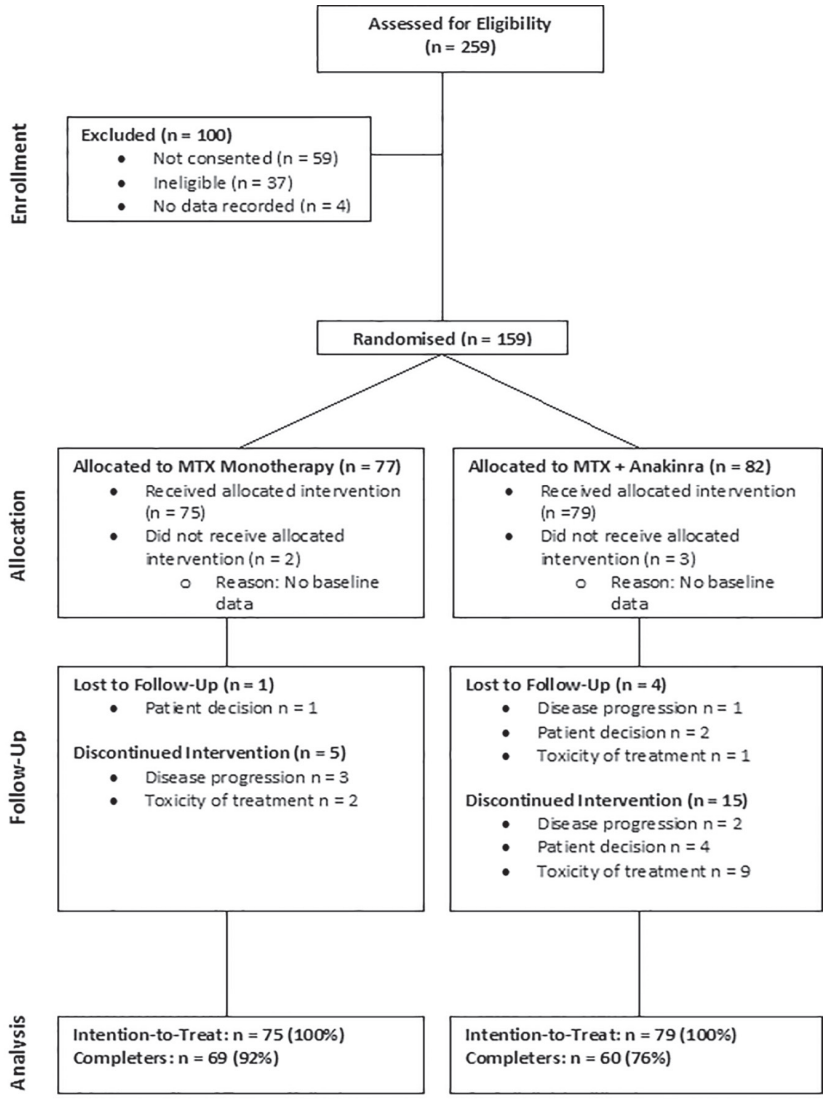

Fig. 1. Consort Flowchart for CARDERA-2.

Results

Participants

259 patients were screened (Fig. 1): 100 were excluded (37 ineligible; 59 declined); 159 were randomised to treatment; 154 received the allocated intervention.

Baseline characteristics

These were similar between groups

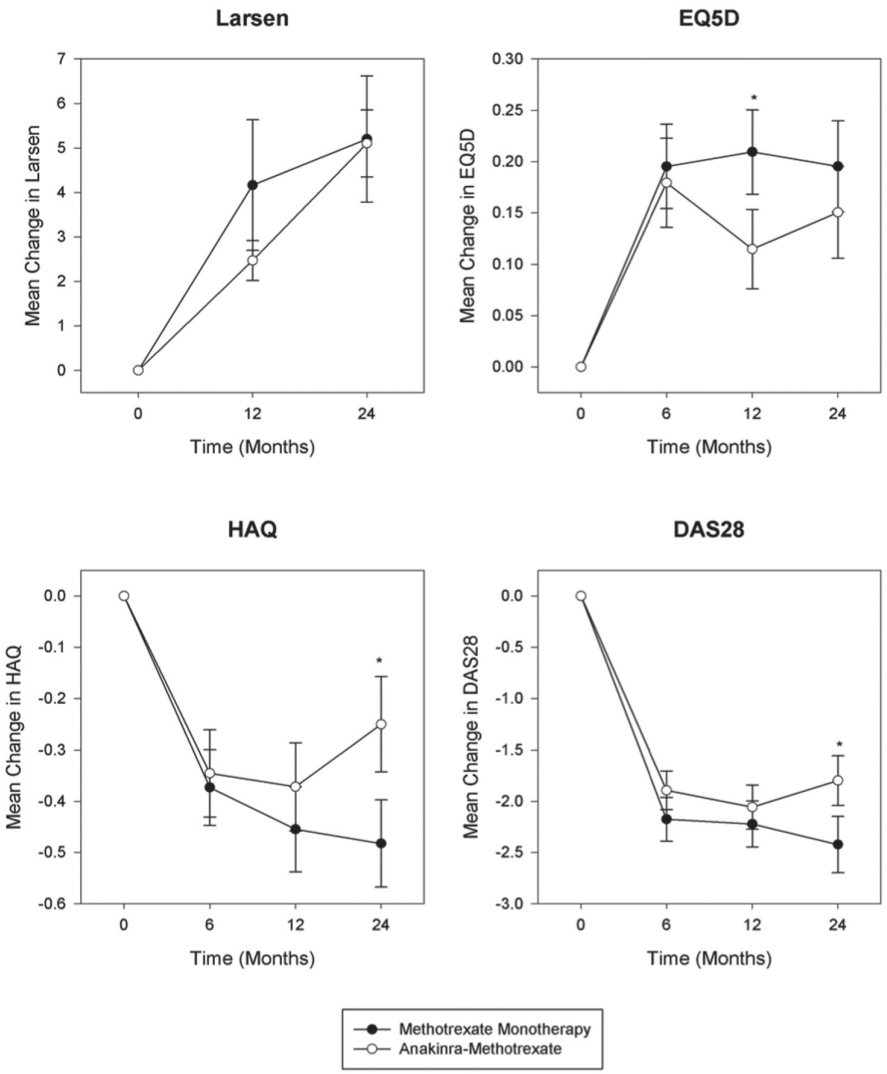

Fig. 2. Treatment effect on Larsen, DAS28, HAQ and EQ-5D scores.
Mean change from baseline with standard error bars shown at each time point for each outcome; *= denotes significant difference between treatment arms at $p<0.05$ (from adjusted linear regression model).

(Table I). Baseline radiological damage was greater in the anakinra-methotrexate group (mean Larsen scores 15.3 *vs*. 7.0).

Patients analysed

Of the 154 patients receiving treatment (Fig. 1), 129 (84%) continued therapy for 12 months (20 discontinued treatment; 5 lost to follow-up). 12 and 24-month data were available for Larsen scores in 144 (94%) and 129 (84%) patients, respectively and for DAS28, HAQ, and EQ-5D scores in 149 (97%) and 129 (84%) patients, respectively.

Primary outcome

Lower Larsen score increases were seen at 12 and 24 months with anakinra-methotrexate (Fig. 2; mean change from baseline of 2.50 and 5.10) compared with methotrexate monotherapy (mean change from baseline of 4.16 and 5.20). These differences between groups were not significant (Table II).

Secondary outcomes

• *DAS28*

Greater DAS28 reductions were seen at 12 and 24 months with methotrexate monotherapy (Fig. 2; mean change from baseline of -2.22 and -2.42) compared with anakinra-methotrexate (mean change from baseline of -2.10 and -1.80). This was significant at 24 months (Table II; adjusted model p=0.04).

• *HAQ*

Greater HAQ score reductions were seen at 12 and 24 months with metho-trexate monotherapy (Fig. 2; mean change from baseline of -0.45 and -0.48) compared with anakinra-methotrexate (mean change from baseline of -0.37 and -0.25). This was significant at 24 months (Table II; adjusted model p=0.02).

• *EQ-5D*

Greater EQ-5D score improvements were seen at 12 and 24 months with methotrexate monotherapy (Fig. 2; mean change from baseline of 0.21 and 0.20) compared with anakinra-methotrexate (mean change from baseline of 0.11 and 0.15). This was significant at 12 months (Table II; adjusted model p=0.03).

• *ACR responder rates*

At 12 months more patients attained an ACR20 and ACR50 response with anakinra-methotrexate compared with methotrexate monotherapy; the opposite was seen for ACR70 responses. None of these differences were significant (Table II).

At 24 months more patients attained ACR20, ACR50 and ACR70 responses with methotrexate monotherapy. A significant difference was seen for ACR20 response rates; the adjusted OR for attaining an ACR20 response with anakinra-methotrexate compared with methotrexate was 0.44 (95% CI 0.21-0.93; p=0.03).

Adverse events

136 adverse events occurred (Table III). More occurred with anakinra-methotrexate than with methotrexate monotherapy (70 *vs*. 66), although this was not significant (Fisher's exact test p=0.99). More serious adverse events occurred with anakinra-methotrexate than with methotrexate monotherapy (11 *vs*. 6; p=0.59).

Withdrawals

Significantly more withdrawals were seen (chi-square test p=0.007) with anakinra-methotrexate than with methotrexate monotherapy (Fig. 1; 19 *vs*. 6 patients). This difference was mainly

Table II. Regression models showing the effect of anakinra on disease outcomes.

Outcome	Model 1 (Unadjusted)				Model 2 (Adjusted)*			
	12 months		24 months		12 months		24 months	
	Linear Regression							
	β (95% CI)	*p*-value	β (95% CI)	*p*-value	β (95% CI)	*p*-value	β (95% CI)	*p*-value
Larsen	-1.70 (-4.73, 1.34)	0.27	-0.10 (-3.27, 3.07)	0.95	-1.88 (-5.33, 1.58)	0.29	-0.05 (-3.08, 2.99)	0.98
HAQ	0.08 (-0.15, 0.32)	0.49	0.23 (-0.02, 0.48)	0.07	0.12 (-0.11, 0.36)	0.29	0.28 (0.04, 0.52)	0.02
EQ-5D	-0.09 (-0.21, 0.02)	0.09	-0.04 (-0.17, 0.08)	0.48	-0.12 (-0.23, -0.01)	0.03	-0.07 (-0.19, 0.05)	0.25
DAS28	0.16 (-0.45, 0.78)	0.60	0.62 (-0.10, 1.35)	0.09	0.29 (-0.31, 0.89)	0.34	0.73 (0.03, 1.44)	0.04
	Logistic Regression							
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
ACR20	1.28 (0.67, 2.45)	0.46	0.50 (0.25, 1.02)	0.06	1.23 (0.63, 2.43)	0.55	0.44 (0.21, 0.93)	0.03
ACR50	1.13 (0.54, 2.33)	0.75	0.63 (0.28, 1.42)	0.26	1.07 (0.60, 2.27)	0.86	0.55 (0.22, 1.33)	0.18
ACR70	0.72 (0.29, 1.77)	0.48	0.68 (0.21, 2.27)	0.53	0.69 (0.26, 1.82)	0.45	0.65 (0.18, 2.38)	0.51

*Model 2 includes following covariates: age, gender, ethnicity, disease duration; methotrexate monotherapy used as reference group in linear and logistic regression models.

Table III. Adverse events.

Body System	Methotrexate Monotherapy (n=75)		Anakinra-Methotrexate (n=79)	
	All	Serious	All	Serious
Total	66	6	70	11
Cardiovascular	4	0	1	1 (chest pain)
Gastrointestinal	12	2 (1 gastric ulcer, 1 jaundice)	12	3 (1 gall stones, 2 gastric ulcers)
Ear, Nose, Throat	3	0	7	0
Endocrine/Metabolic	1	0	0	0
Genitourinary	1	0	2	0
Haematological	1	0	5	0
Mental	1	0	1	0
Musculoskeletal	15	2 (2 RA flares)	10	1 (hip fracture)
Neurological	7	0	3	1 (stroke)
Ophthalmological	2	0	1	0
Respiratory	13	2 (2 chest infections)	9	3 (1 asthma, 1 pulmonary emboli, 1 pharyngitis)
Dermatological	6	0	19	2

due to toxicity; 2 and 10 patients withdrew from receiving methotrexate monotherapy and anakinra-methotrexate, respectively due to toxicity.

Discussion

CARDERA-2 shows anakinra combined with methotrexate is not effective in early, active RA. It had no benefits beyond methotrexate monotherapy on erosive progression, disability, disease activity or quality of life. After 24 months, patients who had received anakinra-methotrexate had significantly more active disease and disability than patients receiving methotrexate monotherapy.

The inefficacy of IL-1 inhibition in early RA was disappointing. There is strong evidence that IL-1 is a pivotal cytokine in established RA. In such patients the IL-1β isoform is abundant in plasma (8) and synovial fluid (9) (compared with controls) and serum levels correlate with disease severity (8). IL-1 inhibition significantly reduces joint destruction in mouse models (10) and established RA patients (11); it also effectively reduces disease activity in established RA (4). Our findings suggest biologic pathways governing RA activity may differ between early and established disease. The apparent worsening of clinical outcomes after 24 months in patients receiving anakinra was unexpected. As it is unlikely that anakinra will be used in this setting, the underlying reasons for this worsening are of no practical clinical consequence and remain unexplained.

Although ineffective in our trial of early RA, there is evidence anakinra is effective in other IL-1 mediated disorders. These diseases include Bechet's disease (12), auto-inflammatory disorders like tumour necrosis factor-receptor associated periodic syndrome (TRAPS) and mevalonate kinase deficiency (MKD) (13), and gout.

Our study has several strengths. The randomisation process was rigorous, outcomes were evaluated by assessors blinded to patient treatment, multiple centres were involved and an ITT analysis was used. It has several limitations. Patients were un-blinded because injection site reactions with anakinra make full blinding impractical. Some data were missing, albeit at low levels. Anakinra dosage was restricted to licensed dosing; it may have been more effective if dose escalated, with such an approach being

evaluated in Behçet's disease (14). Significant differences in baseline Larsen scores were seen between treatment arms; these were, however, small (4% of maximal score) and repeating the linear regression model for changes in Larsen scores, including baseline Larsen scores as a modelling covariate, did not alter our findings. As with other contemporary early RA cohorts, erosive progression was low (only 26% had a minimal clinically important annual increase in Larsen scores of ≥2.3 units over the first 12 months (15)), reducing the power to detect treatment effects on erosive progression.

In conclusion, anakinra is ineffective in early active RA. Our findings support the National Institute for Health and Care Excellence's (NICE) decision to not recommend its use in RA management (1).

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