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Trajectory of intensive treat-to-target disease modifying drug regimen in an observational study of an early rheumatoid arthritis cohort

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ABSTRACT

Objectives: Studies of early rheumatoid arthritis (RA) cohorts have analysed treatment response and prognostic factors at fixed time points. However, in treat-to-target protocols, therapeutic decision-making is dynamic, and responsive to disease activity over time. To determine when a minimal residual disease response target should be expected, our primary objective was to identify the time-dependent therapeutic response to combination disease modifying anti-rheumatic drugs (DMARDs) for 12 months. Our secondary objective determined factors affecting this response trajectory. Design: Observational cohort. Setting: Treat-to-target early RA clinic in Australian tertiary referral hospital. Participants: We enrolled consecutive patients attending an early arthritis clinic with symptom duration less than 12 months, who were diagnosed with RA for the first time between 2004 and 2008. One hundred and one met these eligibility criteria and data were available at baseline through 12 months. Interventions: Intensive DMARDs according to a treat-to-target protocol. Primary and secondary outcome measures: We measured disease activity scores (DAS) at each visit, then analysed therapeutic response and associated factors in a time-dependent fashion over 12 months. Results: The median DAS4vESR of 4.46 at baseline decreased 12 weeks later by 24%, while the proportion with DAS4v $\leq$2.6 increased ($p < 0.01$). DAS4v continued to decrease over 52 weeks. DAS4v reduction of at least -0.45 at 4 weeks was predictive of DAS4v at 28 and 52 weeks. Female gender and an interaction between baseline weight and CRP negatively impacted DAS4v reduction over 4 and 52 weeks. Time-varying effects of blood pressure, neutrophils, ESR and CRP also significantly influenced DAS4v over 52 weeks. Conclusions: Time-dependent data suggest that the largest reduction of DAS4v to combination DMARDs occurs in the first month of therapy, and

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this predicts subsequent response. The data suggest the need for a controlled trial of treatment change within 1 month, in combination DMARD non-responding patients.

Article Summary

Article focus

- Best-practice early RA treatment aims to achieve a target response. In clinic settings of many countries, first-line therapies are DMARDs, including combination DMARDs
- We followed an observational cohort for 12 months in a treat-to-target early RA clinic to identify the time-dependent therapeutic response to combination DMARDs for 12 months and factors affecting this response trajectory

Key messages

- After initiation of combination DMARDs, the largest reduction in disease activity score occurred in the first month, and its magnitude predicted subsequent response
- Disease activity score over 12 months was influenced by female gender and current smoking, and an interactive effect of weight and either CRP or ESR
- The data suggest a need for a controlled trial of treatment change within 1 month, in combination DMARD non-responding patients.

Strengths and Limitations

Strengths

- Monthly observation allowed precise determination of time-dependent therapeutic response and demonstrated an unexpectedly rapid response to combination DMARDs

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- Standardised combination DMARD treat-to-target protocol
- Real-life clinical setting with dynamic therapeutic decision making

Limitations

- Observational cohort study limits conclusions that can be drawn regarding causality, without further testing in a randomised controlled trial
- Relatively small cohort derived from a single centre, with treatment regimen determined within Australian prescribing context, limits generalisability.
- Number of participants limited by lack of baseline or 12 month follow-up data and may have introduced selection bias
- Due to incomplete radiographic data, factors associated with radiographic outcomes could not be determined

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BACKGROUND:

Intervention with early combination disease modifying anti-rheumatic drug (DMARD) therapy favourably influences progression of rheumatoid arthritis (RA) independent of treatment in later years, suggesting that there is a "window of opportunity" in which the disease process can be altered [1, 2]. Moreover, a good response at 6 months to tight disease control using methotrexate predicted outcome after 5 years of treatment in participants in the CAMERA study [3]. The severity of disease varies in RA patients. In those with aggressive disease, damage to articular structures occurs early in the disease process: erosions were detected in 12.8% of patients after a median of 8 weeks in one study [4]. Thus, early evidence and determinants of treatment response to a given regimen are critical, in order to channel patients at greatest risk of poor outcome to more intensive induction regimens or more expensive biologic therapies within that window.

Studies of prognostic factors by statistical modelling have analysed disease progression outcomes including erosions, disease activity score (DAS28) and disability index as measured by Health Assessment Questionnaire (HAQ) at fixed time points – usually 6 or 12 months, with the earliest being 3 months – to determine treatment response and associated factors influencing this. Factors associated with poor radiological outcome include smoking, rheumatoid factor (RF) positivity, the presence of anti-citrullinated peptide autoantibodies (ACPA), HLA-DR genotype, low socioeconomic status and bone oedema on magnetic resonance imaging [5-9]. On the other hand, poor outcome measured by HAQ was associated with high baseline disease activity or HAQ, including RF, DAS28 score, tender and swollen joint counts, ESR and CRP [10, 11]. However, in treat-to-target protocols, such as was used in the TICORA trial and which occur in real-

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life clinic settings, decision-making about dose and drugs is a dynamic process, responsive to the patient's disease activity over time [12]. In many early arthritis protocols, including the current study, patients are treated and monitored intensively during the first 3-6 months, followed by a reduced visit frequency. Longitudinal analysis of all available data, while modelling the trajectories and drawing inferences on the significance of various risk factors, provides higher power and better insight into the dynamic process.

AIMS:

In the current study, our primary objective was to identify the time-dependent therapeutic response in an observational study of combination DMARDs for 12 months in order to determine when a minimal residual disease response target should be expected. Our secondary objective was to determine factors affecting this response trajectory. We therefore gathered disease activity data at each treatment visit then analyzed the disease activity response in a time-dependent fashion. We then determined factors which influenced this time-dependent response to an intensive DMARD regimen.

METHODS:

We enrolled consecutive patients attending a tertiary referral early arthritis clinic with symptom duration less than 12 months, who were diagnosed with RA for the first time between 2004 and 2008. Patients were selected for inclusion in the current study if data were available at baseline through 12 months. One hundred and one patients met these eligibility criteria; however 107 patients who met all other criteria were excluded as

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data were unavailable at either baseline or 12 months. All study participants met the American College of Rheumatology 1987 revised criteria for the classification of RA [13]. Ethical approval for the study was obtained from the Princess Alexandra Hospital Research Ethics Committee.

Referrals from local general practitioners were triaged within 1 week, and patients were generally diagnosed within the next 4 weeks. Since full clinical and laboratory evaluation was available at the first visit to the early arthritis clinic, patients received combination methotrexate (MTX), sulfasalazine (SSZ) and hydroxychloroquine (HCQ) [14], unless contraindicated, immediately after diagnosis and confirmation of active disease by the treating rheumatologist. Treatment was intensified according to a response-driven step-up algorithm, as previously described [15], with remission as the target [16, 17]. Briefly, criteria for dose escalation were either >2 swollen joints and abnormal ESR or CRP, or at least 2 of the following 4 criteria: morning stiffness >30mins, pain or fatigue visual analogue scale (VAS) >30mm, or >2 tender joints. The following medications were prescribed at baseline: MTX 10mg/week, folic acid 5mg/week, SSZ 500mg daily increasing by 500mg at weekly intervals to 1000mg twice daily, HCQ 200mg daily for one week then 400mg daily thereafter. Patients were seen at 4-weekly intervals and the MTX dose was escalated according to treatment response at a conservative rate by 5mg at each visit to a maximum of 25mg weekly. If disease remained active on this combination, SSZ was stopped, MTX reduced to 10mg weekly and leflunomide started at a dose of 20mg daily. MTX dose was titrated back to 25mg weekly, and if this combination failed and the Australian Pharmaceutical Benefit Scheme criteria were met, the patient commenced biologic therapy. Based on these

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criteria, 10% of patients in this setting commenced biologics per year. In general, the use of NSAIDs and oral corticosteroids was minimized, but intra-articular or oral steroids could be administered at the discretion of the treating physician. Large joints were injected with 40-80mg DepoMedrol and smaller joints with 1ml (5.7mg) Celestone. Oral and intra-articular dosage of corticosteroids was recorded monthly.

Response to therapy was measured as follows: the 4 variable DAS28ESR (hereafter referred to as DAS4v) was used as an index of inflammatory control [18], and the mHAQ as an index of disability [19]. Each index was calculated at each visit: baseline, and weeks 4, 8, 12, 16, 22, 28, 36, 44 and 52.

Demographic details were ascertained by questionnaire and included: age at presentation, gender, smoking status and mHAQ. Patients completed VAS for pain, fatigue and their global assessment of disease. The 28 tender and swollen joint counts, height and weight were recorded by the clinical research nurse. Blood was collected at baseline for the analysis of ESR, CRP, LFT, FBC, RF and ACPA.

Basic statistics were presented by number (%) or mean (SD) or median (IQR), as appropriate. Five imputations for missing data on clinical, biochemical and score data were performed using Bayesian Markov chain Monte Carlo multiple-imputation technique. The patterns of missingness were random for all the study parameters. The consistency in the distributions of the 5 imputed data was checked for all study parameters. Given the skewed DAS and mHAQ scores, the medians and their 95% confidence intervals (CI) are presented. The changes in these scores over the study

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period are presented by median and 95% CI, and the significance levels (p values) are based on the appropriate non-parametric test.

Generalized multivariate linear regression models with Gamma distribution and Identity link were used to identify the statistically significant ($p \leq 0.10$) risk factors and their possible interaction effects on disease activity scores at week 4 of the study. The possible consistency in the effect sizes of the statistically significant risk factors (at week 4) were also assessed on the disease activity scores at week 12 of the study. Combining the 10 longitudinal measurements obtained over one year of the study, the time varying effects of individual risk factors on the disease activity scores were explored using generalized estimating equation (GEE) regression approach with Gamma distribution and identity link function under the assumption of 'unstructured' correlation structure.

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RESULTS:

Time-dependent therapeutic response to combination DMARDs for 12 months

One hundred and one patients were included in the study. The baseline characteristics of the patients are shown in Table 1. All except 4 patients took at least two and up to three of the following DMARDs in combination during the 12 months study: Methotrexate, Sulfasalazine, Hydroxychloroquine and Leflunomide. These 4 patients took Methotrexate monotherapy.

The median disease activity score at baseline was 4.46 for DAS4v (Table 2). Four of the 12 patients with baseline DAS ≤2.6 were taking steroids prior to referral. There was, a highly significant ($p<0.001$) DAS reduction of 24% at 28 weeks (Table 2). We also observed a significant increase in the proportion of patients with minimal residual, (DAS28 scores ≤2.6) and low disease (DAS28 scores ≤3.2) over the treatment period ($p<0.01$) (Table 2). Consistent with this, the patients' pain scores improved highly significantly by 31% and 56% at the end of 6-month and one-year of treatment respectively. The improvement in mHAQ from baseline to 6 months, but not between 6 and 12 months of treatment, was significant. The average annual change was 0.30 units (Table 2).

Analysis of the change in DAS4v over time showed a progressive reduction over 52 weeks, with the steepest drop between baseline and 4 weeks (Figure 1). The median (95% CI) of changes in DAS4v scores at 4, 28 and 52 weeks were -0.45 (-0.84, -0.07), -0.86 (-1.30, -0.41), and -1.35 (-1.67, -1.03) respectively ($p<0.01$ at week 52). The changing patterns of the distribution of DAS4v scores over time are evident from the

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density plots in Figure 2. Although a significant shift in the distribution of DAS4v at 4 weeks from baseline is evident from the density plot, the distributions overlap at 4, 28 and 52 weeks.

Analysis of the individual components of the DAS scores over this period demonstrated that patient global score, swollen and tender joint counts all fell most steeply between baseline and 4 weeks (Figure 2). While this was not the case for the fall in either ESR or CRP, similar steep falls in fatigue score, morning stiffness and physician global scores occurred between baseline and 4 weeks. Thus most measures of disease activity fell most rapidly in the first 4 weeks after DMARD initiation. In contrast, ESR fell for 3 months before reaching a plateau, while CRP fell progressively for 6 months.

Factors affecting the response trajectory in early RA patients treated with combination DMARDs

To determine whether the fall in DAS4v at 4 weeks predicted the DAS score at 28 and 52 weeks, we first calculated that the median level of change in DAS4v score at 4 weeks was -0.45. This was clinically discriminatory: at 4 weeks, 52% had no change or an increase in DAS4v while 48% improved from baseline DAS4v. The number and proportion of patients receiving steroids is indicated in Table 3. While baseline steroids impacted the likelihood of improvement at 4 weeks, this was not statistically significant (69% of patients receiving steroids improved and 53% not receiving steroids improved; odds ratio for improvement with steroids 1.95, p=0.12). Patients with reduction in DAS4v score at 4 weeks of at least -0.45 were three times more likely [OR (95% CI): 3.10 (1.2, 8.0)] at 28 weeks and 17 times more likely [OR (95% CI): 17.14 (4.52,

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64.94)] at 52 weeks to maintain the same or reduced DAS4v score as achieved after 4 weeks of treatment. Univariate modelling of factors affecting outcome showed that female sex, smoking status and increasing ALT at baseline negatively affected DAS4v at 4 weeks, but these effects became less significant by 12 weeks (Table 4). An interaction between baseline weight and CRP negatively affected DAS at both week 4 and 12. Patients taking steroid did not have a significantly different disease score, and anti-CCP and RF titre did not impact 4 week DAS.

Combining baseline characteristics and the longitudinal measurements obtained over one year, we explored the time varying effects of individual risk factors on DAS4v in a univariate model. DAS4v over 52 weeks was again influenced by female gender and current smoking, and an interactive effect of weight and either CRP or ESR. Time varying effects of systolic and diastolic blood pressure, neutrophil counts, ESR and CRP also significantly influenced DAS4v observed over 52 weeks (Table 4). Over the course of the study, DAS4v was increased by 0.66 in those patients taking steroids ($p < 0.01$). These data are in keeping with the use of steroid in this study at the clinician's discretion, to provide additional control for disease activity that was not controlled by the DMARD protocol.

We found that the relationship between mHAQ and DAS4v for the cohort was significantly correlated at baseline, 4 weeks, 28 weeks and 52 weeks ($p<0.001$), with this correlation becoming progressively tighter over time as DAS and mHAQ fell. Thus, functional outcome after 1 year of early RA treatment is highly dependent on achievement of low disease activity.

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DISCUSSION:

Our study describes the response of a group of patients with early RA to intensive conventional DMARD therapy in a time-dependent fashion over the first year. Baseline characteristics were in line with previous cohorts of patients with early RA. However, our baseline DAS scores were relatively low, reflecting our rapid triage and clinical and laboratory assessment of early arthritis referrals. A key finding from the time-dependent analysis of response, is that the majority of disease activity measures fall most rapidly in the first 4 weeks after commencing intensive DMARD treatment. There was a subsequent slow and progressive reduction in DAS until week 52. Moreover, the fall in DAS4v at 4 weeks predicted the DAS score at 28 and 52 weeks. This observation suggests that for patients who fail to respond within 4 weeks to combination DMARD treatment, few gains are made by continuing to apply the same DMARD treat-to-target algorithm for 6-12 months. On the other hand, continued effort in applying a treat-to-target combination DMARD algorithm is likely to be effective over the ensuing months in patients who make a moderate response by week 4. Our data suggest that combination DMARDs act unexpectedly rapidly, as patients' use of steroids did not influence the reduction in DAS. In support of this conclusion regarding steroids, in a study of 61 patients with early RA treated according to a similar response-driven step-up combination DMARD algorithm, Proudman *et al* obtained an almost identical 6 month remission rate (DAS28<2.6 in 29%), despite infrequent use of corticosteroids [17].

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The current study has a number of limitations. Firstly, our interpretation that the magnitude of the fall in DAS4v after 1 month predicts 1 year outcome is limited by the observational study design. However, the question of whether outcome could be improved in patients with a minimal treatment response within 1 month could be tested in a randomised controlled trial comparing switch to biologic therapy with continued combination DMARDs. Secondly, this is a relatively small cohort derived from a single centre, with the treatment regimen determined within the Australian prescribing context. The number of participants was limited by lack of baseline or 12 month follow-up data and this may have introduced selection bias towards a more compliant group. While these factors may limit generalisability to other prescribing environments or clinical settings, the strengths of this study are that monthly observations allowed precise determination of time-dependent response and were able to demonstrate an unexpectedly rapid response to combination DMARDs. Furthermore, patients received a standardised combination DMARD treat-to-target protocol, reducing the confounding effect of treatment decisions based on individual clinician preference.

Finally the exploratory nature of the study in a relatively small sample could introduce false positive associations. By regression analysis, we identified female gender, current smoking, ALT and an interaction between weight and CRP as significant determinants of disease activity over 4 and 52 weeks. Females and current smokers were found in several studies, including those of early RA, to achieve lower reductions in disease activity or remission than men [20, 21]. The interaction between weight and inflammation in RA is intriguing and has been noted previously in insulin resistant states [22]. In patients with active RA, those with high BMI responded less well to

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infliximab [23]. We also identified significant time-varying effects of blood pressure, gender, age, weight and inflammatory markers on disease activity. The interaction between disease activity and cardiovascular risk is well documented in RA, including early RA, and traditional cardiovascular risk factors may also impact the activity of inflammatory disease over time [15, 24-26]. However, it is unknown whether control of cardiovascular risk factors can in turn impact inflammatory disease control.

In this study we were limited to analysis of disease and functional score, as radiographic data were not sufficiently complete to allow measurement of structural damage. However, this issue has been addressed by others, where biomarkers such as ACPA antibodies, RF, CRP and cartilage oligomeric matrix protein can add power to predictive models of bone erosion in early RA [27]. In contrast, we found no impact of ACPA or RF on DAS. Our data confirm a strong relationship between disease activity and functional score that appears to strengthen over time, a finding that is supported by data from the BeST cohort [16]. We would anticipate that functional disability would be minimized by early treatment with combination DMARDs as shown previously [28, 29].

Since they are traditionally thought to be slow acting, previous studies of DMARD monotherapy in early RA have not analyzed time-dependent data from 4 weeks. Although it remains possible that a similar response might be observed in some patients starting DMARD monotherapy, we suggest this rapid response may be a unique feature of intensive combination DMARD initiation in early RA. The risks and benefits of intensive DMARD therapy (combinations allowing switching to achieve tight control)

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versus monotherapy in early RA deserve further study, considering overall inconclusive evidence to support combination DMARD therapy in RA [30]. The need to identify patients with more aggressive disease prompted one group to undertake a trial of a stratified treatment plan based on the likelihood of persistent arthritis, with the aim of minimizing over- and under-treatment in early RA [31]. Our data suggest that very early response to an intensive DMARD strategy that minimizes under-treatment predicts response for the first year.

Data from the ERAN study show that patients with moderate disease activity at 1 year are unlikely to achieve better control of their disease if the same protocol is continued, and a good response at 6 months in the CAMERA study predicted outcome at 5 years [3, 32]. Our data, collected in a cohort of early RA patients with relatively low baseline DAS, likely reflect the trajectory of patients meeting criteria for RA early in disease, and which would be captured in organized clinical settings using the recently-published new classification criteria [33].

CONCLUSIONS :

With the availability of increasing numbers of treatment options, application of strategies that identify early non-responders to intensive DMARD combinations, has clear implications for treatment stratification within the window of opportunity. Our time-dependent data suggest the need for a controlled trial of early treatment change in patients who fail to respond to combination DMARDs in the first month of therapy. Female gender, smoking, over-weight and abnormal LFT increase the risk of early poor response.

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DATA SHARING, COMPETING INTERESTS AND FUNDING

Technical appendix, statistical code, and dataset available from the corresponding author at Dryad repository, who will provide a permanent, citable and open access home for the dataset. The authors declare no competing interests in relation to this article.

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CONTRIBUTORSHIP

DW, SP, RT: Conception and design

DW, HP, ED: acquisition of data, analysis and interpretation of data

DW, SP, RT: Drafting the article or revising it critically for important intellectual content, and final approval before submission.

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TABLES:

Table 1. Baseline characteristics of the patients

Baseline variable	Value
Female*	60 (59.4%)
Age†, years	54 (12)
Smoking	
Current Smokers	26 (25.7%)
Ex-Smokers	29 (28.7%)
Weight†, Kg	77.10 (19.68)
SBP†, mm Hg	127 (15)
DBP†, mm Hg	73 (10)
RF*	89 (88.1%)
ACPA*	51 (50.5%)
ESR$, mm/hour	25 (12, 46)
CRP$, mg/liter	9.7 (19, 39)
Lymphocytes†, x 10^9/L	1.94 (0.67)
Neutrophils†, x 10^9/L	5.12 (2.50)
LFT (AST) $, U/L	20.50 (16.50, 24.00)
LFT (ALT) $, U/L	19 (14, 27)
eGFR$, mL/min	89 (74, 90)
Glucose$, mmol/L	5.2 (4.9, 5.75)

* Values are n (%); † values are the median (SD); $ values are the median (IQR). SD = standard deviation; IQR = interquartile range; RF = Rheumatoid Factor; SBP = systolic blood pressure; DBP = diastolic blood pressure; ACPA = anti-citrullinated peptide

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antibody; ESR = erythrocyte sedimentation ratio; CRP = C reactive protein; LFT = liver function test; AST = aspartate aminotransferase; ALT = alanine aminotransferase; eGFR = estimated glomerular filtration rate.

Table 2. Change in median pain VAS scores, DAS and HAQ scores (95% CI) over 1 year

	Baseline	6 month	1 year	Change at 6 months	p	Change at 1 year	p
Pain Score	55 (48, 62)	37.9 (31.7, 44.1)	24.2 (17.7, 30.6)	-21.9 (-30.8, -13)	<0.001	-27.4 (-35.6, -19.1)	<0.001
DAS4v	4.5 (4.1, 4.8)	3.4 (3.1, 3.7)	3.2 (2.9, 3.4)	-1.3 (-1.8, -0.8)	<0.001	-1.5 (-2, -1.1)	<0.001
mHAQ	0.6 (0.5, 0.8)	0.44(0.3, 0.6)	0.3 (0.2, 0.4)	-0.3 (-0.5, -0.1)	0.003	-0.3 (-0.4, -0.2)	<0.001
Proportion of patients with:							
DAS ≤ 2.6	12 (14.8%)	25 (25%)	29 (29%)				
DAS ≤ 3.2	18 (22%)	48 (48%)	52 (52%)				

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Table 3. Frequency of steroid use over the study

Treated with:	Study duration (weeks)					
	0 (0)	**4**	**8**	**12**	**16**	**24**
Oral Steroid n (%)	16 (15.8)	17 (16.8)	14 (13.9)	11 (10.9)	1 (1)	1 (1)
IA steroid	21 (20.7)	2 (2)	4 ()	2 (2)	0	0
Any steroid	37 (36.7)	19 (18.8)	18 (17.8)	13 (12.9)	1 (1)	1 (1)
Oral and IA steroid	3 (3)	1 (1)	2 (2)	0	0	0

IA intra-articular

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Table 4. Variables influencing DAS scores at 4 and 12 weeks of study – Univariate regression

	DAS4v Week 4		DAS4v Week 12	
	ß	p	ß	p
Female	0.68	0.009	0.46	0.059
Smoking				
Ex-smokers vs non-smokers	-0.55	0.026	-0.17	0.53
Current smokers vs non-smokers	-0.80	0.003	-0.42	0.10
LFT (ALT)	0.03	0.01	0.04	0.63
Weight*CRP	0.002	0.029	0.002	0.02
Oral or IA Steroid	0.11	0.67	0.01	0.98
Anti-CCP > 6	0.0004	0.99	0.67	0.08

Values are regression coefficient (ß) and p-value. Regression co-efficient at each time point for RF = 0. CRP = C reactive protein; LFT = liver function test; ALT = alanine aminotransferase.

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Table 5. Effects of time-varying risk factors individually on DAS28 scores over 1 year of study – Univariate regression

	DAS4v		
	ß	95% CI	p
Female	0.45	0.09, 0.81	0.014
Age	0.001	-0.13, 0.02	0.82
Smoking:			
Ex-smokers vs non-smokers	-0.27	-70, 0.16	0.22
Current smokers vs non-smokers	-0.48	-0.91, -0.06	0.026
SBP	0.10	0.08, 0.20	<0.001
DBP	0.10	0.04, 0.20	0.004
Lymphocyte	0.04	-0.09, 0.17	0.55
Neutrophil	0.16	0.10, 0.22	<0.001
ESR	0.03	0.03, 0.04	<0.001
CRP	0.02	0.01, 0.02	<0.001
LFT-AST	-0.004	-0.01, 0.003	0.25
LFT-ALT	-0.003	-0.009, 0.004	0.44
Weight*CRP	0.002	0.001, 0.003	<0.001
Weight*ESR	0.004	0.003, 0.005	<0.001
Oral or IA steroid	0.66	0.34, 0.99	P<0.01
Anti-CCP > 6	0.001	-0.001, 0.002	0.36

Regression co-efficient at each time point for RF = 0.

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FIGURES :

Figure 1. Distribution of DAS4v over the study period. A: The median and 95% CI are plotted for each visit over the 52 week study period. **B:** Changes in DAS4v over 4, 28 and 52 weeks are indicated. **C:** The changing distribution in DAS4v in the sample is plotted at baseline, 4, 28 and 52 weeks.

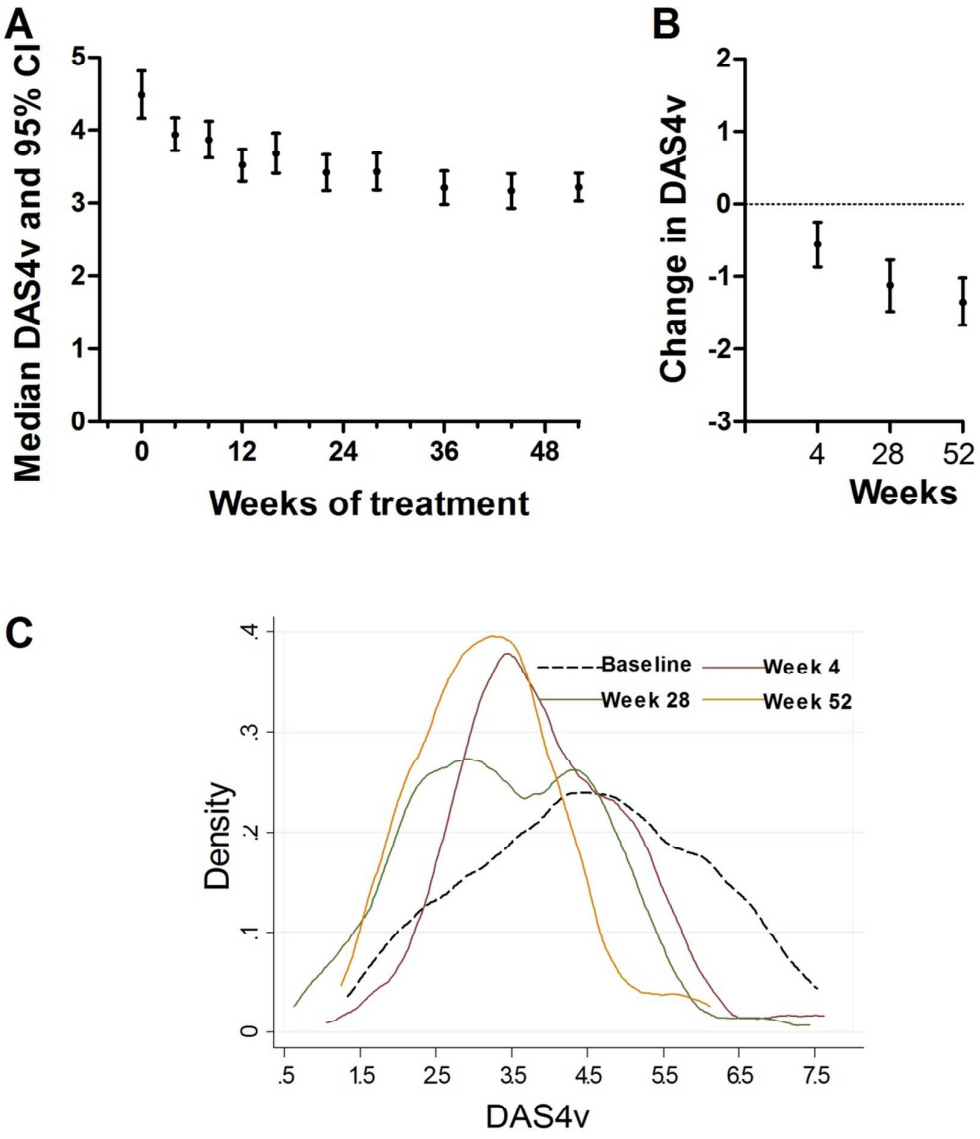
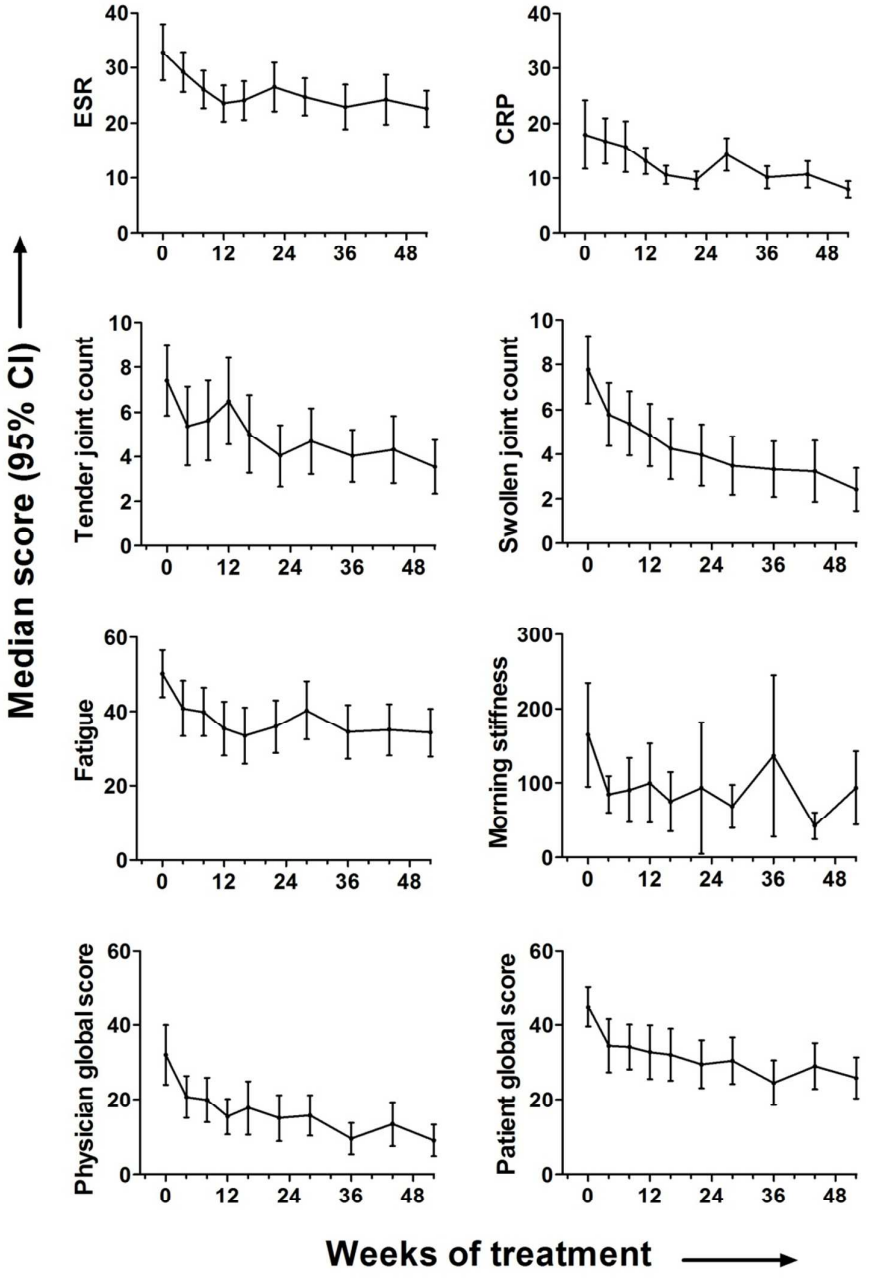


Figure 2. Variation in the disease activity parameters over the study period. The median and 95% CI are plotted for each visit over the 52 week study period for ESR, CRP, tender joint count, swollen joint count, fatigue, morning stiffness, patient global and physician global scores.



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	x
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	x
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	x
Objectives	3	State specific objectives, including any prespecified hypotheses	x
Methods			
Study design	4	Present key elements of study design early in the paper	x
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	x
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	x
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	x
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	x
Bias	9	Describe any efforts to address potential sources of bias	x
Study size	10	Explain how the study size was arrived at	x
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	x
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	x
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	x
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	x
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	x
		(b) Indicate number of participants with missing data for each variable of interest	x
		(c) Summarise follow-up time (eg, average and total amount)	x
Outcome data	15*	Report numbers of outcome events or summary measures over time	x
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	x

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		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	x
Discussion			
Key results	18	Summarise key results with reference to study objectives	x
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	x
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	x
Generalisability	21	Discuss the generalisability (external validity) of the study results	x
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	x

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Trajectory of intensive treat-to-target disease modifying drug regimen in an observational study of an early rheumatoid arthritis cohort

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Trajectory of intensive treat-to-target disease modifying drug regimen in an observational study of an early rheumatoid arthritis cohort

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Short title: Trajectory of intensive treat-to-target DMARDs in RA

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ABSTRACT

Objectives: Studies of early rheumatoid arthritis (RA) cohorts have analysed treatment response and prognostic factors at fixed time points. However, in treat-to-target protocols, therapeutic decision-making is dynamic, and responsive to disease activity over time. To determine when a minimal residual disease response target should be expected, our primary objective was to identify the time-dependent therapeutic response to combination disease modifying anti-rheumatic drugs (DMARDs) for 12 months. Our secondary objective determined factors affecting this response trajectory. Design: Observational cohort. Setting: Treat-to-target early RA clinic in Australian tertiary referral hospital. Participants: We enrolled consecutive patients attending an early arthritis clinic with symptom duration less than 12 months, who were diagnosed with RA for the first time between 2004 and 2008. One hundred and one met these eligibility criteria and data were available at baseline through 12 months. Interventions: Intensive DMARDs according to a treat-to-target protocol. Primary and secondary outcome measures: We measured disease activity scores (DAS) at each visit, then analysed therapeutic response and associated factors in a time-dependent fashion over 12 months. Results: The median DAS4vESR of 4.46 at baseline decreased 12 weeks later by 24%, while the proportion with DAS4v $\leq$2.6 increased ($p < 0.01$). DAS4v continued to decrease over 52 weeks. DAS4v reduction of at least -0.45 at 4 weeks was predictive of DAS4v at 28 and 52 weeks. Female gender, current smoking, primary education and an interaction between baseline weight and CRP negatively impacted DAS4v reduction over 4 and 52 weeks. Time-varying effects of blood pressure, neutrophils, ESR and CRP also significantly influenced DAS4v over 52 weeks. Conclusions: Time-dependent data suggest that the largest reduction of DAS4v to combination DMARDs occurs in the

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first month of therapy, and this predicts subsequent response. Variables known to impact long-term treatment response in RA also impacted early DAS4v response to combination DMARDs.

Article Summary

Article focus

- Best-practice early RA treatment aims to achieve a target response. In clinic settings of many countries, first-line therapies are DMARDs, including combination DMARDs
- We followed an observational cohort for 12 months in a treat-to-target early RA clinic to identify the time-dependent therapeutic response to combination DMARDs for 12 months and factors affecting this response trajectory

Key messages

- After initiation of combination DMARDs, the largest reduction in disease activity score occurred in the first month, and its magnitude predicted subsequent response
- Disease activity score over 12 months was influenced by female gender and current smoking, education level and an interactive effect of weight and either CRP or ESR
- The data suggest clinical response to combination DMARDs may be more rapid than previously appreciated, and treatment response in the first month may have prognostic significance
- These hypotheses require further testing in other cohorts

Strengths and Limitations

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Strengths

- Monthly observation allowed precise determination of time-dependent therapeutic response and demonstrated an unexpectedly rapid response to combination DMARDs
- Standardised combination DMARD treat-to-target protocol
- Real-life clinical setting with dynamic therapeutic decision making

Limitations

- Observational cohort study limits conclusions that can be drawn regarding causality, without further testing in a randomised controlled trial
- Relatively small cohort derived from a single centre, with treatment regimen determined within Australian prescribing context, and exclusions due to missing data limit generalisability.
- Number of participants limited by lack of baseline or 12 month follow-up data and may have introduced selection bias
- Due to incomplete radiographic data, factors associated with radiographic outcomes could not be determined

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BACKGROUND:

Intervention with early combination disease modifying anti-rheumatic drug (DMARD) therapy favourably influences progression of rheumatoid arthritis (RA) independent of treatment in later years, suggesting that there is a "window of opportunity" in which the disease process can be altered [1, 2]. Moreover, a good response at 6 months to tight disease control using methotrexate predicted outcome after 5 years of treatment in participants in the CAMERA study [3]. The severity of disease varies in RA patients. In those with aggressive disease, damage to articular structures occurs early in the disease process: erosions were detected in 12.8% of patients after a median of 8 weeks in one study [4]. Thus, early evidence and determinants of treatment response to a given regimen are critical, in order to channel patients at greatest risk of poor outcome to more intensive induction regimens or more expensive biologic therapies within that window.

Studies of prognostic factors by statistical modelling have analysed disease progression outcomes including erosions, disease activity score (DAS28) and disability index as measured by Health Assessment Questionnaire (HAQ) at fixed time points – usually 6 or 12 months, with the earliest being 3 months – to determine treatment response and associated factors influencing this. Factors associated with poor radiological outcome include smoking, rheumatoid factor (RF) positivity, the presence of anti-citrullinated peptide autoantibodies (ACPA), HLA-DR genotype, low socioeconomic status and bone oedema on magnetic resonance imaging [5-9]. On the other hand, poor outcome measured by HAQ was associated with high baseline disease activity or HAQ, including RF, DAS28 score, tender and swollen joint counts, ESR and CRP [10, 11]. However, in treat-to-target protocols, such as was used in the TICORA trial and which occur in real-

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life clinic settings, decision-making about dose and drugs is a dynamic process, responsive to the patient's disease activity over time [12]. In many early arthritis protocols, including the current study, patients are treated and monitored intensively during the first 3-6 months, followed by a reduced visit frequency. Longitudinal analysis of all available data, while modelling the trajectories and drawing inferences on the significance of various risk factors, provides higher power and better insight into the dynamic process.

AIMS:

In the current study, our primary objective was to identify the time-dependent therapeutic response in an observational study of combination DMARDs for 12 months in order to determine when a minimal residual disease response target should be expected. Our secondary objective was to determine factors affecting this response trajectory. We therefore gathered disease activity data at each treatment visit then analyzed the disease activity response in a time-dependent fashion. We then determined factors which influenced this time-dependent response to an intensive DMARD regimen.

METHODS:

We enrolled consecutive patients referred by general practitioners from a relatively socio-economically disadvantaged catchment (60% referrals of employed individuals working in manual industries) to an early arthritis clinic in a public teaching hospital, with symptom duration less than 2 years, who were diagnosed with RA for the first time between 2004 and 2008. Patients were selected for inclusion in the current study if data

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were available at baseline through 12 months; however data were not required at every time point for inclusion. Two hundred and six patients were referred with possible RA and 101 patients met these eligibility criteria; 49 did not have RA, and 54 patients who met all other criteria were excluded as data were unavailable at 12 months. Of these, 7 were seen once and diagnosed with RA then treated elsewhere, and the remainder were reviewed at least once but not at 12 months. All study participants met the American College of Rheumatology 1987 revised criteria for the classification of RA [13]. Ethical approval for retrospective data analysis was obtained from the Metro South Human Research Ethics Committee.

Referrals from local general practitioners were triaged within 1 week, and patients were generally diagnosed within the next 4 weeks. Since full clinical and laboratory evaluation was available at the first visit to the early arthritis clinic, patients received combination methotrexate (MTX), sulfasalazine (SSZ) and hydroxychloroquine (HCQ) [14], unless contraindicated, immediately after diagnosis and confirmation of RA by the treating rheumatologist. Treatment was intensified according to a response-driven step-up algorithm, as previously described [15], with remission as the target [16, 17]. Briefly, criteria for dose escalation were either >2 swollen joints and abnormal ESR or CRP, or at least 2 of the following 4 criteria: morning stiffness >30mins, pain or fatigue visual analogue scale (VAS) >30mm, or >2 tender joints. The following medications were prescribed at baseline: MTX 10mg/week, folic acid 5mg/week, SSZ 500mg daily increasing by 500mg at weekly intervals to 1000mg twice daily, HCQ 200mg daily for one week then 400mg daily thereafter. Patients were seen at 4-weekly intervals and the MTX dose was escalated according to treatment response at a conservative rate by 5mg

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at each visit to a maximum of 25mg weekly. If disease remained active on this combination, SSZ was stopped, MTX reduced to 10mg weekly and leflunomide started at a dose of 20mg daily. MTX dose was titrated back to 25mg weekly, and if this combination failed and the Australian Pharmaceutical Benefit Scheme criteria were met, the patient commenced biologic therapy. Based on these criteria, 10% of patients in this setting commenced biologics per year. In general, the use of NSAIDs and oral corticosteroids was minimized, but intra-articular or oral steroids could be administered at the discretion of the treating physician. Large joints were injected with 40-80mg DepoMedrol and smaller joints with 1ml (5.7mg) Celestone. Oral and intra-articular dosage of corticosteroids was recorded monthly.

Response to therapy was measured as follows: the 4 variable DAS28ESR (hereafter referred to as DAS4v) was used as an index of inflammatory control [18], and the mHAQ as an index of disability [19]. Each index was calculated at each visit: baseline, and weeks 4, 8, 12, 16, 22, 28, 36, 44 and 52.

Demographic details were ascertained by questionnaire and included: age at presentation, symptom duration, level of education, gender, current, ex-smokers and non-smokers and mHAQ. Patients completed VAS for pain, fatigue and their global assessment of disease. The 28 tender and swollen joint counts, height, weight and blood pressure (BP) were recorded by the clinical research nurse. Blood was collected at baseline for the analysis of ESR, CRP, LFT, FBC, RF and ACPA. ACPA were measured at Queensland Health Pathology using the anti-CCP2 ELISA (Axis-Shield) test, with the cut-off of 6 for a positive test.

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Basic statistics were presented by number (%) or mean (SD) or median (IQR), as appropriate. Five imputations for missing data on clinical, biochemical and score data were performed using Bayesian Markov chain Monte Carlo multiple-imputation technique. Of those who met eligibility criteria for study inclusion, not all patients attended for all visits, however the patterns of missingness were random for all the study parameters. The consistency in the distributions of the 5 imputed data was checked for all study parameters. Given the skewed DAS and mHAQ scores, the medians and their 95% confidence intervals (CI) are presented. The changes in these scores over the study period are presented by median and 95% CI. Significance levels (p values) are based on the appropriate non-parametric test.

Generalized multivariate linear regression models with Gamma distribution and Identity link were used to identify the statistically significant ($p \leq 0.10$) risk factors and their possible interaction effects on disease activity scores at week 4 of the study. The possible consistency in the effect sizes of the statistically significant risk factors (at week 4) were also assessed on the disease activity scores at week 12 of the study. Combining the 10 longitudinal measurements obtained over one year of the study, the time varying effects of individual risk factors on the disease activity scores were explored using generalized estimating equation (GEE) regression approach with Gamma distribution and identity link function under the assumption of 'unstructured' correlation structure.

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RESULTS:

Time-dependent therapeutic response to combination DMARDs for 12 months

One hundred and one patients were included in the study and 54 (of whom 7 were only seen once) were excluded due to missing 12 month follow-up data. The baseline characteristics of included and excluded patients are shown in Table 1. Except for a lower systolic BP in excluded subjects, there were no significant differences between included and excluded subjects. All except 4 patients took at least two and up to three of the following DMARDs in combination during the 12 months study: Methotrexate, Sulfasalazine, Hydroxychloroquine and Leflunomide. These 4 patients took Methotrexate monotherapy.

The median disease activity score at baseline was 4.46 for DAS4v (Table 2). Four of the 12 patients with baseline DAS ≤2.6 (minimal disease activity) were taking steroids prior to referral. There was a highly significant ($p<0.001$) DAS reduction of 24% at 28 weeks (Table 2). We also observed a significant increase in the proportion of patients with minimal residual, (DAS28 ≤2.6) and low disease (DAS28 s ≤3.2) over the treatment period ($p<0.01$) (Table 2). Consistent with this, the patients' pain scores improved highly significantly by 31% and 56% at the end of 6-month and one-year of treatment respectively. The improvement in mHAQ from baseline to 6 months, but not between 6 and 12 months of treatment, was significant. The average annual change was 0.30 units (Table 2).

Analysis of the change in DAS4v over time showed a progressive reduction over 52 weeks, with the steepest drop between baseline and 4 weeks (Figure 1). The median

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(95% CI) of changes in DAS4v at 4, 28 and 52 weeks were -0.45 (-0.84, -0.07), -0.86 (-1.30, -0.41), and -1.35 (-1.67, -1.03) respectively ($p<0.01$ at week 52). The changing patterns of the distribution of DAS4v over time are evident from the density plots in Figure 2. Although a significant shift in the distribution of DAS4v at 4 weeks from baseline is evident from the density plot, the distributions overlap at 4, 28 and 52 weeks.

Analysis of the individual components of the DAS over this period demonstrated that patient global score, swollen and tender joint counts all fell most steeply between baseline and 4 weeks (Figure 2). While this was not the case for the fall in either ESR or CRP, similar steep falls in fatigue score, morning stiffness and physician global scores occurred between baseline and 4 weeks. Thus most measures of disease activity fell most rapidly in the first 4 weeks after DMARD initiation. In contrast, ESR fell for 3 months before reaching a plateau, while CRP fell progressively for 6 months.

Factors affecting the response trajectory in early RA patients treated with combination DMARDs

To determine whether the fall in DAS4v at 4 weeks predicted the DAS at 28 and 52 weeks, we first calculated that the median level of change in DAS4v at 4 weeks was -0.45. This was clinically discriminatory: at 4 weeks, 52% had no change or an increase in DAS4v while 48% improved from baseline DAS4v. The number and proportion of patients receiving steroids is indicated in Table 3. While baseline steroids impacted the likelihood of improvement at 4 weeks, this was not statistically significant (69% of patients receiving steroids improved and 53% not receiving steroids improved; odds ratio for improvement with steroids 1.95, $p=0.12$). Patients with reduction in DAS4v at

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4 weeks of at least -0.45 were three times more likely [OR (95% CI): 3.10 (1.2, 8.0)] at 28 weeks and 17 times more likely [OR (95% CI): 17.14 (4.52, 64.94)] at 52 weeks to maintain the same or reduced DAS4v as achieved after 4 weeks of treatment. Univariate modelling of factors affecting outcome showed that female sex, smoking status and increasing ALT at baseline negatively affected DAS4v at 4 weeks, but these effects became less significant by 12 weeks (Table 4). An interaction between baseline weight and CRP negatively affected DAS at both week 4 and 12. Patients taking steroid did not have a significantly different disease score, and symptom duration before RA diagnosis, anti-CCP or RF titre did not impact 4 week DAS. The reduction in DAS4v at 4 weeks was significantly greater in patients with tertiary than with primary education.

Combining baseline characteristics and the longitudinal measurements obtained over one year, we explored the time varying effects of individual risk factors on DAS4v in a univariate model. DAS4v over 52 weeks was again influenced by female gender and current smoking, and an interactive effect of weight and either CRP or ESR. Time varying effects of systolic and diastolic blood pressure, neutrophil counts, ESR and CRP also significantly influenced DAS4v observed over 52 weeks (Table 4). At week 52, the largest reduction in DAS4v was observed in patients with tertiary education (3.57), compared with that observed among patients with secondary (2.56) or primary education (1.33). Symptom duration prior to diagnosis did not significantly influence DAS4v over 52 weeks. Over the course of the study, DAS4v was increased by 0.66 in those patients taking steroids ($p < 0.01$). These data are in keeping with the use of steroid in this study at the clinician's discretion, to provide additional control for disease activity that was not controlled by the DMARD protocol.

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We found that the relationship between mHAQ and DAS4v for the cohort was significantly correlated at baseline, 4 weeks, 28 weeks and 52 weeks ($p<0.001$), with this correlation becoming progressively tighter over time as DAS and mHAQ fell. Thus, functional outcome after 1 year of early RA treatment is highly dependent on achievement of low disease activity.

DISCUSSION:

Our study describes the response of a group of patients with early RA to intensive conventional DMARD therapy in a time-dependent fashion over the first year. Baseline characteristics were in line with previous cohorts of patients with early RA. However, our baseline DAS scores were relatively low, reflecting our rapid triage and clinical and laboratory assessment of early arthritis referrals. Surprisingly, the time-dependent analysis of DAS response showed that the majority of disease activity measures fall most rapidly in the first 4 weeks after commencing intensive DMARD treatment in this population. There was a subsequent slow and progressive reduction in DAS until week 52. This fall in DAS4v at 4 weeks appeared to be clinically meaningful, as it predicted the DAS at 28 and 52 weeks. This observation suggests that for patients who failed to respond within 4 weeks to combination DMARD treatment, few gains were made by continuing to apply the same DMARD treat-to-target algorithm for 6-12 months. This was reflected in the similar proportion of patients with minimal or low disease activity between 6 and 12 months. By this stage patients had progressed through the combination DMARD algorithm, for which the next step would be biologics. However, because their disease activity is minimal or low, they failed to qualify for biologics

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based on Australia's Pharmaceutical Benefit Scheme (PBS) requirements (http://www.medicareaustralia.gov. au/provider/pbs/drugs2/rheumatoid.jsp) [20]. On the other hand, our data suggest the hypothesis that continued effort in applying a treat-to-target combination DMARD algorithm is likely to be effective over the ensuing months in patients who make a moderate response by week 4. Our data further suggest that combination DMARDs act unexpectedly rapidly in this early RA population, as patients' use of steroids did not influence the reduction in DAS. In support of this conclusion regarding steroids, in a study of 61 patients with early RA treated according to a similar response-driven step-up combination DMARD algorithm, Proudman *et al* obtained an almost identical 6 month minimal disease activity rate (DAS28<2.6 in 29%), despite infrequent use of corticosteroids [17].

The current study has a number of limitations. Firstly, our interpretation that the magnitude of the fall in DAS4v after 1 month predicts 1 year outcome is limited by the observational study design. However, the question of whether outcome could be improved in patients with a minimal treatment response within 1 month could be tested in a randomised controlled trial comparing switch to biologic therapy with continued combination DMARDs. Secondly, this is a relatively small cohort derived from a single centre with referrals derived from a relatively socio-economically disadvantaged catchment, with the treatment regimen determined within the Australian prescribing context. At the time of recruitment, 1987 ACR criteria were used to diagnose RA, which would have limited capacity to diagnose less severe patients. The number of participants was limited by lack of baseline or 12 month follow-up data and this may have introduced selection bias towards a more compliant group. The small sample size

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and number of exclusions due to incomplete data limit generalisability to other prescribing environments or clinical settings, and further studies are needed to test the generalisability of our findings. For example it is possible that those excluded had a different disease trajectory due to differences risk for poor outcome or differences in adverse events. A sub-analysis of the trajectory excluded patients was not possible because of the low number of paired baseline and 4 week DAS4v measurements in this group. On the other hand, there were no differences in the baseline characteristics of the excluded patients (except systolic BP). Furthermore, almost all factors associated with 4 week DAS4v response have been previously demonstrated to affect disease outcome in longer-term and larger studies. The strengths of this study are that it analyses real-world data, monthly observations allowed precise determination of time-dependent response, and patients received a standardised combination DMARD treat-to-target protocol, reducing the confounding effect of treatment decisions based on individual clinician preference.

The exploratory nature of the study in a relatively small sample could introduce false positive associations. Although it possible that the rapid 4 week response to combination DMARDs represents regression to the mean, the continued good response of these patients argues against this. Our data also are consistent with recent studies demonstrating that early good response to combination therapy (in the TEAR and RAPID 1 trials) is associated with a continued good response [21, 22]. In these studies, rapid response was ascertained 12 weeks after initiation of combination therapy. By regression analysis, we identified female gender, current smoking, education level, ALT and an interaction between weight and CRP as significant determinants of disease

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activity over 4 and 52 weeks. Females, current smokers and low levels of education were found in several studies, including those of early RA, to achieve lower reductions in disease activity or remission [23-26]. However, no study has previously determined that the impact of these variables may occur within weeks of commencing treatment. The interaction between weight and inflammation in RA is intriguing and has been noted previously in insulin resistant states [27]. In patients with active RA, those with high BMI responded less well to infliximab [28]. We also identified significant time-varying effects of blood pressure, gender, age, weight and inflammatory markers on disease activity. The interaction between disease activity and cardiovascular risk is well documented in RA, including early RA, and traditional cardiovascular risk factors may also impact the activity of inflammatory disease over time [15, 29-31]. However, it is unknown whether control of cardiovascular risk factors can in turn impact inflammatory disease control.

In this study we were limited to analysis of disease and functional score, as radiographic data were not sufficiently complete to allow measurement of structural damage. However, this issue has been addressed by others, where biomarkers such as ACPA antibodies, RF, CRP and cartilage oligomeric matrix protein can add power to predictive models of bone erosion in early RA [32]. In contrast, we found no impact of ACPA or RF on DAS. Our data confirm a strong relationship between disease activity and functional score that appears to strengthen over time, a finding that is supported by data from the BeST cohort [16]. We would anticipate that functional disability would be minimized by early treatment with combination DMARDs as shown previously [33, 34].

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Since they are traditionally thought to be slow acting, previous studies of DMARD monotherapy in early RA have not analyzed time-dependent data from 4 weeks. Although it remains possible that a similar response might be observed in some patients starting DMARD monotherapy, we suggest this rapid response may be a unique feature of intensive combination DMARDs (with multiple mechanisms of action) initiation in early RA, which is the RA population most responsive to therapeutic intervention [35, 36]. The risks and benefits of intensive DMARD therapy (combinations allowing switching to achieve tight control) versus monotherapy in early RA deserve further study, considering inconsistent evidence to support combination DMARD therapy in RA [36, 37]. The need to identify patients with more aggressive disease prompted one group to undertake a trial of a stratified treatment plan based on the likelihood of persistent arthritis, with the aim of minimizing over- and under-treatment in early RA [38]. Our data suggest the hypothesis that very early response to an intensive DMARD strategy that minimizes under-treatment predicts response for the first year.

Data from the ERAN study show that patients with moderate disease activity at 1 year are unlikely to achieve better control of their disease if the same protocol is continued, and a good response at 6 months in the CAMERA study predicted outcome at 5 years [3, 39]. Our data, collected in a cohort of early RA patients with relatively low baseline DAS, likely reflect the trajectory of patients meeting criteria for RA early in disease, and which would be captured in organized clinical settings using the recently-published new classification criteria [40].

CONCLUSIONS :

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With the availability of increasing numbers of treatment options, application of strategies that identify early non-responders to intensive DMARD combinations, has clear implications for treatment stratification within the window of opportunity. Time-dependent data suggest clinical response to combination DMARDs may be more rapid than previously appreciated, and treatment response in the first month may have prognostic significance. Confirmation in other cohorts will be required to determine the generalisability of this notion.

DATA SHARING, COMPETING INTERESTS AND FUNDING

No additional data are available. The authors declare no competing interests in relation to this article. Supported by NHMRC grants 351439 and 569938. R.T. is supported by Arthritis Queensland and an ARC Future Fellowship.

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TABLES:

Table 1. Baseline characteristics of the patients

Baseline variable	Value	
	Included patients (n=101)	Excluded patients (n=54)
Female*	60 (59.4%)	44 (81%)
Age†, years	54 (12)	48 (15)
Symptom duration, months$	12 (5, 12)	6 (4, 12)
Smoking		
Current Smokers	26 (25.7%)	8 (15%)
Ex-Smokers	29 (28.7%)	26 (48%)
Education		
Primary		5 (14%)
Secondary		24 (66%)
Tertiary		9 (24%)
Weight†, Kg	77.10 (19.68)	80 (24)
SBP†, mm Hg	127 (15)	120 (17)**
DBP†, mm Hg	73 (10)	70 (10)
RF*	89 (88.1%)	42 (77%)
ACPA*	51 (50.5%)	9 (36%)
ESR$, mm/hour	25 (12, 46)	16 (10, 34)
CRP$, mg/liter	9.7 (19, 39)	6 (2, 12)
Lymphocytes†, x 10^9/L	1.94 (0.67)	2.1 (1.3, 2.5)
Neutrophils†, x 10^9/L	5.12 (2.50)	5 (3, 6.8)
LFT (AST) $, U/L	20.50 (16.50, 24.00)	18.5 (17, 23)

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LFT (ALT) [$], U/L	19 (14, 27)	19 (14, 23)

* Values are n (%); [†] values are the median (SD); [$] values are the median (IQR). SD = standard deviation; IQR = interquartile range; RF = Rheumatoid Factor; ACPA = anti-citrullinated peptide antibody; ESR = erythrocyte sedimentation ratio; CRP = C reactive protein; LFT = liver function test; AST = aspartate aminotransferase; ALT = alanine aminotransferase**p=0.002..

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Table 2. Change in median pain VAS scores, DAS and HAQ scores (95% CI) over 1 year

	Baseline	6 month	1 year	Change at 6 months	p	Change at 1 year	p
Pain Score	55 (48, 62)	37.9 (31.7, 44.1)	24.2 (17.7, 30.6)	-21.9 (-30.8, -13)	<0.001	-27.4 (-35.6, -19.1)	<0.001
DAS4v	4.5 (4.1, 4.8)	3.4 (3.1, 3.7)	3.2 (2.9, 3.4)	-1.3 (-1.8, -0.8)	<0.001	-1.5 (-2, -1.1)	<0.001
mHAQ	0.6 (0.5, 0.8)	0.44(0.3, 0.6)	0.3 (0.2, 0.4)	-0.3 (-0.5, -0.1)	0.003	-0.3 (-0.4, -0.2)	<0.001
Proportion of patients with:							
DAS ≤ 2.6	12 (14.8%)	25 (25%)	29 (29%)				
DAS ≤ 3.2	18 (22%)	48 (48%)	52 (52%)				

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Table 3. Frequency of steroid use over the study

Treated with:	Study duration (weeks)					
	0 (0)	**4**	**8**	**12**	**16**	**24**
Oral Steroid n (%)	16 (15.8)	17 (16.8)	14 (13.9)	11 (10.9)	1 (1)	1 (1)
IA steroid	21 (20.7)	2 (2)	4 (4)	2 (2)	0	0
Any steroid	37 (36.7)	19 (18.8)	18 (17.8)	13 (12.9)	1 (1)	1 (1)
Oral and IA steroid	3 (3)	1 (1)	2 (2)	0	0	0

IA intra-articular

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Table 4. Variables influencing DAS scores at 4 and 12 weeks of study – Univariate regression

	DAS4v Week 4		DAS4v Week 12	
	ß	p	ß	p
Female	0.68	0.009	0.46	0.059
Smoking				
Ex-smokers vs non-smokers	-0.55	0.026	-0.17	0.53
Current smokers vs non-smokers	-0.80	0.003	-0.42	0.10
LFT (ALT)	0.03	0.01	0.04	0.63
Weight*CRP	0.002	0.029	0.002	0.02
Oral or IA Steroid	0.11	0.67	0.01	0.98
Anti-CCP > 6	0.0004	0.99	0.67	0.08

Values are regression coefficient (ß) and p-value. Regression co-efficient at each time point for RF = 0. CRP = C reactive protein; LFT = liver function test; ALT = alanine aminotransferase.

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Table 5. Effects of time-varying risk factors individually on DAS28 scores over 1 year of study – Univariate regression

	DAS4v		
	ß	95% CI	p
Female	0.45	0.09, 0.81	0.014
Age	0.001	-0.13, 0.02	0.82
Smoking:			
Ex-smokers vs non-smokers	-0.27	-70, 0.16	0.22
Current smokers vs non-smokers	-0.48	-0.91, -0.06	0.026
SBP	0.10	0.08, 0.20	<0.001
DBP	0.10	0.04, 0.20	0.004
Lymphocyte	0.04	-0.09, 0.17	0.55
Neutrophil	0.16	0.10, 0.22	<0.001
ESR	0.03	0.03, 0.04	<0.001
CRP	0.02	0.01, 0.02	<0.001
LFT-AST	-0.004	-0.01, 0.003	0.25
LFT-ALT	-0.003	-0.009, 0.004	0.44
Weight*CRP	0.002	0.001, 0.003	<0.001
Weight*ESR	0.004	0.003, 0.005	<0.001
Oral or IA steroid	0.66	0.34, 0.99	P<0.01
Anti-CCP > 6	0.001	-0.001, 0.002	0.36

Regression co-efficient at each time point for RF = 0.

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FIGURES :

Figure 1. Distribution of DAS4v over the study period. A: The median and 95% CI are plotted for each visit over the 52 week study period. **B:** Changes in DAS4v over 4, 28 and 52 weeks are indicated. **C:** The changing distribution in DAS4v in the sample is plotted at baseline, 4, 28 and 52 weeks.

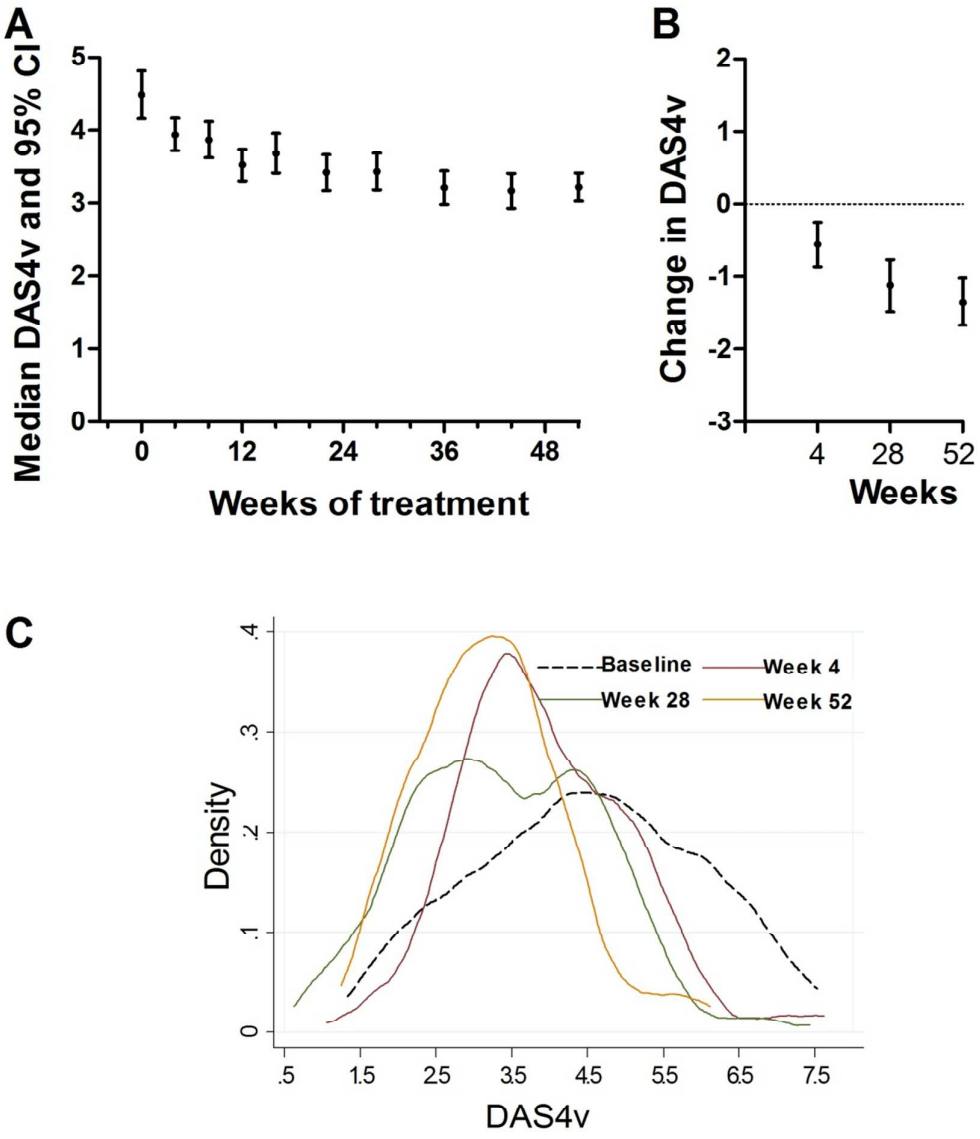
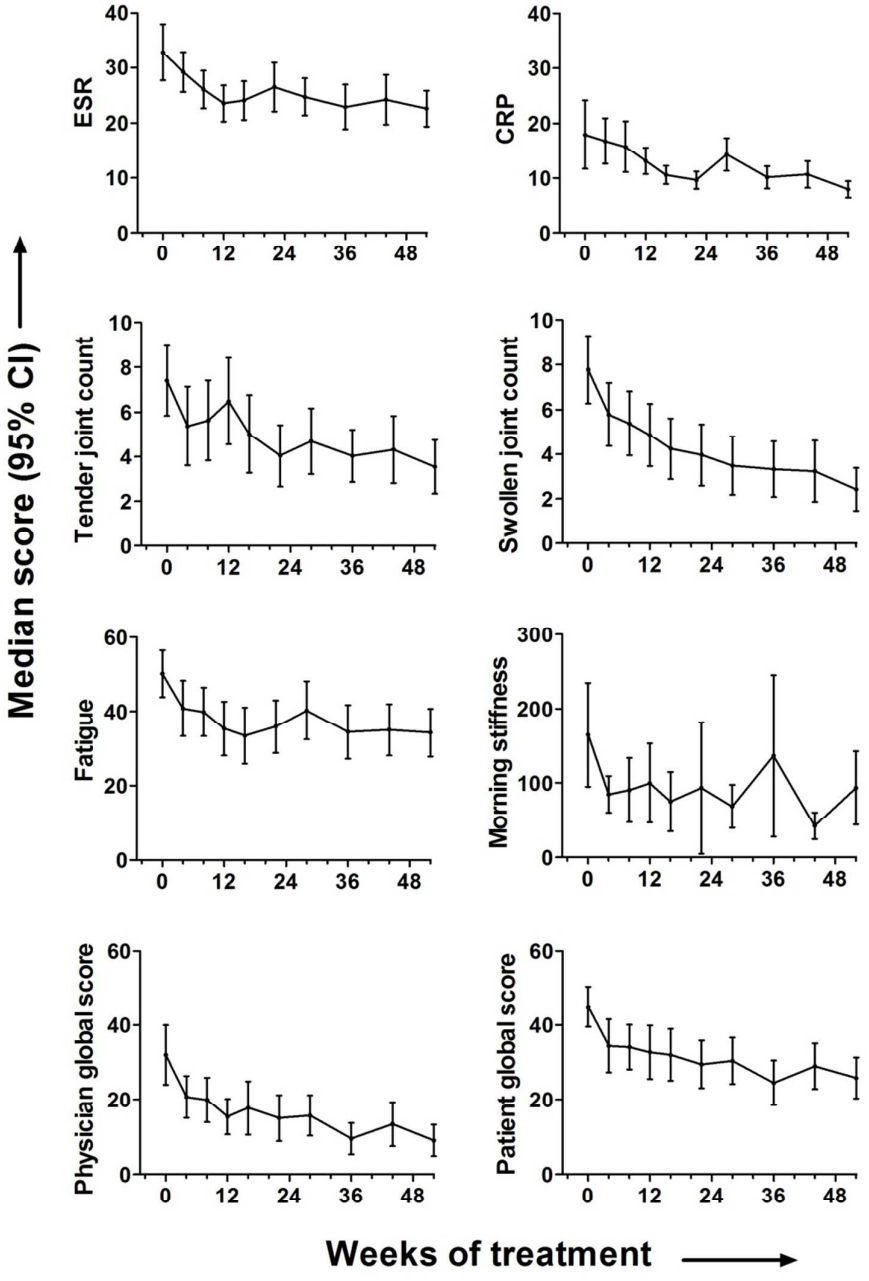


Figure 2. Variation in the disease activity parameters over the study period. The median and 95% CI are plotted for each visit over the 52 week study period for ESR, CRP, tender joint count, swollen joint count, fatigue, morning stiffness, patient global and physician global scores.



Trajectory of intensive treat-to-target disease modifying drug regimen in an observational study of an early rheumatoid arthritis cohort

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ABSTRACT

Objectives: Studies of early rheumatoid arthritis (RA) cohorts have analysed treatment response and prognostic factors at fixed time points. However, in treat-to-target protocols, therapeutic decision-making is dynamic, and responsive to disease activity over time. To determine when a minimal residual disease response target should be expected, our primary objective was to identify the time-dependent therapeutic response to combination disease modifying anti-rheumatic drugs (DMARDs) for 12 months. Our secondary objective determined factors affecting this response trajectory. Design: Observational cohort. Setting: Treat-to-target early RA clinic in Australian tertiary referral hospital. Participants: We enrolled consecutive patients attending an early arthritis clinic with symptom duration less than 12 months, who were diagnosed with RA for the first time between 2004 and 2008. One hundred and one met these eligibility criteria and data were available at baseline through 12 months. Interventions: Intensive DMARDs according to a treat-to-target protocol. Primary and secondary outcome measures: We measured disease activity scores (DAS) at each visit, then analysed therapeutic response and associated factors in a time-dependent fashion over 12 months. Results: The median DAS4vESR of 4.46 at baseline decreased 12 weeks later by 24%, while the proportion with DAS4v ≤2.6 increased (p <0.01). DAS4v continued to decrease over 52 weeks. DAS4v reduction of at least -0.45 at 4 weeks was predictive of DAS4v at 28 and 52 weeks. Female gender, current smoking, primary education and an interaction between baseline weight and CRP negatively impacted DAS4v reduction over 4 and 52 weeks. Time-varying effects of blood pressure, neutrophils, ESR and CRP also significantly influenced DAS4v over 52 weeks. Conclusions: Time-dependent data suggest that the largest reduction of DAS4v to combination DMARDs occurs in the

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first month of therapy, and this predicts subsequent response. Variables known to impact long-term treatment response in RA also impacted early DAS4v response to combination DMARDs.~~The data suggest the need for a controlled trial of treatment change within 1 month, in combination DMARD non responding patients.~~

Article Summary

Article focus

- Best-practice early RA treatment aims to achieve a target response. In clinic settings of many countries, first-line therapies are DMARDs, including combination DMARDs
- We followed an observational cohort for 12 months in a treat-to-target early RA clinic to identify the time-dependent therapeutic response to combination DMARDs for 12 months and factors affecting this response trajectory

Key messages

- After initiation of combination DMARDs, the largest reduction in disease activity score occurred in the first month, and its magnitude predicted subsequent response
- Disease activity score over 12 months was influenced by female gender and current smoking, education level and an interactive effect of weight and either CRP or ESR
- The data suggest ~~a need for a controlled trial of treatment change within 1 month, in~~clinical response to combination DMARDs ~~non responding patients~~may be more rapid than previously appreciated, and treatment response in the first month may have prognostic significance
- These hypotheses require further testing in other cohorts~~.~~

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Strengths and Limitations

Strengths

- Monthly observation allowed precise determination of time-dependent therapeutic response and demonstrated an unexpectedly rapid response to combination DMARDs
- Standardised combination DMARD treat-to-target protocol
- Real-life clinical setting with dynamic therapeutic decision making

Limitations

- Observational cohort study limits conclusions that can be drawn regarding causality, without further testing in a randomised controlled trial
- Relatively small cohort derived from a single centre, with treatment regimen determined within Australian prescribing context, and exclusions due to missing data limits generalisability.
- Number of participants limited by lack of baseline or 12 month follow-up data and may have introduced selection bias
- Due to incomplete radiographic data, factors associated with radiographic outcomes could not be determined

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BACKGROUND:

Intervention with early combination disease modifying anti-rheumatic drug (DMARD) therapy favourably influences progression of rheumatoid arthritis (RA) independent of treatment in later years, suggesting that there is a "window of opportunity" in which the disease process can be altered [1, 2]. Moreover, a good response at 6 months to tight disease control using methotrexate predicted outcome after 5 years of treatment in participants in the CAMERA study [3]. The severity of disease varies in RA patients. In those with aggressive disease, damage to articular structures occurs early in the disease process: erosions were detected in 12.8% of patients after a median of 8 weeks in one study [4]. Thus, early evidence and determinants of treatment response to a given regimen are critical, in order to channel patients at greatest risk of poor outcome to more intensive induction regimens or more expensive biologic therapies within that window.

Studies of prognostic factors by statistical modelling have analysed disease progression outcomes including erosions, disease activity score (DAS28) and disability index as measured by Health Assessment Questionnaire (HAQ) at fixed time points – usually 6 or 12 months, with the earliest being 3 months – to determine treatment response and associated factors influencing this. Factors associated with poor radiological outcome include smoking, rheumatoid factor (RF) positivity, the presence of anti-citrullinated peptide autoantibodies (ACPA), HLA-DR genotype, low socioeconomic status and bone oedema on magnetic resonance imaging [5-9]. On the other hand, poor outcome measured by HAQ was associated with high baseline disease activity or HAQ, including RF, DAS28 score, tender and swollen joint counts, ESR and CRP [10, 11]. However, in treat-to-target protocols, such as was used in the TICORA trial and which occur in real-

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life clinic settings, decision-making about dose and drugs is a dynamic process, responsive to the patient's disease activity over time [12]. In many early arthritis protocols, including the current study, patients are treated and monitored intensively during the first 3-6 months, followed by a reduced visit frequency. Longitudinal analysis of all available data, while modelling the trajectories and drawing inferences on the significance of various risk factors, provides higher power and better insight into the dynamic process.

AIMS:

In the current study, our primary objective was to identify the time-dependent therapeutic response in an observational study of combination DMARDs for 12 months in order to determine when a minimal residual disease response target should be expected. Our secondary objective was to determine factors affecting this response trajectory. We therefore gathered disease activity data at each treatment visit then analyzed the disease activity response in a time-dependent fashion. We then determined factors which influenced this time-dependent response to an intensive DMARD regimen.

METHODS:

We enrolled consecutive patients ~~attending~~ referred by general practitioners from a relatively socio-economically disadvantaged catchment (60% referrals of employed individuals working in manual industries) to an ~~a tertiary referral~~ early arthritis clinic in a public teaching hospital, with symptom duration less than ~~12 months~~2 years, who were diagnosed with RA for the first time between 2004 and 2008. Patients were

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selected for inclusion in the current study if data were available at baseline through 12 months; however data were not required at every time point for inclusion. Two hundred and six patients were referred with possible RA and ~~One hundred and one~~101 patients met these eligibility criteria; 49 did not have RA, and ~~however 107~~ 54 patients who met all other criteria were excluded as data were unavailable at ~~either baseline or~~ 12 months. Of these, 7 were seen once and diagnosed with RA then treated elsewhere, and the remainder were reviewed at least once but not at 12 months. All study participants met the American College of Rheumatology 1987 revised criteria for the classification of RA [13]. Ethical approval for retrospective data analysis~~the study~~ was obtained from the Metro South Human Research Ethics Committee ~~Committee~~.

Referrals from local general practitioners were triaged within 1 week, and patients were generally diagnosed within the next 4 weeks. Since full clinical and laboratory evaluation was available at the first visit to the early arthritis clinic, patients received combination methotrexate (MTX), sulfasalazine (SSZ) and hydroxychloroquine (HCQ) [14], unless contraindicated, immediately after diagnosis and confirmation of ~~active disease~~RA by the treating rheumatologist. Treatment was intensified according to a response-driven step-up algorithm, as previously described [15], with remission as the target [16, 17]. Briefly, criteria for dose escalation were either >2 swollen joints and abnormal ESR or CRP, or at least 2 of the following 4 criteria: morning stiffness >30mins, pain or fatigue visual analogue scale (VAS) >30mm, or >2 tender joints. The following medications were prescribed at baseline: MTX 10mg/week, folic acid 5mg/week, SSZ 500mg daily increasing by 500mg at weekly intervals to 1000mg twice daily, HCQ 200mg daily for one week then 400mg daily thereafter. Patients were seen

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at 4-weekly intervals and the MTX dose was escalated according to treatment response at a conservative rate by 5mg at each visit to a maximum of 25mg weekly. If disease remained active on this combination, SSZ was stopped, MTX reduced to 10mg weekly and leflunomide started at a dose of 20mg daily. MTX dose was titrated back to 25mg weekly, and if this combination failed and the Australian Pharmaceutical Benefit Scheme criteria were met, the patient commenced biologic therapy. Based on these criteria, 10% of patients in this setting commenced biologics per year. In general, the use of NSAIDs and oral corticosteroids was minimized, but intra-articular or oral steroids could be administered at the discretion of the treating physician. Large joints were injected with 40-80mg DepoMedrol and smaller joints with 1ml (5.7mg) Celestone. Oral and intra-articular dosage of corticosteroids was recorded monthly.

Response to therapy was measured as follows: the 4 variable DAS28ESR (hereafter referred to as DAS4v) was used as an index of inflammatory control [18], and the mHAQ as an index of disability [19]. Each index was calculated at each visit: baseline, and weeks 4, 8, 12, 16, 22, 28, 36, 44 and 52.

Demographic details were ascertained by questionnaire and included: age at presentation, symptom duration, level of education, gender, ~~smoking status~~current, ex-smokers and non-smokers and mHAQ. Patients completed VAS for pain, fatigue and their global assessment of disease. The 28 tender and swollen joint counts, height, ~~and~~ weight and blood pressure (BP) were recorded by the clinical research nurse. Blood was collected at baseline for the analysis of ESR, CRP, LFT, FBC, RF and ACPA. ACPA

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were measured at Queensland Health Pathology using the anti-CCP2 ELISA (Axis-Shield) test, with the cut-off of 6 for a positive test.

Basic statistics were presented by number (%) or mean (SD) or median (IQR), as appropriate. Five imputations for missing data on clinical, biochemical and score data were performed using Bayesian Markov chain Monte Carlo multiple-imputation technique. Of those who met eligibility criteria for study inclusion, not all patients attended for all visits, however ~~T~~the patterns of missingness were random for all the study parameters. The consistency in the distributions of the 5 imputed data was checked for all study parameters. Given the skewed DAS and mHAQ scores, the medians and their 95% confidence intervals (CI) are presented. The changes in these scores over the study period are presented by median and 95% CI., ~~and the s~~Significance levels (p values) are based on the appropriate non-parametric test.

Generalized multivariate linear regression models with Gamma distribution and Identity link were used to identify the statistically significant ($p \leq 0.10$) risk factors and their possible interaction effects on disease activity scores at week 4 of the study. The possible consistency in the effect sizes of the statistically significant risk factors (at week 4) were also assessed on the disease activity scores at week 12 of the study. Combining the 10 longitudinal measurements obtained over one year of the study, the time varying effects of individual risk factors on the disease activity scores were explored using generalized estimating equation (GEE) regression approach with Gamma distribution and identity link function under the assumption of 'unstructured' correlation structure.

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RESULTS:

Time-dependent therapeutic response to combination DMARDs for 12 months

One hundred and one patients were included in the study and 54 (of whom 7 were only seen once) were excluded due to missing 12 month follow-up data. The baseline characteristics of the included and excluded patients are shown in Table 1. Except for a lower systolic BP in excluded subjects, there were no significant differences between included and excluded subjects. All except 4 patients took at least two and up to three of the following DMARDs in combination during the 12 months study: Methotrexate, Sulfasalazine, Hydroxychloroquine and Leflunomide. These 4 patients took Methotrexate monotherapy.

The median disease activity score at baseline was 4.46 for DAS4v (Table 2). Four of the 12 patients with baseline DAS ≤2.6 (minimal disease activity) were taking steroids prior to referral. There was a highly significant ($p<0.001$) DAS reduction of 24% at 28 weeks (Table 2). We also observed a significant increase in the proportion of patients with minimal residual, (DAS28 scores ≤2.6) and low disease (DAS28 scores ≤3.2) over the treatment period ($p<0.01$) (Table 2). Consistent with this, the patients' pain scores improved highly significantly by 31% and 56% at the end of 6-month and one-year of treatment respectively. The improvement in mHAQ from baseline to 6 months, but not between 6 and 12 months of treatment, was significant. The average annual change was 0.30 units (Table 2).

Analysis of the change in DAS4v over time showed a progressive reduction over 52 weeks, with the steepest drop between baseline and 4 weeks (Figure 1). The median

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(95% CI) of changes in DAS4v ~~scores~~ at 4, 28 and 52 weeks were -0.45 (-0.84, -0.07), -0.86 (-1.30, -0.41), and -1.35 (-1.67, -1.03) respectively ($p<0.01$ at week 52). The changing patterns of the distribution of DAS4v ~~scores~~ over time are evident from the density plots in Figure 2. Although a significant shift in the distribution of DAS4v at 4 weeks from baseline is evident from the density plot, the distributions overlap at 4, 28 and 52 weeks.

Analysis of the individual components of the DAS ~~scores~~ over this period demonstrated that patient global score, swollen and tender joint counts all fell most steeply between baseline and 4 weeks (Figure 2). While this was not the case for the fall in either ESR or CRP, similar steep falls in fatigue score, morning stiffness and physician global scores occurred between baseline and 4 weeks. Thus most measures of disease activity fell most rapidly in the first 4 weeks after DMARD initiation. In contrast, ESR fell for 3 months before reaching a plateau, while CRP fell progressively for 6 months.

Factors affecting the response trajectory in early RA patients treated with combination DMARDs

To determine whether the fall in DAS4v at 4 weeks predicted the DAS ~~score~~ at 28 and 52 weeks, we first calculated that the median level of change in DAS4v ~~score~~ at 4 weeks was -0.45. This was clinically discriminatory: at 4 weeks, 52% had no change or an increase in DAS4v while 48% improved from baseline DAS4v. The number and proportion of patients receiving steroids is indicated in Table 3. While baseline steroids impacted the likelihood of improvement at 4 weeks, this was not statistically significant (69% of patients receiving steroids improved and 53% not receiving steroids improved;

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odds ratio for improvement with steroids 1.95, p=0.12). Patients with reduction in DAS4v ~~score~~ at 4 weeks of at least -0.45 were three times more likely [OR (95% CI): 3.10 (1.2, 8.0)] at 28 weeks and 17 times more likely [OR (95% CI): 17.14 (4.52, 64.94)] at 52 weeks to maintain the same or reduced DAS4v ~~score~~ as achieved after 4 weeks of treatment. Univariate modelling of factors affecting outcome showed that female sex, smoking status and increasing ALT at baseline negatively affected DAS4v at 4 weeks, but these effects became less significant by 12 weeks (Table 4). An interaction between baseline weight and CRP negatively affected DAS at both week 4 and 12. Patients taking steroid did not have a significantly different disease score, and symptom duration before RA diagnosis, anti-CCP ~~and~~or RF titre did not impact 4 week DAS. The reduction in DAS4v at 4 weeks was significantly greater in patients with tertiary than with primary education.

Combining baseline characteristics and the longitudinal measurements obtained over one year, we explored the time varying effects of individual risk factors on DAS4v in a univariate model. DAS4v over 52 weeks was again influenced by female gender and current smoking, and an interactive effect of weight and either CRP or ESR. Time varying effects of systolic and diastolic blood pressure, neutrophil counts, ESR and CRP also significantly influenced DAS4v observed over 52 weeks (Table 4). At week 52, the largest reduction in DAS4v was observed in patients with tertiary education (3.57), compared with that observed among patients with secondary (2.56) or primary education (1.33). Symptom duration prior to diagnosis did not significantly influence DAS4v over 52 weeks. Over the course of the study, DAS4v was increased by 0.66 in those patients taking steroids ($p < 0.01$). These data are in keeping with the use of

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steroid in this study at the clinician's discretion, to provide additional control for disease activity that was not controlled by the DMARD protocol.

We found that the relationship between mHAQ and DAS4v for the cohort was significantly correlated at baseline, 4 weeks, 28 weeks and 52 weeks ($p<0.001$), with this correlation becoming progressively tighter over time as DAS and mHAQ fell. Thus, functional outcome after 1 year of early RA treatment is highly dependent on achievement of low disease activity.

DISCUSSION:

Our study describes the response of a group of patients with early RA to intensive conventional DMARD therapy in a time-dependent fashion over the first year. Baseline characteristics were in line with previous cohorts of patients with early RA. However, our baseline DAS scores were relatively low, reflecting our rapid triage and clinical and laboratory assessment of early arthritis referrals. Surprisingly, ~~A key finding from~~ the time-dependent analysis of DAS response~~, is~~ showed that the majority of disease activity measures fall most rapidly in the first 4 weeks after commencing intensive DMARD treatment in this population. There was a subsequent slow and progressive reduction in DAS until week 52. This ~~Moreover, the~~ fall in DAS4v at 4 weeks appeared to be clinically meaningful, as it predicted the DAS ~~score~~ at 28 and 52 weeks. This observation suggests that for patients who failed to respond within 4 weeks to combination DMARD treatment, few gains ~~are~~were made by continuing to apply the same DMARD treat-to-target algorithm for 6-12 months. This was reflected in the similar proportion of patients with minimal or low disease activity between 6 and 12

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months. By this stage patients had progressed through the combination DMARD algorithm, for which the next step would be biologics. However, because their disease activity is minimal or low, they failed to qualify for biologics based on Australia's Pharmaceutical Benefit Scheme (PBS) requirements (http://www.medicareaustralia.gov.au/provider/pbs/drugs2/rheumatoid.jsp) [20]. On the other hand, our data suggest the hypothesis that continued effort in applying a treat-to-target combination DMARD algorithm is likely to be effective over the ensuing months in patients who make a moderate response by week 4. Our data further suggest that combination DMARDs act unexpectedly rapidly in this early RA population, as patients' use of steroids did not influence the reduction in DAS. In support of this conclusion regarding steroids, in a study of 61 patients with early RA treated according to a similar response-driven step-up combination DMARD algorithm, Proudman *et al* obtained an almost identical 6 month ~~remission~~ minimal disease activity rate (DAS28<2.6 in 29%), despite infrequent use of corticosteroids [17].

The current study has a number of limitations. Firstly, our interpretation that the magnitude of the fall in DAS4v after 1 month predicts 1 year outcome is limited by the observational study design. However, the question of whether outcome could be improved in patients with a minimal treatment response within 1 month could be tested in a randomised controlled trial comparing switch to biologic therapy with continued combination DMARDs. Secondly, this is a relatively small cohort derived from a single centre with referrals derived from a relatively socio-economically disadvantaged catchment, with the treatment regimen determined within the Australian prescribing context. At the time of recruitment, 1987 ACR criteria were used to diagnose RA,

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which would have limited capacity to diagnose less severe patients. The number of participants was limited by lack of baseline or 12 month follow-up data and this may have introduced selection bias towards a more compliant group. ~~While these factors may~~The small sample size and number of exclusions due to incomplete data limit generalisability to other prescribing environments or clinical settings, and further studies are needed to test the generalisability of our findings. For example it is possible that those excluded had a different disease trajectory due to differences risk for poor outcome or differences in adverse events. A sub-analysis of the trajectory excluded patients was not possible because of the low number of paired baseline and 4 week DAS4v measurements in this group. On the other hand, there were no differences in the baseline characteristics of the excluded patients (except systolic BP). Furthermore, almost all factors associated with 4 week DAS4v response have been previously demonstrated to affect disease outcome in longer-term and larger studies. T~~t~~he strengths of this study are that it analyses real-world data, monthly observations allowed precise determination of time-dependent response, and ~~and were able to demonstrate an unexpectedly rapid response to combination DMARDs. Furthermore,~~ patients received a standardised combination DMARD treat-to-target protocol, reducing the confounding effect of treatment decisions based on individual clinician preference.

~~Finally t~~The exploratory nature of the study in a relatively small sample could introduce false positive associations. Although it possible that the rapid 4 week response to combination DMARDs represents regression to the mean, the continued good response of these patients argues against this. Our data also are consistent with recent studies demonstrating that early good response to combination therapy (in the TEAR and

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RAPID 1 trials) is associated with a continued good response [21, 22]. In these studies, rapid response was ascertained 12 weeks after initiation of combination therapy. By regression analysis, we identified female gender, current smoking, education level, ALT and an interaction between weight and CRP as significant determinants of disease activity over 4 and 52 weeks. Females, ~~and~~ current smokers and low levels of education were found in several studies, including those of early RA, to achieve lower reductions in disease activity or remission ~~than men~~ [23-26]. However, no study has previously determined that the impact of these variables may occur within weeks of commencing treatment. The interaction between weight and inflammation in RA is intriguing and has been noted previously in insulin resistant states [27]. In patients with active RA, those with high BMI responded less well to infliximab [28]. We also identified significant time-varying effects of blood pressure, gender, age, weight and inflammatory markers on disease activity. The interaction between disease activity and cardiovascular risk is well documented in RA, including early RA, and traditional cardiovascular risk factors may also impact the activity of inflammatory disease over time [15, 29-31]. However, it is unknown whether control of cardiovascular risk factors can in turn impact inflammatory disease control.

In this study we were limited to analysis of disease and functional score, as radiographic data were not sufficiently complete to allow measurement of structural damage. However, this issue has been addressed by others, where biomarkers such as ACPA antibodies, RF, CRP and cartilage oligomeric matrix protein can add power to predictive models of bone erosion in early RA [32]. In contrast, we found no impact of ACPA or RF on DAS. Our data confirm a strong relationship between disease activity

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and functional score that appears to strengthen over time, a finding that is supported by data from the BeST cohort [16]. We would anticipate that functional disability would be minimized by early treatment with combination DMARDs as shown previously [33, 34].

Since they are traditionally thought to be slow acting, previous studies of DMARD monotherapy in early RA have not analyzed time-dependent data from 4 weeks. Although it remains possible that a similar response might be observed in some patients starting DMARD monotherapy, we suggest this rapid response may be a unique feature of intensive combination DMARDs (with multiple mechanisms of action) initiation in early RA, which is the RA population most responsive to therapeutic intervention [35, 36]. The risks and benefits of intensive DMARD therapy (combinations allowing switching to achieve tight control) versus monotherapy in early RA deserve further study, considering inconsistent evidence to support combination DMARD therapy in RA [36, 37]. The need to identify patients with more aggressive disease prompted one group to undertake a trial of a stratified treatment plan based on the likelihood of persistent arthritis, with the aim of minimizing over- and under-treatment in early RA [38]. Our data suggest the hypothesis that very early response to an intensive DMARD strategy that minimizes under-treatment predicts response for the first year.

Data from the ERAN study show that patients with moderate disease activity at 1 year are unlikely to achieve better control of their disease if the same protocol is continued, and a good response at 6 months in the CAMERA study predicted outcome at 5 years [3, 39]. Our data, collected in a cohort of early RA patients with relatively low baseline

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DAS, likely reflect the trajectory of patients meeting criteria for RA early in disease, and which would be captured in organized clinical settings using the recently-published new classification criteria [40].

CONCLUSIONS :

With the availability of increasing numbers of treatment options, application of strategies that identify early non-responders to intensive DMARD combinations, has clear implications for treatment stratification within the window of opportunity. Time-dependent data suggest clinical response to combination DMARDs may be more rapid than previously appreciated, and treatment response in the first month may have prognostic significance. Confirmation in other cohorts will be required to determine the generalisability of this notion.

~~Our time dependent data suggest the need for a controlled trial of early treatment change in patients who fail to respond to combination DMARDs in the first month of therapy. Female gender, smoking, over weight and abnormal LFT increase the risk of early poor response.~~

DATA SHARING, COMPETING INTERESTS AND FUNDING

No additional data are available. The authors declare no competing interests in relation to this article. Supported by NHMRC grants 351439 and 569938. R.T. is supported by Arthritis Queensland and an ARC Future Fellowship.

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TABLES:

Table 1. Baseline characteristics of the patients

Baseline variable	Value	
~~Baseline variable~~	Included patients (n=101)	Excluded patients (n=54)
Female*	60 (59.4%)	44 (81%)
Age†, years	54 (12)	48 (15)
Symptom duration, months$	12 (5, 12)	6 (4, 12)
Smoking		
Current Smokers	26 (25.7%)	8 (15%)
Ex-Smokers	29 (28.7%)	26 (48%)
Education		
Primary		5 (14%)
Secondary		24 (66%)
Tertiary		9 (24%)
Weight†, Kg	77.10 (19.68)	80 (24)
SBP†, mm Hg	127 (15)	120 (17)**
DBP†, mm Hg	73 (10)	70 (10)
RF*	89 (88.1%)	42 (77%)
ACPA*	51 (50.5%)	9 (36%)
ESR$, mm/hour	25 (12, 46)	16 (10, 34)
CRP$, mg/liter	9.7 (19, 39)	6 (2, 12)
Lymphocytes†, x 10^9/L	1.94 (0.67)	2.1 (1.3, 2.5)
Neutrophils†, x 10^9/L	5.12 (2.50)	5 (3, 6.8)
LFT (AST) $, U/L	20.50 (16.50, 24.00)	18.5 (17, 23)

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LFT (ALT) [$], U/L	19 (14, 27)	19 (14, 23)
~~eGFR[$], mL/min~~	~~89 (74, 90)~~	
~~Glucose[$], mmol/L~~	~~5.2 (4.9, 5.75)~~	

* Values are n (%); [†] values are the median (SD); [$] values are the median (IQR). SD = standard deviation; IQR = interquartile range; RF = Rheumatoid Factor; ~~SBP = systolic blood pressure; DBP = diastolic blood pressure;~~ ACPA = anti-citrullinated peptide antibody; ESR = erythrocyte sedimentation ratio; CRP = C reactive protein; LFT = liver function test; AST = aspartate aminotransferase; ALT = alanine aminotransferase~~;~~ **p=0.002.~~eGFR = estimated glomerular filtration rate~~.

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Table 2. Change in median pain VAS scores, DAS and HAQ scores (95% CI) over 1 year

	Baseline	6 month	1 year	Change at 6 months	p	Change at 1 year	p
Pain Score	55 (48, 62)	37.9 (31.7, 44.1)	24.2 (17.7, 30.6)	-21.9 (-30.8, -13)	<0.001	-27.4 (-35.6, -19.1)	<0.001
DAS4v	4.5 (4.1, 4.8)	3.4 (3.1, 3.7)	3.2 (2.9, 3.4)	-1.3 (-1.8, -0.8)	<0.001	-1.5 (-2, -1.1)	<0.001
mHAQ	0.6 (0.5, 0.8)	0.44(0.3, 0.6)	0.3 (0.2, 0.4)	-0.3 (-0.5, -0.1)	0.003	-0.3 (-0.4, -0.2)	<0.001
Proportion of patients with:							
DAS ≤ 2.6	12 (14.8%)	25 (25%)	29 (29%)				
DAS ≤ 3.2	18 (22%)	48 (48%)	52 (52%)				

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Table 3. Frequency of steroid use over the study

Treated with:	Study duration (weeks)					
	0 (0)	**4**	**8**	**12**	**16**	**24**
Oral Steroid n (%)	16 (15.8)	17 (16.8)	14 (13.9)	11 (10.9)	1 (1)	1 (1)
IA steroid	21 (20.7)	2 (2)	4 (4)	2 (2)	0	0
Any steroid	37 (36.7)	19 (18.8)	18 (17.8)	13 (12.9)	1 (1)	1 (1)
Oral and IA steroid	3 (3)	1 (1)	2 (2)	0	0	0

IA intra-articular

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Table 4. Variables influencing DAS scores at 4 and 12 weeks of study – Univariate regression

	DAS4v Week 4		DAS4v Week 12	
	ß	p	ß	p
Female	0.68	0.009	0.46	0.059
Smoking				
Ex-smokers vs non-smokers	-0.55	0.026	-0.17	0.53
Current smokers vs non-smokers	-0.80	0.003	-0.42	0.10
LFT (ALT)	0.03	0.01	0.04	0.63
Weight*CRP	0.002	0.029	0.002	0.02
Oral or IA Steroid	0.11	0.67	0.01	0.98
Anti-CCP > 6	0.0004	0.99	0.67	0.08

Values are regression coefficient (ß) and p-value. Regression co-efficient at each time point for RF = 0. CRP = C reactive protein; LFT = liver function test; ALT = alanine aminotransferase.

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Table 5. Effects of time-varying risk factors individually on DAS28 scores over 1 year of study – Univariate regression

	DAS4v		
	ß	95% CI	p
Female	0.45	0.09, 0.81	0.014
Age	0.001	-0.13, 0.02	0.82
Smoking:			
Ex-smokers vs non-smokers	-0.27	-70, 0.16	0.22
Current smokers vs non-smokers	-0.48	-0.91, -0.06	0.026
SBP	0.10	0.08, 0.20	<0.001
DBP	0.10	0.04, 0.20	0.004
Lymphocyte	0.04	-0.09, 0.17	0.55
Neutrophil	0.16	0.10, 0.22	<0.001
ESR	0.03	0.03, 0.04	<0.001
CRP	0.02	0.01, 0.02	<0.001
LFT-AST	-0.004	-0.01, 0.003	0.25
LFT-ALT	-0.003	-0.009, 0.004	0.44
Weight*CRP	0.002	0.001, 0.003	<0.001
Weight*ESR	0.004	0.003, 0.005	<0.001
Oral or IA steroid	0.66	0.34, 0.99	P<0.01
Anti-CCP > 6	0.001	-0.001, 0.002	0.36

Regression co-efficient at each time point for RF = 0.

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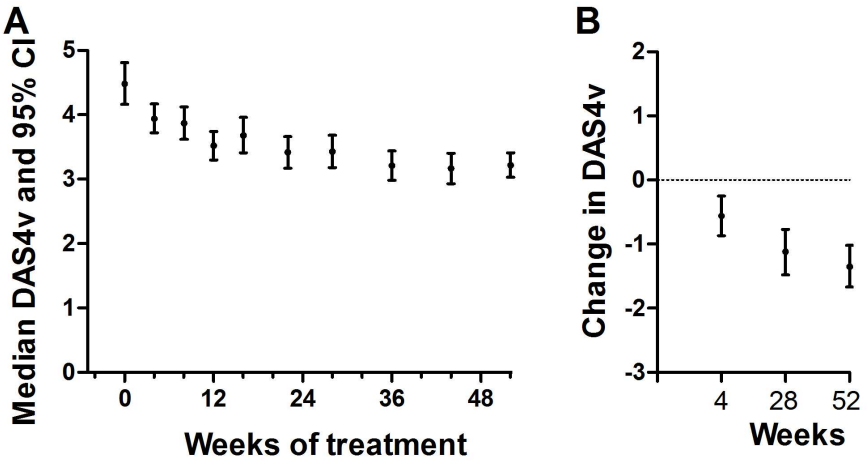
FIGURES :

Figure 1. Distribution of DAS4v over the study period. A: The median and 95% CI are plotted for each visit over the 52 week study period. **B:** Changes in DAS4v over 4, 28 and 52 weeks are indicated. **C:** The changing distribution in DAS4v in the sample is plotted at baseline, 4, 28 and 52 weeks.



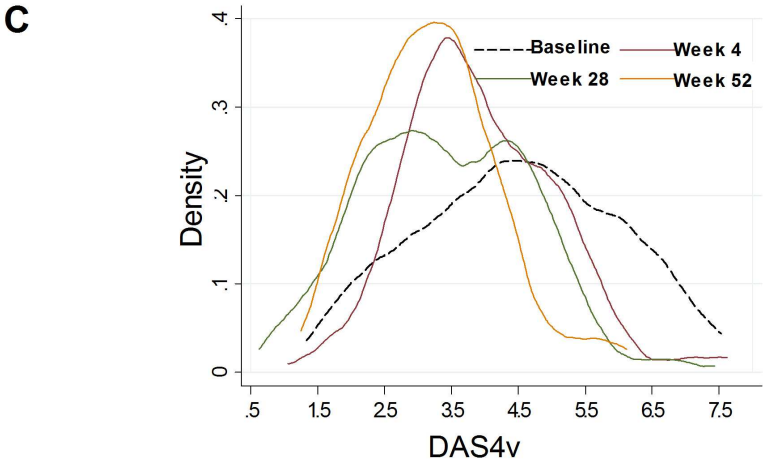
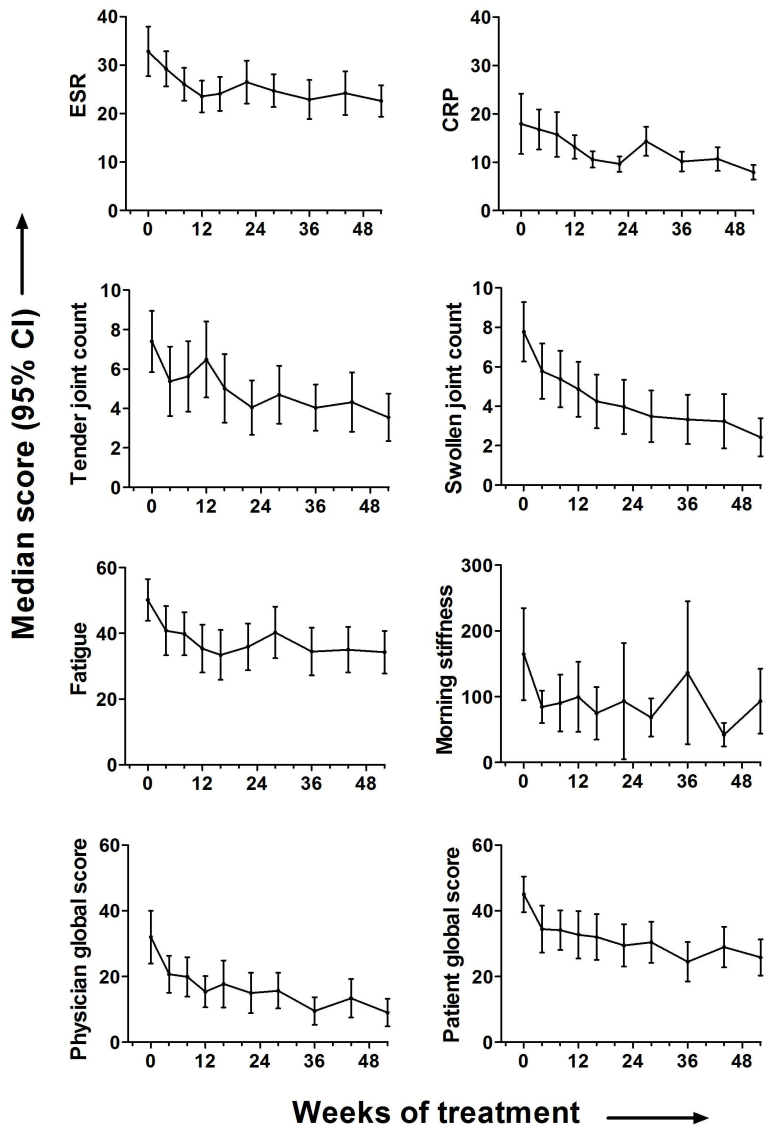


Figure 2. Variation in the disease activity parameters over the study period. The median and 95% CI are plotted for each visit over the 52 week study period for ESR, CRP, tender joint count, swollen joint count, fatigue, morning stiffness, patient global and physician global scores.



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	x
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	x
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	x
Objectives	3	State specific objectives, including any prespecified hypotheses	x
Methods			
Study design	4	Present key elements of study design early in the paper	x
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	x
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	x
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	x
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	x
Bias	9	Describe any efforts to address potential sources of bias	x
Study size	10	Explain how the study size was arrived at	x
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	x
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	x
		(*b*) Describe any methods used to examine subgroups and interactions	x
		(*c*) Explain how missing data were addressed	x
		(*d*) If applicable, explain how loss to follow-up was addressed	x
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	x
		(b) Give reasons for non-participation at each stage	x
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	x
		(b) Indicate number of participants with missing data for each variable of interest	x
		(c) Summarise follow-up time (eg, average and total amount)	x
Outcome data	15*	Report numbers of outcome events or summary measures over time	x
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	x

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		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	x
Discussion			
Key results	18	Summarise key results with reference to study objectives	x
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	x
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	x
Generalisability	21	Discuss the generalisability (external validity) of the study results	x
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	x

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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