Variation and implications of treatment decisions in early Rheumatoid Arthritis: results from a nationwide cohort study

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ABSTRACT

Objectives: Trial data have provided an evidence base to guide early treatment in rheumatoid arthritis (RA). Few studies have investigated rheumatologists' adherence to guidelines, and subsequent impact on outcomes. The objectives of this study are to characterise baseline prescribing for patients with RA across the National Health Service, identifying treatment decisions that associate with patient outcomes.

Methods: A nationwide audit of RA collected information on treatment choices, disease activity scores, and sociodemographic factors at baseline. Treatment response was assessed at three months. Multilevel regression models were used to characterise departmental variations in prescribing. Heat maps were used to visualise geographical variation. Mixed

effects regression models were constructed to assess the relationship between treatment decisions and disease outcomes, adjusting for patient and department level covariates. **Results:** a total of 7,154 patients with a diagnosis of RA were recruited from 136 departments. There was broad variation in prescribing choices, even between departments near one another, with evidence of substantial deviation from guidelines. Over 75% of patients received glucocorticoids, fewer than half received combination conventional disease modifying antirheumatic drugs. Early glucocorticoid therapy associated with achieving a good treatment response, odds ratio 1.93 (95% confidence interval 1.31 to 2.84, p value 0.001). The association was maintained following propensity modelling and imputation.

Conclusion: Guideline adherence varies between departments and cannot be explained by case-mix alone. Departments that prescribe early adjunctive steroid achieve better short-term outcomes. Further research should work to ensure that the early arthritis evidence base translates into better outcomes for patients.

KEY WORDS: Early rheumatoid arthritis**,** Health services research**,** Treatment decisions

Rheumatology key messages

1. This study is the first to characterise early RA national treatment variations between departments.
2. Early RA treatment decisions predict patient outcomes as early as three months after diagnosis.
3. Treating RA according to guidelines varies, improving compliance is an efficient intervention to improve outcomes.

INTRODUCTION

Trial data support prompt commencement of therapy in newly diagnosed rheumatoid arthritis (RA)(1). This has led to the widespread adoption of a 'treat to target' approach with aggressive escalation of therapy in the first three months following diagnosis. The initial drug strategy may involve one or more conventional disease modifying antirheumatic drug (cDMARD), with or without glucocorticoids. Clinician preference and comfort with certain medications continue to be key in therapy selection(2). European and American guidelines for newly diagnosed RA recommend(3-5):

- First line treatment with a cDMARD preferably methotrexate, with dose escalation;
- Consideration of short-term bridging glucocorticoids, and;
- Combination disease modifying treatment if treatment target is not achieved despite dose escalation.

Previous guidance advocated combination cDMARD therapy and glucocorticoids as first line therapy. A review of the trial data comparing cDMARD monotherapy to combination therapy showed inconsistent evidence of benefit in terms of disease activity, patient reported outcomes, or adverse events, from adding a second disease modifying therapy at baseline(6).

The shift in emphasis away from recommending glucocorticoids in all patients at baseline was driven by a review of trial data that identified a single study(7) which was found to have a substantial risk of bias(8). It was concluded that further evidence was required to assess if glucocorticoids are beneficial in early RA. A further review of four trials reported improvements in disease activity, but with a high risk of bias and a lack of statistical power to

meet primary endpoints. The authors concluded that combining glucocorticoid therapy and cDMARDs may be beneficial(6).

Trial data have given an inconsistent picture of the most efficacious pharmacologic approach in early RA. Consequently, guidelines allow treating physicians flexibility in their initial treatment approaches. This inevitably leads to variation in therapy choices. Large observational prospective cohorts offer an opportunity to assess the degree of prescribing variation and its subsequent impact on disease outcomes in a heterogenous population.

Objectives

Here we will utilise a large national early RA cohort to characterise cDMARD and glucocorticoid prescribing patterns across England and Wales, and identify treatment decisions that associate with improved clinical outcomes.

METHODS

Sample and measures

The first National clinical audit of early inflammatory arthritis (EIA) ran from early 2014 to late 2015 across England and Wales. During this time, UK guidelines advocated treatment initiation with combination cDMARDs and glucocorticoids to all patients.

Adult patients presenting with symptoms consistent with RA were eligible for inclusion. This included any patient with a new onset of inflammatory arthritis >six weeks duration and either a positive rheumatoid factor (RF) or anti-cyclic citrullinated protein (anti-CCP) antibody or a swollen joint count ≥five.

Treatment decisions in early RA

All rheumatology departments were required to participate. Information was collected via physician and patient questionnaires at the initial rheumatology appointment. Demographic information was collected including age, gender, smoking status, ethnicity, work status, and partial patient postcode. Clinical information collected included time to referral, rheumatology review, treatment initiation including therapy choices, and if the referral letter suggested a diagnosis of EIA. Laboratory investigations including anti-CCP antibody status, RF antibody status, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were recorded. Examination findings including tender and swollen joint counts and a patient reported visual analogue scale of global health were also collected. A proxy rank of the index of multiple deprivation (IMD), a composite measure of socioeconomic position (SEP), was calculated from partial patient postcodes by identifying all lower super output areas (LSOAs) covered by each postcode. The corresponding IMD scores were then averaged for each patient, allowing calculation of a ranking of SEP across the cohort.

The disease activity score (DAS-28) is a validated measure of RA disease activity that is widely used to assess response to treatment(9). It incorporates the tender and swollen joint counts, a patient reported global health and either ESR or CRP to provide a score of disease activity ranging from 0 to 10, with a higher score indicating greater severity. The European League Against Rheumatism (EULAR) has developed a DAS-28 response criteria, stratifying patients as having achieved a good, moderate or no response to therapy(10).

Those with a diagnosis of RA had a DAS-28 score calculated at baseline and three months follow up. The scores were used to identify if patients had achieved a good EULAR DAS-28 response to therapy at three months follow up.

Patient and Public Involvement

A patient representative was engaged and consulted in the design and delivery of the national audit project. Approval to conduct research using these National Clinical Audit data was obtained from HQIP. No informed patient consent was required, as this dataset was created from routinely collected data during clinical practice.

Statistical analysis

Baseline and demographic variables, including prescribing patterns, were described using summary statistics, assessing differences between two treatment response groups at three months follow up: (1) patients that achieved a good EULAR DAS-28 response, and; (2) patients that achieved moderate or no EULAR DAS-28 response. Frequencies and patterns of missing data were assessed and tabulated.

Variation in prescribing

To characterise departmental variations in prescribing, mixed-effects logistic regression models were constructed with department included as a random effect. The random effect can be considered as capturing the difference between the department mean and the overall mean for the sample, allowing for the estimate of case-mix adjusted rates. Departmental effects on the proportion of patients prescribed glucocorticoids, methotrexate, and combination cDMARD therapy were plotted on three separate caterpillar graphs.

In order to provide a geographical picture of prescribing variation, departmental prescribing of glucocorticoids, methotrexate and combination cDMARDs were presented in heatmaps by linking the national audit dataset to longitude and latitude coordinates data. Mapping was

performed using the grmap software package, an update of the spmap program developed in 2007(11), in Stata 15.

Treatment decisions and disease outcome

Three mixed effects logistic regression models were constructed to assess the relationship between baseline treatment decisions and disease activity at three months follow up:

Model 1. cDMARD combination therapy vs cDMARD monotherapy as a predictor of achieving a good EULAR DAS-28 response;

Model 2. Methotrexate therapy vs no methotrexate therapy as a predictor of achieving a good EULAR DAS-28 response, and;

Model 3. Glucocorticoid therapy vs no glucocorticoid therapy as a predictor of achieving a good EULAR DAS-28 response.

The three models contain overlapping groups and are designed to test three distinct hypotheses, rather than to compare between models. Covariate selection across the three models was determined a priori. The models were run unadjusted initially. They were then repeated with adjustment for: age; gender; ethnicity; smoking status; proxy IMD quintile; work status; symptom duration; autoimmune antibody status; referral time; rheumatologist review time. A propensity score weighted estimate was also calculated for each model to account for confounding by indication. Further details of this can be found in the supplementary material, section Propensity modelling, supplementary tables S1A, S1B, and S1C, available at *Rheumatology* online). The department where rheumatology care took place was included in all the models as a random effect. Incomplete data were handled by two

approaches, repeated for all three models: (1) non-responder imputation (NRI), whereby those with insufficient data to calculate a EULAR DAS-28 disease response were assumed to have not achieved a good response, and; multiple imputation (MI) using iterative chained equations with 20 cycles to impute incomplete confounder, predictor, and outcome variables. All analyses were conducted using Stata version 15 statistical software package.

RESULTS

Between February 2014 and October 2015, 7,154 patients with a diagnosis of RA were recruited to the National Clinical Audit from across England and Wales. Table 1 details baseline and demographic characteristics including prescribing choices and proportions of missing data. 2,256 (32%) had sufficient information at baseline and three months follow up to allow calculation of a EULAR DAS-28 treatment response. The mean DAS-28 score remained moderately elevated at 3 months follow up, with a mean of 3.5 (SD 1.5).

Table 2 details baseline and demographic characteristics stratified by EULAR DAS-28 response. There were a lower proportion of females, a lower median symptom duration, and a higher proportion of patients reviewed by a rheumatologist within 21 days of referral in the good treatment response group. Demographic differences between those with and without complete DAS-28 data are detailed in Supplementary Table S2, available at *Rheumatology* online).

Variation in prescribing

Median Departmental prescribing of glucocorticoids was 83% (Interquartile range (IQR) 73% to 89%) of patients seen. Combination cDMARD median prescribing proportion was 36% (IQR

19% to 57%), while methotrexate departmental median prescribing proportion was 77% (IQR 66% to 88%).

Figure 1 shows the variation in the baseline prescribing of: (a) combination cDMARDs; (b) inclusion of methotrexate as a first line agent, and; (c) glucocorticoids. The figure displays adjusted point estimates with confidence intervals. Where the confidence interval boundaries do not cross the horizontal mean bar, this is evidence of clinically significant variation in practice not explained by patient characteristics. There was variation in practice in all prescribing characteristics assessed. The magnitude of variation is greatest in the prescribing of combination cDMARDs between the departments included.

Prescribing variations are presented as heat maps in figure 2. There was broad variation across geographic regions. In general, there was marked variation identified even within close geographical areas. For example, there were striking prescribing differences between departments within Greater London.

Treatment decisions and disease outcome

Adjusted mixed effects logistic regression models showed an association between baseline glucocorticoids and achieving a good EULAR DAS-28 response at three months follow up, with an odds ratio of 1.93 (95% confidence interval 1.31 to 2.84, p value 0.001). Neither combination cDMARD therapy (versus monotherapy) nor methotrexate (versus non-methotrexate cDMARD strategies) predicted a good EULAR DAS-28 response. Odds ratios and confidence intervals are detailed in table 3. The propensity score weighted estimates were similar to the fully adjusted models, with a small strengthening of the association between baseline glucocorticoids and a good EULAR DAS-28 response (odds ratio 2.02, 95% confidence interval 1.31 to 3.11). The results were consistent when analyses were repeated in propensity

weighted and imputation models (see table 3 and Supplementary Table S3, available at *Rheumatology* online).

DISCUSSION

This analysis has characterised prescribing patterns across England and Wales using a national prospective cohort. In comparison with other cohorts disease activity at three months was high, with a mean DAS-28 of 3.5 at follow up, compared to 3 month DAS-28 scores of 2.2 in a Scandinavian cohort (12). The observed difference in disease severity may be due to variations in sociodemographic and ethnic mix of sample populations, and/or local guidelines placing a greater emphasis on early intra-articular glucocorticoid administration for swollen joints, which has been shown to associate with improved outcomes (13). The UK guidelines in contrast suggest that short course bridging glucocorticoids should be considered to control disease activity but does not discuss route of administration.

There were substantial differences in prescribing rates of glucocorticoids, combination cDMARDs, and methotrexate between departments. This is consistent with previous work on cDMARD UK prescribing patterns(14, 15).

The adjusted models suggest that this high degree of variation cannot be explained by local differences in patient factors such as SEP, or departmental factors such as staffing levels. It is more likely that the observed variation is due to clinician preferences driven by a lack of agreement from clinical trial data on the most efficacious treatment approach.

Treatment decisions in early RA

The heat maps indicated that there was no clear geographical pattern in prescribing decisions. Nearby departments often displayed disparate clinical behaviours. This reinforces the view that clinician preference is the main driver behind the observed variation. Vast efforts and resource are invested globally in the creation of evidence-based guidelines. Guidelines for prescribing in early RA currently advocate initial cDMARD monotherapy with consideration of glucocorticoids, and escalation to combination cDMARD therapy if disease control is not achieved. It should be noted that at the time of data collection UK guidelines recommended combination cDMARD therapy at baseline(3). Under 40% of patients received combination cDMARDs in line with the old guidance. The level of variation presented here in newly diagnosed RA is substantial. It is unlikely that this observation is unique to England and Wales(16-18). As a community, rheumatologists need to find consensus on the value of guideline compliance, and how can they best disseminate the information and improve uptake amongst colleagues.

Glucocorticoid use at baseline associated with achieving a good disease outcome at 3 months follow up in a mixed effects logistic regression model with extensive adjustment for confounding. This is consistent with trial data(18-20) and supports the role of glucocorticoids at diagnosis in RA to achieve low disease activity as rapidly as possible. The efficacy of glucocorticoids must be balanced with their associated side effects. Combined trial data suggest low dose or short term glucocorticoid use leads to few adverse events, whereas observational studies suggest associations between low dose glucocorticoids and cardiovascular disease, infection, and osteoporosis(21). Adverse event information was not collected as part of this study, so its impact on the findings here cannot be assessed. In contrast to glucocorticoids, there was no association between inclusion of methotrexate in the initial treatment strategy or combination cDMARD therapy and a good disease outcome.

This is consistent with the lack of consensus reported in trial data(6). An important caveat is that the data included here are limited to three months follow up, which may be too short to capture the effect of slower acting therapies. Furthermore, trial data support the role of cDMARDs in combination with biologic DMARD therapy, particularly methotrexate(22). This could not be assessed here due to the length of follow up.

This is an observational study so causality cannot be inferred from the findings. The results represent a picture of 'real world' prescribing practices and their impact on heterogenous populations, outside the controlled conditions found in clinical trials. The associations remained statistically significant even after adjustment for confounders. A limitation of this study is that follow up was only captured to three months, with no data collected on comorbidities. cDMARDs typically require two to three months of therapy before improvements in disease activity are appreciated. With a longer follow up it is possible that combination cDMARD and methotrexate therapy would have associated with improved outcomes, with a reduction in the efficacious effect of glucocorticoids due to adverse effect burden. A key determinant of glucocorticoid adverse effects and course length is the route of administration, with those commenced on oral glucocorticoids more likely to be exposed to higher doses and more adverse effects as a result. The route of glucocorticoid administration was not collected as part of the national audit, so cannot be commented on further here. However, given the importance of achieving low disease activity as rapidly as possible(23), the data presented here in support of glucocorticoid use deserve careful thought.

The national audit relied on clinician goodwill for data collection and case ascertainment. It is likely that there was incomplete case capture and a skew towards departments with sufficient staffing and infrastructure to assist with data collection. It is possible that prescribing

variation is wider than we have reported. Within the patients recruited, there was a high degree of incomplete data, particularly follow up DAS-28. This was handled using MI and NRI approaches, with consistency in the findings. The proportion of missing follow up DAS-28 data varied between departments but was not predictive of DAS-28 response in sensitivity analyses. Despite these mitigations, the proportions of missing outcome data are a limitation of this study.

CONCLUSION

Despite much work on clinical guidelines, clinicians still vary enormously in their practice when managing RA. In the real-world setting, such decisions do appear to correlate with clinical outcome. Early use of steroids predicts a better chance of EULAR DAS response. In contrast the selection of cDMARD strategy appeared not to predict response.

New therapies licensed for RA over the next decade will bring incremental benefits to patients at a high economic cost. Understanding how we can ensure optimal care across healthcare systems using existing therapies offers a simple and cost-effective alternative to improve patient care.

Disclosure statement:

JG has received honoraria from Abbvie, Celgene, Janssen, Pfizer, and UCB; MY has received honoraria from UCB. The other authors have declared no conflicts of interest.

FUNDING

This work was supported by The British Society for Rheumatology and Versus Arthritis, who fund MYs' salary.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the contribution of Dr Neil Snowden to the National Early Inflammatory Arthritis Audit and this study.

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Table 1. Baseline characteristics, quality of care, and therapy choices for all patients diagnosed with rheumatoid arthritis.

N = 7154		Number Missing (%)
Age, mean (SD)	58 2 (15.2)	39 (0.5)
Female, %	63.5	39 (0.5)
IMD rank, median (Q1, Q3)	645 (303 to 1035)	814 (11.4)
White European, %	90.8	1095 (15.3)
Current smoker, %	22.1	1334 (18.6)
Full time paid employment, %	39.4	1429 (20.0)
Seropositive, %	78.1	1874 (26.2)
Baseline DAS-28, mean (SD)	5.1 (1.4)	2477 (34.6)
Follow up DAS-28, mean (SD)	3.5 (1.5)	4485 (62.5)
Rheumatology Departments	136	0
Symptom duration in days, median (Q1, Q3)	102 (52 to 218)	0
Referral within 3 days, %	16.7	0
Review within 21 days, %	38.0	68 (1.0)

Treatment within 90 days, %	60.1	935 (13.1)
Baseline Therapy		
cDMARD combination therapy, %	39.9	1603 (22.4)
Glucocorticoid therapy, %	80.0	126 (1.8)
Methotrexate therapy, %	73.9	1482 (20.7)

Patients who were positive for RF and/or anti-CCP were considered seropositive. cDMARD = conventional disease modifying antirheumatic drug.

Table 2. Baseline characteristics and referral/review/treatment times, stratified by EULAR DAS28 response.

	Achieved moderate or no EULAR DAS response	Achieved good EULAR DAS response	p value
	(N = 1378)	(N = 878)	
Age, mean (SD)	59.1 (14.2)	59.7 (14.6)	0.37
Female	915 (67.0%)	530 (60.6%)	0.002
IMD rank, median (Q1, Q3)	626 (301, 1046)	668 (326, 1006)	0.52
White European	1132 (91.0%)	714 (92.0%)	0.43
Current smoker	298 (25.0%)	167 (22.2%)	0.16
Full time paid employment	448 (38.3%)	264 (35.8%)	0.27
Seropositive	937 (83.7%)	605 (85.1%)	0.44
Symptom duration in days, median (Q1, Q3)	103 (53, 225)	89 (50, 75)	0.0013
Referral letter states EIA	1256 (91.2%)	798 (90.9%)	0.83
Referral within 3 days	207 (15.0%)	139 (15.8%)	0.60
Review within 21 days	508 (36.9%)	392 (44.6%)	<0.0001
Treatment within 90 days	844 (68.7%)	546 (72.1%)	0.11

Patients who were positive for RF and/or anti-CCP were considered seropositive.

Table 3. Mixed effects models of treatment decisions associations with a good EULAR28 response.

Good EULAR DAS-28 response	Odds Ratio	95% confidence interval	p value
Monotherapy and combination therapy (monotherapy = reference)			
Unadjusted (N = 1,921)	0.93	0.76 to 1.14	0.50
Adjusted (N = 1,037)	1.02	0.77 to 1.34	0.91
Propensity (N = 1,037)	0.93	0.62 to 1.39	0.72
Multiple Imputation	1.05	0.90 to 1.23	0.52
Methotrexate therapy (no methotrexate therapy = reference)			
Unadjusted (N = 1,945)	0.89	0.71 to 1.13	0.36
Adjusted (N = 1,050)	0.88	0.64 to 1.22	0.45
Propensity (N = 1,045)	0.89	0.59 to 1.34	0.59
Multiple Imputation	0.99	0.80 to 1.22	0.92
Glucocorticoid therapy (no glucocorticoid therapy = reference)			
Unadjusted (N = 2,242)	1.63	1.23 to 2.15	0.001
Adjusted (N = 1,211)	1.93	1.31 to 2.84	0.001
Propensity (N = 1,211)	2.01	1.31 to 3.11	0.002
Multiple Imputation	1.63	1.36 to 1.96	<0.001

Further detail on propensity and imputation models are in the supplementary material, available at Rheumatology *online. Adjustment for age, gender, ethnicity, smoking status, work status, index of multiple deprivation, referral time, rheumatology review time, antibody status, and symptom duration. The department where treatment took place was included as a random effect in all models.*

Figure legends

Figure 1. Caterpillar plots of combination cDMARD, methotrexate, glucocorticoid prescribing by department. (1a) combination cDMARD, (1b) methotrexate, (1c) glucocorticoid prescribing by department.

Figure 2. Heat maps of combination cDMARD, methotrexate, glucocorticoid prescribing by department. 1a) combination cDMARD, (1b) methotrexate, (1c) glucocorticoid prescribing by department

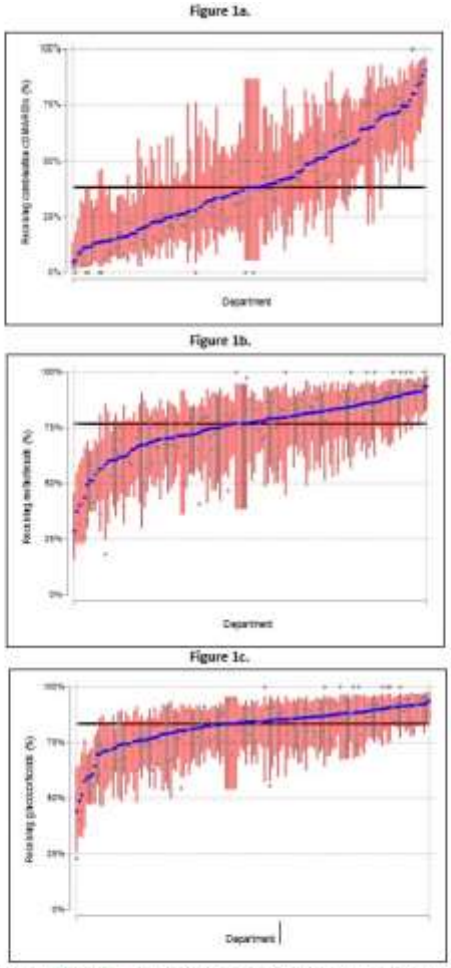
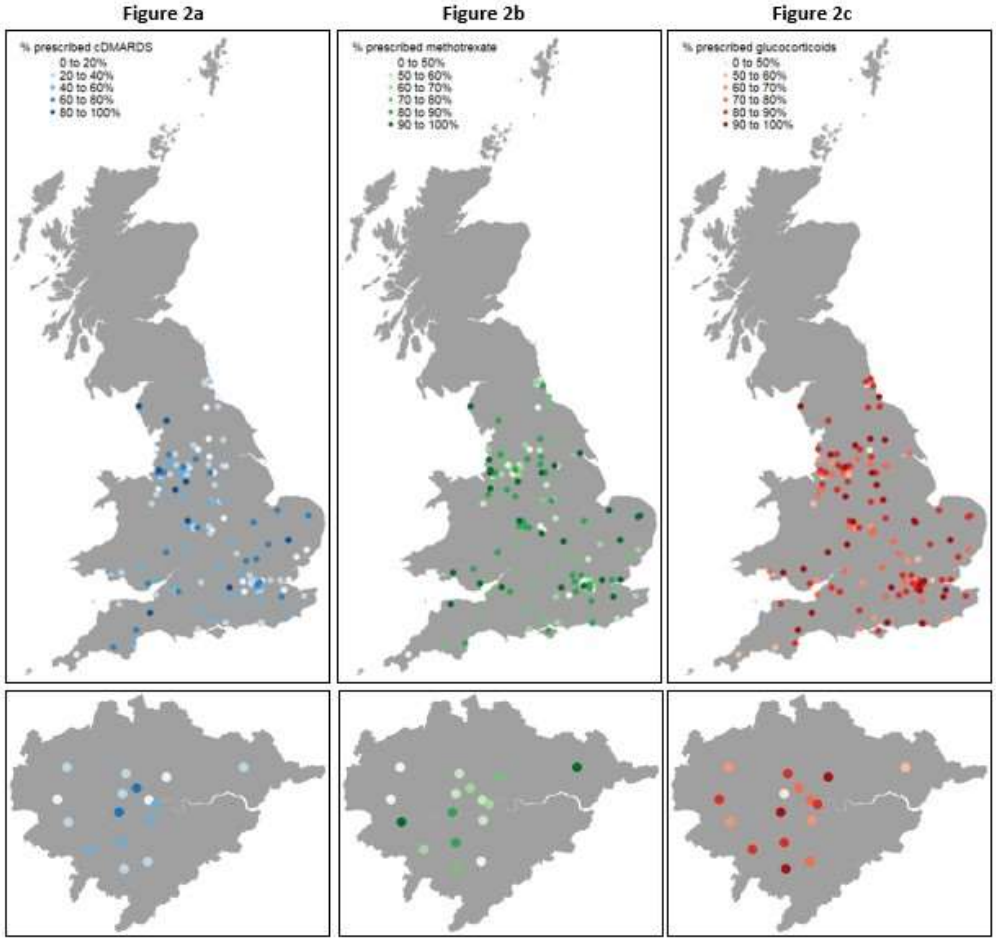


Figure 1. Caterpillar plots of (1a) combination cDMARD, (1b) methotrexate, and (1c) glucocorticoid prescribing by department. The gray markers are the departmental proportions of prescribing (the number prescribed a given drug as a proportion of patients seen in that department). The blue markers are the predicted random departmental effect on prescribing from the mixed effects models, with 95% confidence intervals in red. The black horizontal line represents the overall mean.

Figure 1. Caterpillar plots of (1a) combination cDMARD, (1b) methotrexate, and (1c) glucocorticoid prescribing by department. The gray markers are the departmental proportions of prescribing (the number prescribed a given drug as a proportion of patients seen in that department). The blue markers are the predicted random departmental effect on prescribing from the mixed effects models, with 95% confidence intervals in red. The black horizontal line represents the overall mean.

212x220mm (96 x 96 DPI)

Figure 2. Heat maps of departmental prescribing.



Heat maps of combination cDMARDs (2a), methotrexate (2b), and glucocorticoids (2c) prescribing across England and Wales, with a zoomed in view of Greater London. Prescribing varied widely across England and Wales, with no clear regional patterns.

Heat maps of combination cDMARDs (2a), methotrexate (2b), and glucocorticoids (2c) prescribing across England and Wales, with a zoomed in view of Greater London. Prescribing varied widely across England and Wales, with no clear regional patterns

161x177mm (96 x 96 DPI)

SUPPLEMENTARY MATERIAL

Propensity modelling.

Baseline patient covariates, determined a priori, were included in three logistic regression models to predict three baseline treatment choices:

- DMARD monotherapy vs DMARD combination therapy;
- methotrexate vs no methotrexate;
- glucocorticoid therapy vs no glucocorticoid therapy.

The models were used to calculate propensity scores for each patient. The propensity score model included age, sex, ethnicity, smoking status, work status, SEP, autoimmune antibody status, and symptom duration. On assessment of the model, the inverse of the probability performed the best across the three treatment choices when comparing standardised differences. The tables below detail the weighted means and standardised means, before and after propensity model weighting.

Supplementary Table S1A: Propensity modelling for DMARD monotherapy vs DMARD combination therapy.

Before weighting			
	DMARD combination therapy	DMARD monotherapy	Standardised difference
age	57.24	57.84	-0.042
proportion male	0.36	0.38	-0.031
proportion white	0.92	0.91	0.033
proportion smokers	0.24	0.26	-0.037
proportion in paid work	0.42	0.38	0.08
deprivation quintile	3.1	3.03	0.05
proportion autoantibody positive	0.8	0.78	0.058
symptom duration (days)	231.79	294.62	-0.097
After weighting			
age	57.58	57.6	-0.002
proportion male	0.37	0.37	-0.003
proportion white	0.91	0.91	0
proportion smokers	0.25	0.25	0.001
proportion in paid work	0.4	0.4	-0.002
deprivation quintile	3.05	3.05	-0.001
proportion autoantibody positive	0.79	0.79	0.001
symptom duration (days)	266.51	270.19	-0.006

Supplementary Table 1B: Propensity modelling for methotrexate vs no methotrexate therapy.

Before weighting			
	Methotrexate therapy	No Methotrexate therapy	Standardised difference
age	57.83	57.15	0.046
proportion male	0.37	0.36	0.037
proportion white	0.92	0.88	0.138
proportion smokers	0.24	0.26	-0.042
proportion in paid work	0.41	0.37	0.078
deprivation quintile	3.06	3.04	0.013
proportion autoantibody positive	0.78	0.8	-0.048
symptom duration (days)	253.38	309.93	-0.082
After weighting			
age	57.66	57.68	-0.002
proportion male	0.37	0.37	0.001
proportion white	0.91	0.91	0.001
proportion smokers	0.25	0.25	0.001
proportion in paid work	0.4	0.4	0.003
deprivation quintile	3.05	3.05	0.002
proportion autoantibody positive	0.79	0.79	-0.007
symptom duration (days)	275.87	277.59	-0.003

Supplementary Table 1C: Propensity modelling for glucocorticoid therapy vs no glucocorticoid therapy.

Before weighting			
	Glucocorticoid therapy	No Glucocorticoid therapy	Standardised difference
age	58.3	55.01	0.223
proportion male	0.37	0.35	0.042
proportion white	0.91	0.86	0.159
proportion smokers	0.24	0.23	0.023
proportion in paid work	0.38	0.45	-0.142
deprivation quintile	3.04	3.06	-0.011
proportion autoantibody positive	0.78	0.78	-0.005
symptom duration (days)	251.84	345.66	-0.134
After weighting			
age	57.66	57.66	0
proportion male	0.37	0.36	0.007
proportion white	0.9	0.9	0.003
proportion smokers	0.24	0.25	-0.014
proportion in paid work	0.39	0.39	0.001
deprivation quintile	3.05	3.04	0.005
proportion autoantibody positive	0.78	0.79	-0.015
symptom duration (days)	286.51	286.54	0

Handling missing data

There were high levels of missing data, detailed in table 1 of the paper. A breakdown of demographic differences between those with and without complete DAS-28 outcome data is detailed in table 2. Two approaches were taken to account for this: (1) Non responder imputation, and; (2) Multiple imputations using chained equations.

Supplementary Table S2: Patient demographics stratified by those with complete and incomplete DAS-28 data.

	Complete DAS-28 data at baseline and follow up	Incomplete DAS-28 data at baseline or follow up	p values
	(N = 2256)	(N = 4898)	
Age, mean (SD)	59.3 (14.4)	57.6 (15.6)	<0.0001
Female	64.5%	63.4%	0.37
IMD rank, median (Q1, Q3)	626 (297, 1016)	640 (300, 1022)	0.69
White European	91.4%	90.5%	0.24
Current Smoker	24.0%	21.2%	0.017
Full time paid employment	37.3%	40.4%	0.026
Seropositive	84.3%	74.8%	<0.0001
DAS-28 at baseline, mean (SD)	5.2 (1.3)	4.9 (1.4)	<0.0001
Symptom duration in days, median (Q1, Q3)	96 (51, 204)	107 (54, 234)	0.0097

Supplementary Table S3: Mixed effects logistic regression models following non responder imputation.

Good EULAR DAS-28 response	Odds Ratio	95% confidence interval	p value
Monotherapy and combination therapy (monotherapy = reference)			
Adjusted	1.14	0.90 to 1.46	0.3
Methotrexate therapy (no methotrexate therapy = reference)			
Adjusted	1.24	0.95 to 1.64	0.1
Glucocorticoid therapy (no glucocorticoid therapy = reference)			
Adjusted	2.53	1.79 to 3.58	<0.001

Figure 1a.

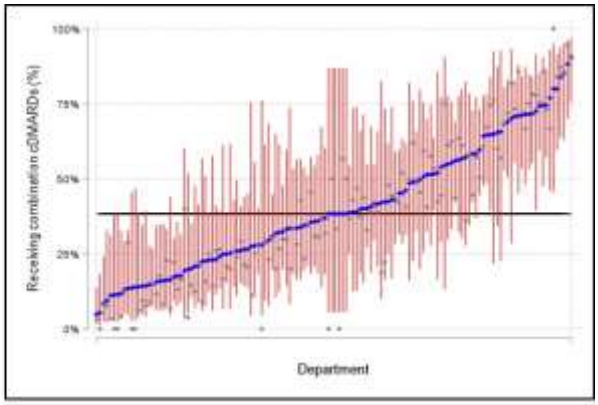


Figure 1b.

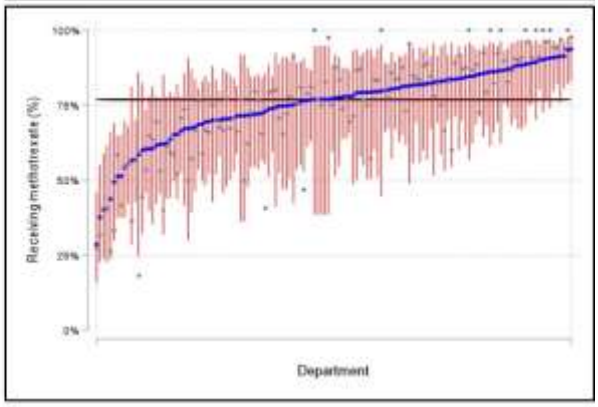


Figure 1c.

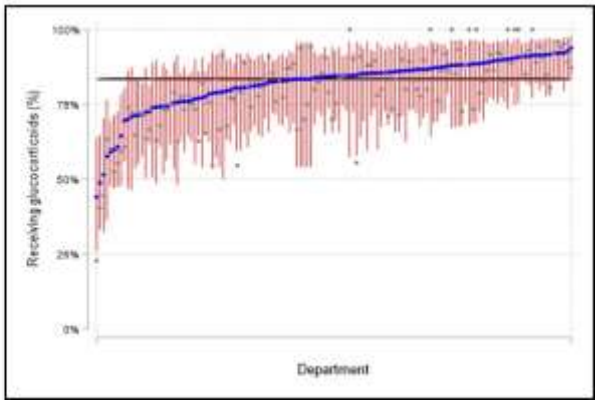


Figure 2a.

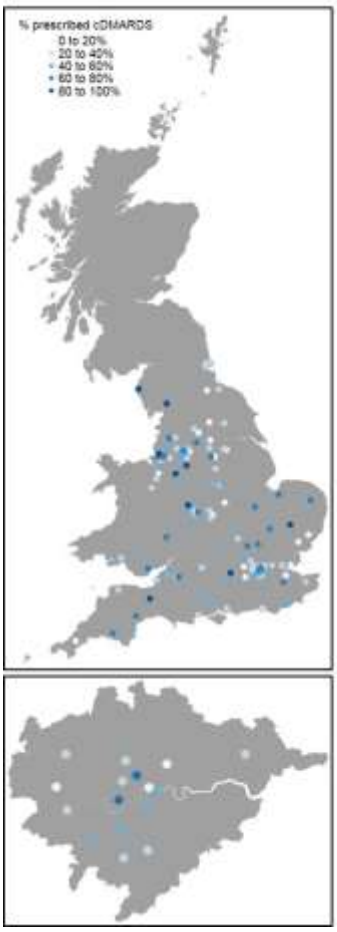


Figure 2b.

Figure 2c.