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

**AUTHORS.**

Mark Yates; The Centre for Rheumatic Diseases, School of Immunology, Infection & Inflammatory Disease, King's College London, London, UK.

Alexander J MacGregor; Norwich Medical School, University of East Anglia, Norwich, UK.

Jo Ledingham; Department of Rheumatology, Queen Alexandra Hospital, Portsmouth, UK.

Sam Norton; Institute of Psychiatry, Kings College London, London, UK.

Katie Bechman; The Centre for Rheumatic Diseases, School of Immunology, Infection & Inflammatory Disease, King's College London, London, UK.

Ali Rivett; CEO, British Society for Rheumatology, London, UK

Elaine M Dennison; MRC Epidemiology Unit, University of Southampton, Southampton, UK

James B Galloway; The Centre for Rheumatic Diseases, School of Immunology, Infection & Inflammatory Disease, King's College London, London, UK.

**CORRESPONDENCE ADDRESS AND CONTACT DETAILS.** Dr Mark Yates, Room 3.46 Weston Education Centre, Cutcombe Road, London, SE5 9RJ. [mark.yates@kcl.ac.uk](mailto:mark.yates@kcl.ac.uk). +447835150827.

**KEY WORDS**

1. Early rheumatoid arthritis
2. Health services research
3. Treatment decisions

**KEY MESSAGES**

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

**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.

**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;
* Identify treatment decisions that associate with improved clinical outcomes.

**MATERIALS AND 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.

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.

**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 supplement (supplementary 1, supplementary tables 1a, 1b, and 1c). 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 the supplementary material (supplementary table 2).

**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 3 for details).

**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.

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.

**SUPPLEMENTARY MATERIAL**

See separate file for propensity, NRI, and MI models.

**COMPETING INTERESTS**

James Galloway has received honoraria from Abbvie, Celgene, Janssen, Pfizer, and UCB.

Mark Yates has received honoraria from UCB.

**FUNDING**

This work was supported by The British Society for Rheumatology and Versus Arthritis, who fund Mark Yates’ salary.

**ACKNOWLEDGEMENTS**

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

**REFERENCES**

1. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet (London, England). 2004;364(9430):263-9.

2. Curtis JR, Chen L, Harrold LR, Narongroeknawin P, Reed G, Solomon DH. Physician preference motivates the use of anti-tumor necrosis factor therapy independent of clinical disease activity. Arthritis care & research. 2010;62(1):101-7.

3. NICE. Rheumatoid arthritis in adults: management 2018 [Available from: <https://www.nice.org.uk/guidance/NG100>.

4. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Annals of the rheumatic diseases. 2017;76(6):960-77.

5. Singh JA, Saag KG, Bridges SL, Jr., Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016;68(1):1-26.

6. Chatzidionysiou K, Emamikia S, Nam J, Ramiro S, Smolen J, van der Heijde D, et al. Efficacy of glucocorticoids, conventional and targeted synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the 2016 update of the EULAR recommendations for the management of rheumatoid arthritis. Annals of the rheumatic diseases. 2017;76(6):1102-7.

7. Ding C-Z, Yao Y, Feng X-B, Fang Y, Zhao C, Wang Y. Clinical analysis of chinese patients with rheumatoid arthritis treated with leflunomide and methotrexate combined with different dosages of glucocorticoid. Current therapeutic research, clinical and experimental. 2012;73(4-5):123-33.

8. NICE. Rheumatoid arthritis in adults: diagnosis and management. Evidence review H Glucocorticoids 2018 [Available from: <https://www.nice.org.uk/guidance/ng100/evidence/evidence-review-h-glucocorticoids-pdf-4903172325>.

9. van der Heijde DM, van 't Hof M, van Riel PL, van de Putte LB. Development of a disease activity score based on judgment in clinical practice by rheumatologists. J Rheumatol. 1993;20(3):579-81.

10. Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. Rheum Dis Clin North Am. 2009;35(4):745-57, vii-viii.

11. Pisati M. SPMAP: Stata module to visualize spatial data. Statistical Software Components: Boston College Department of Economics; 2007.

12. Rannio T, Asikainen J, Hannonen P, Yli-Kerttula T, Ekman P, Pirilä L, et al. Three out of four disease-modifying anti-rheumatic drug-naïve rheumatoid arthritis patients meet 28-joint Disease Activity Score remission at 12 months: results from the FIN-ERA cohort. Scandinavian Journal of Rheumatology. 2017;46(6):425-31.

13. Rantalaiho V, Kautiainen H, Korpela M, Puolakka K, Blafield H, Ilva K, et al. Physicians' adherence to tight control treatment strategy and combination DMARD therapy are additively important for reaching remission and maintaining working ability in early rheumatoid arthritis: a subanalysis of the FIN-RACo trial. Annals of the rheumatic diseases. 2014;73(4):788-90.

14. Garrood T, Shattles W, Scott DL. Treating early rheumatoid arthritis intensively: current UK practice does not reflect guidelines. Clin Rheumatol. 2011;30(1):103-6.

15. Edwards CJ, Campbell J, van Staa T, Arden NK. Regional and temporal variation in the treatment of rheumatoid arthritis across the UK: a descriptive register-based cohort study. 2012;2(6):e001603.

16. Ferraz-Amaro I, Seoane-Mato D, Sanchez-Alonso F, Martin-Martinez MA. Synthetic disease-modifying antirheumatic drug prescribing variability in rheumatoid arthritis: a multilevel analysis of a cross-sectional national study. Rheumatol Int. 2015;35(11):1825-36.

17. Kim SC, Yelin E, Tonner C, Solomon DH. Changes in use of disease-modifying antirheumatic drugs for rheumatoid arthritis in the United States during 1983-2009. Arthritis Care Res (Hoboken). 2013;65(9):1529-33.

18. Crane MM, Juneja M, Allen J, Kurrasch RH, Chu ME, Quattrocchi E, et al. Epidemiology and Treatment of New-Onset and Established Rheumatoid Arthritis in an Insured US Population. Arthritis Care Res (Hoboken). 2015;67(12):1646-55.

19. Nam JL, Villeneuve E, Hensor EMA, Conaghan PG, Keen HI, Buch MH, et al. Remission induction comparing infliximab and high-dose intravenous steroid, followed by treat-to-target: a double-blind, randomised, controlled trial in new-onset, treatment-naive, rheumatoid arthritis (the IDEA study). Annals of the rheumatic diseases. 2014;73(1):75-85.

20. Svensson B, Boonen A, Albertsson K, van der Heijde D, Keller C, Hafström I, et al. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: A two-year randomized trial. Arthritis & Rheumatism. 2005;52(11):3360-70.

21. Ruyssen-Witrand A, Constantin A. Controversies in rheumatoid arthritis glucocorticoid therapy. Joint Bone Spine. 2018;85(4):417-22.

22. Burmester G-R, Kivitz AJ, Kupper H, Arulmani U, Florentinus S, Goss SL, et al. Efficacy and safety of ascending methotrexate dose in combination with adalimumab: the randomised CONCERTO trial. Annals of the rheumatic diseases. 2015;74(6):1037-44.

23. van der Kooij SM, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Peeters AJ, van Krugten MV, Breedveld FC, et al. Probability of continued low disease activity in patients with recent onset rheumatoid arthritis treated according to the disease activity score. Annals of the rheumatic diseases. 2008;67(2):266-9.

**TABLES**

**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, referral and review times, and therapy choices, stratified by good EULAR DAS-28 response at three months follow up.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | 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 logistic regression models of three key treatment decisions associations with EULAR DAS-28 treatment response at three months follow up. Unadjusted, adjusted, propensity weighted, and multiple imputation results.**

|  |  |  |  |
| --- | --- | --- | --- |
| 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. 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.*