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# Pretreatment absolute monocyte counts are associated with biological disease-modifying anti-rheumatic drug non-response in patients with rheumatoid arthritis

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**Objective:** Previous publications have reported that increased absolute monocyte counts are associated with treatment non-response in patients with rheumatoid arthritis (RA). This study investigated whether full blood count (FBC) components from routine clinical testing before treatment with a biological disease-modifying anti-rheumatic drug (bDMARD) were associated with treatment non-response after 6 months of treatment.

**Method:** From a UK-based prospective multicentre study of patients with RA starting a bDMARD, data from 246 patients attending five of the participating centres were retrieved. FBC components were analysed for their association with European Alliance of Associations for Rheumatology non-response after 6 months of treatment using backward stepwise logistic regression, adjusting for potential confounders. Final models underwent resampling with 200 repeats of out-of-bag bootstrapping to assess model performance using area under the receiver operating characteristics (AUROC) curves. Model fit was compared using the Akaike information criterion (AIC).

**Results:** After 6 months of treatment, the only FBC component predictive of non-response was pretreatment absolute monocyte count [adjusted odds ratio ($OR_{adj}$) 9.56, 95% confidence intervals (CI) 1.61-59.86, p = 0.01, AUROC = 60.42%). The model including monocytes as a predictor demonstrated superior performance to the covariates-only model (AIC 184.36 vs 188.51, respectively).

**Conclusion:** In the largest study to date, increasing absolute monocyte counts were associated with bDMARD non-response after 6 months of treatment, replicating previous reports. Validation and mechanistic studies are required to inform future treatment selection.

Patients with rheumatoid arthritis (RA) with inadequately controlled disease on conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) therapy can be escalated to biological disease-modifying anti-rheumatic drug (bDMARD) therapy.

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However, bDMARDs are not a panacea and treatment response is variable; ≤ 40% of patients treated with tumour necrosis factor inhibitors (TNFi) do not achieve disease control (1, 2). Although a large body of research exists to enhance the understanding of RA, it is still not possible to predict the response of a patient to any given drug (3).

Several routinely collected patient and disease-related features correlate with response to medication in RA. For example, male sex is associated with improved treatment response (4), but smoking is associated with worse response (5). These patient characteristics are not sufficiently predictive of treatment outcome to influence treatment choice, and reveal no insight into any underlying biological mechanisms driving variation in response.

To address this, several investigators have assessed the role of immunological biomarkers in predicting treatment response. Previous, modestly sized, studies have reported associations between blood-based B-cell, T-cell, natural killer cell, and monocyte composition with poorer outcomes (6–8). Others suggest that neutrophils may influence ongoing disease activity in RA (9). Such studies have largely relied on detailed phenotyping using laboratory techniques that are impractical and time consuming to implement in busy clinical laboratories (10, 11).

Full blood counts (FBCs) are routinely measured in patients commencing bDMARDs as part of pharmacovigilance. Few studies have assessed the utility of these routinely collected data in predicting response to therapy. The aim of this study was to investigate whether FBC components from routine clinical testing before treatment with a bDMARD were associated with treatment non-response after 6 months.

## Method

### Ethical approval and informed consent

The Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate (BRAGGSS) obtained a favourable ethics opinion from the North West–Greater Manchester South Research Ethics Committee (REC, reference: 04/Q1403/37). This study was conducted in compliance with the Declaration of Helsinki. All participants gave written informed consent.

### Study participants

Patients with RA (1987 American College of Rheumatology classification criteria) were recruited to BRAGGSS, a prospective multicentre UK-based observational study. The current study consisted of participants who were white European, starting a bDMARD (any line of treatment), and aged ≥ 18 years. BRAGGSS was originally designed as a genetics study, which is why patients of a single ethnicity were initially recruited.

Each participant required an FBC measurement from ≤ 12 weeks before or 2 weeks after starting bDMARD treatment, and a Disease Activity Score based on 28-joint count including serum C-reactive protein (DAS28-CRP) measured at baseline (pretreatment) and after 6 months of treatment. The follow-up time-point of 6 months was chosen to reflect current UK bDMARD prescribing practice. Participants were recruited between 2009 and 2015 from secondary care rheumatology departments; for this study, data were selected from five regional centres (North-West England) participating in BRAGGSS for manual FBC data extraction at each site. Participants were opportunistically recruited over several years; a sample size calculation was not applied.

Clinical data including DAS28-CRP subcomponents were collected. DAS28-CRP was calculated using the four-component algorithm, consisting of: tender and swollen joint counts (28 joints), patient visual analogue scale of global health (0–100 mm), and high-sensitivity C-reactive protein (CRP) measured using enzyme-linked immunosorbent assay, at the National Institute for Health and Care Research (NIHR) National Biosample Centre (Milton Keynes, UK). FBC data were collected from each participating centre and were processed locally.

### Statistical analysis

All analyses were carried out in R version 4.4.1 (12); specific R packages are stated in the Supplementary Methods. Missing values were imputed using random forest, a machine learning algorithm. For DAS28-CRP subcomponents, values were imputed for each time-point separately to improve imputation accuracy; as DAS28-CRP values are likely to change over time with treatment, so imputed values would not be affected by other samples demonstrating improved/worsening DAS28-CRP over time if analysed at separate time-points. Once missing subcomponents had been imputed, total DAS28-CRP values were calculated at baseline and 6 months; European Alliance of Associations for Rheumatology (EULAR) response criteria (13) were calculated at 6 months.

The following pre-treatment FBC components (absolute values) were included in the analysis: haemoglobin (g/dL), haematocrit (L/L), mean corpuscular volume (MCV) (fL), platelets ($\times 10^9$/L), neutrophils ($\times 10^9$/L), lymphocytes ($\times 10^9$/L), eosinophils ($\times 10^9$/L), and monocytes ($\times 10^9$/L). Excluded components are stated in the Supplementary Methods.

The main outcome variable of interest was EULAR non-response at 6 months, as previously defined (13). All FBC components were assessed for their univariable and adjusted associations with EULAR non-response

using logistic regression. Analysis was adjusted for the following potential confounders: age at recruitment, biological sex, concurrent csDMARD therapy, TNFi as choice of bDMARD, centre of recruitment, pretreatment DAS28-CRP, rheumatoid factor (RF) and/or anti-citrullinated protein antibody (ACPA) seropositivity, RA disease duration before commencing bDMARD, and current smoking status. Secondary analysis of associations between FBC components and DAS28 subcomponents was carried out using linear regression, both unadjusted and adjusted for potential confounders.

Backward stepwise selection was used to remove non-significant FBC components ($p \geq 0.05$) from a full multivariable model of association with EULAR non-response containing all FBC components and potential confounders. A likelihood ratio test was used to compare models at each step to determine the statistical significance of removing each component.

The ability of the final model to discriminate between responders and non-responders was assessed using the area under the receiver operating characteristics (AUROC) curve. Because performance was assessed using the same data used to build the models, the AUROC curve value was produced using 200 bootstrapped data sets. Performance was assessed using classification error (percentage of false positives and negatives), accuracy (percentage of true positives and negatives) and AUROC, and model fit was compared using the Akaike information criterion (AIC).

## Results

### Study participants

In total, 220 participants were eligible for analysis; their summary characteristics are detailed in Table 1. Baseline monocyte counts stratified by treatment response status are presented in Supplementary Figure 1.

### Non-response at 6 months

Thirty-four participants (15.45%) were non-responders. The results of the univariable logistic regression with EULAR non-response are shown in Supplementary Table S6. The results of the univariable linear regression of FBC components with DAS28 and its subcomponents are available in Supplementary Tables S1–S5. Following backward stepwise logistic regression, the only FBC component significantly associated with non-response was monocyte count [adjusted odds ratio ($OR_{adj}$) 9.56 per $10^9$/L monocytes, 95% confidence interval (CI) 1.61–59.86, p = 0.01] (Table 2). In the univariable analysis, monocyte count was associated with CRP ($\beta_{adj}$ 18.07 per $10^9$/L monocytes, 95% CI 2.58–33.55, p = 0.02) (Supplementary Table S4). A likelihood ratio test demonstrated that monocytes were a significant variable in the model (p = 0.01). After bootstrapping, the monocytes with covariates model had a modestly superior AUROC compared to the covariates-only model (60.42% vs 58.47%, respectively) and improved model fit (AIC 184.36 vs 188.51). Classification error and accuracy were similar between models. Full comparison statistics are available in Supplementary Table S7 and receiver operating characteristics (ROC) curves of the two models are presented in Figure 1.

## Discussion

In a cohort of patients with active RA, we report that increasing absolute monocyte count measured in clinical laboratories is significantly associated with non-response to a bDMARD after 6 months of treatment.

Our results agree with those from previous smaller studies:. Chara et al (n = 35) (6) and Eakin et al (n = 62) (7) found that monocyte counts were associated with poor treatment response and increased disease activity. Meusch et al (n = 20) found that reduced monocyte spontaneous apoptosis was associated with moderate/poor EULAR response (11), providing a possible mechanistic explanation. The association between CRP and monocytes is likely to be driving the association with poor EULAR response.

A strength of our study is that it is the largest to date examining associations between pretreatment FBC components and bDMARD treatment response; previous studies have been modest in size. The predictors of interest are routinely measured in most patients prior to commencing bDMARDs and do not require additional complicated laboratory tests. The 2019 British Society for Rheumatology guidelines for bDMARD therapy pretreatment investigations list FBC as necessary for all patients (14), so these data should be available for all patients. The ready availability of FBC gives this predictor an advantage over others that may require more complex and costly measurement.

Although this is the largest of its kind, this study remains under-powered, as evidenced by the wide confidence intervals for monocyte count in the final model, which could indicate overfitting. Model predictive capabilities were probably affected by wide class imbalance between responders and non-responders. Treatment groups were heterogeneous, which may have weakened associations. The omission of non-white participants because of the original study design could mean that findings are not generalizable to more diverse populations. Data on steroid use were only available for seven out of 220 participants owing to the observational nature of this study, so analyses were not adjusted for this potential confounder. Similarly, no information was available on individual concurrent csDMARD agents, so the analysis could not be limited to agents more likely to influence immunogenicity to bDMARD agents, such as methotrexate.

Table 1. Baseline characteristics of patients recruited to the study, stratified by treatment response according to EULAR response criteria after 6 months of treatment.

| Characteristic | Whole population {% missing before imputation} | Treatment responders (good/ moderate response) (n = 186) | Treatment non-responders (poor response) (n = 34) |
|---|---|---|---|
| Female sex | 170 (77.3) {0.0} | 144 (77.4) | 26 (76.5) |
| Age (years) | 58.1 [48.4, 66.1] {0.0} | 58.1 [48.0, 65.8] | 57.0 [52.4, 67.5] |
| Disease duration prior to starting bDMARD (years) | 10.0 [4.2, 18.5] {1.6} | 9.2 [4.2, 18.6] | 11.8 [5.1, 18.4] |
| Concurrent csDMARD | 183 (83.2) | 156 (83.9) | 27 (79.4) |
| DAS28† | 5.5 [5.0, 6.1] | 5.5 [5.2, 6.1] | 5.0 [4.7, 5.5] |
| Tender joint count | 12 [8, 16] {7.5} | 12 [8, 17] | 10 [6, 14] |
| Swollen joint count | 7 [4, 10] {8.0} | 7 [4, 10] | 6 [2, 9] |
| Patient global health VAS | 80 [65, 90] {8.0} | 80 [69, 90] | 70 [55, 80] |
| CRP | 10.6 [4.0, 27.3] {6.7} | 11.3 [4.3, 27.0] | 8.3 [3.7, 35.5] |
| Ever seropositive (RF and/or ACPA) | 210 (95.5) {27.8} | 178 (95.7) | 32 (94.1) |
| Current smoker | 44 (20.0) {29.4} | 39 (21.0) | 5 (14.7) |
| Choice of bDMARD | 54 (24.6) | 50 (26.9) | 4 (11.8) |
| Adalimumab‡ | 15 (6.8) | 14 (7.5) | 1 (2.9) |
| Certolizumab‡ | 87 (39.6) | 74 (39.8) | 13 (38.2) |
| Etanercept‡ | 6 (2.7) | 5 (2.7) | 1 (2.9) |
| Golimumab‡ | 1 (0.5) | 1 (0.5) | 0 (0.0) |
| Infliximab‡ | 163 (74.1) | 144 (77.4) | 19 (55.9) |
| Total TNFi | 15 (6.8) | 12 (6.5) | 3 (8.8) |
| Abatacept | 23 (10.5) | 14 (7.5) | 9 (26.5) |
| Rituximab | 19 (8.6) {0.0} | 16 (8.6) | 3 (8.8) |
| Tocilizumab | | | |
| FBC component | | | |
| Haemoglobin (g/dL) | 128.0 [118.0, 137.0] | 129.0 [118.0, 138.8] | 125.0 [118.8, 133.0] |
| Haematocrit (L/L) | 0.364 [0.384, 0.410] | 0.390 [0.365, 0.411] | 0.379 [0.366, 0.401] |
| MCV (fL) | 89.6 [85.5, 93.3] | 89.5 [86.0, 93.3] | 91.7 [85.0, 95.2] |
| Platelets ($\times 10^9$/L) | 289 [241, 356] | 287 [238, 354] | 300 [251, 352] |
| Neutrophils ($\times 10^9$/L) | 5.1 [3.9, 6.6] | 5.0 [3.9, 6.5] | 5.3 [3.9, 6.7] |
| Lymphocytes ($\times 10^9$/L) | 1.8 [1.4, 2.2] | 1.8 [1.4, 2.2] | 1.8 [1.5, 2.0] |
| Eosinophils ($\times 10^9$/L) | 0.1 [0.1, 0.2] | 0.1 [0.1, 0.2] | 0.1 [0.1, 0.2] |
| Monocytes ($\times 10^9$/L) | 0.6 [0.5, 0.8] | 0.6 [0.5, 0.8] | 0.7 [0.5, 1.0] |

Data are shown as median [interquartile range] or n (%).
† Percentages of missing values are included for all time-points for DAS28 subcomponents.
‡ TNFi agent.
EULAR, European Alliance of Associations for Rheumatology; bDMARD, biological disease-modifying anti-rheumatic drug; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; DAS28, Disease Activity Score based on 28-joint count; VAS, visual analogue scale; CRP, C-reactive protein; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibody; TNFi, tumour necrosis factor inhibitor; FBC, full blood count; MCV, mean corpuscular volume.

Given that this study is underpowered, the findings cannot be immediately transferred to clinical practice without validation in larger, independent cohorts. Because of the design, it is not possible to obtain further validation data within this cohort at present, but future predictive power will be increased by analysing larger cohorts, and potentially also by including other biomarkers measured in the same patients. Including deeper molecular phenotyping was outside the scope of this study, however, as we sought to explore whether a readily available clinical measurement could be predictive of treatment response.

Monocyte subsets are not measured routinely as part of UK health service care. Rather, only absolute monocyte counts are included in FBC reporting. Therefore, from the data presented here, it cannot be determined whether a specific monocyte subset or subsets may be driving the association between monocyte count and treatment non-response. A more mechanistic experimental design would be required to determine this.

Although interlaboratory variability in FBC measurement and reporting was possible, results were adjusted for centre of recruitment to mitigate this risk. Inclusion of patients from different centres could even be seen as a strength, demonstrating replication across cohorts. Our findings suggest that patients with increased pretreatment absolute monocyte counts may represent a subgroup of patients with more refractory disease. Understanding whether these patients would respond more favourably to therapies with different modes of action could enable more personalized treatment. This would require a larger study including patients on multiple different agents to power subgroup analysis by drug.

Table 2. Final logistic regression model of predictors of non-response following negative stepwise multivariable regression of all full blood count components, after 6 months of treatment with a biological disease-modifying anti-rheumatic drug.

| Predictor | $OR_{adj}$ (95% CI) | p |
|---|---|---|
| Monocytes, per $10^9$/L | 9.56 (1.61–59.86) | 0.01* |
| Age, per year | 0.99 (0.95–1.03) | 0.51 |
| Seropositivity for RF and/or ACPA | 0.50 (0.09–4.04) | 0.47 |
| Female sex | 1.55 (0.58–4.60) | 0.40 |
| Concurrent csDMARD | 0.96 (0.34–2.97) | 0.94 |
| Disease duration | 1.02 (0.97–1.06) | 0.46 |
| Centre | | |
| 1 | Reference | Reference |
| 2 | 1.22 (0.44–3.40) | 0.70 |
| 3 | 0.40 (0.08–1.60) | 0.22 |
| 4 | 1.06 (0.24–4.06) | 0.93 |
| 5 | 0.31 (0.02–2.04) | 0.31 |
| Current smoking | 0.85 (0.25–2.54) | 0.78 |
| TNFi biologic | 0.36 (0.14–0.89) | 0.03* |
| Pretreatment DAS28, per unit | 0.34 (0.19–0.58) | 1.54E-04* |

RF, rheumatoid factor; ACPA, anti-citrullinated protein antibody; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; TNFi, tumour necrosis factor inhibitor; DAS28, Disease Activity Score based on 28-joint count; $OR_{adj}$, adjusted odds ratio; CI, confidence interval.
*$p < 0.05$.

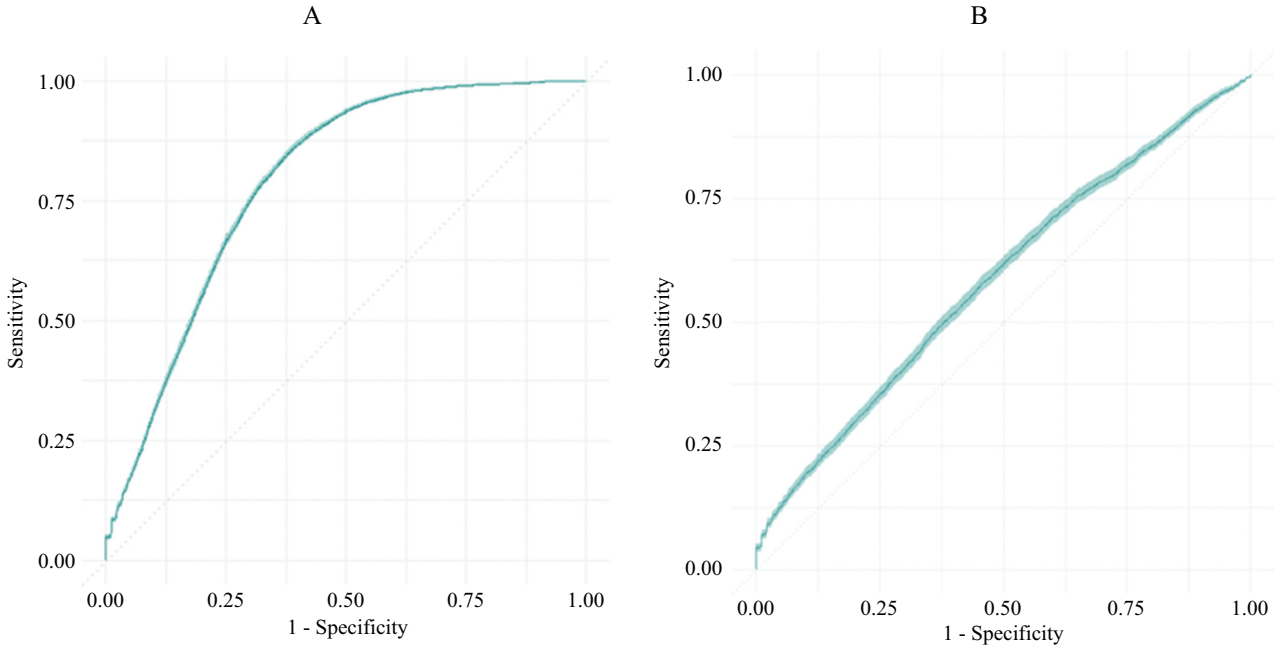


Figure 1. Receiver operating characteristics (ROC) curves demonstrating model performance at predicting non-response. All curves were generated following resampling and prediction using 200 repeats of out-of-bag bootstrapping. (A) ROC curve for monocytes with covariates model after 6 months of treatment with a biological disease-modifying anti-rheumatic drug (bDMARD). (B) ROC curve for covariates-only model after 6 months of treatment with a bDMARD.

## Conclusion

In this longitudinal study of patients with RA, we demonstrate that pretreatment monocyte count is associated with non-response to bDMARDs, with results in keeping with previous, smaller studies. Further validation and assessment of predictive utility are required before these findings can be translated to clinical practice.

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PH has received honoraria for speaking for Novartis and Janssen. MB has been sponsored to attend regional, national, and international meetings by UCB Celltech, Roche/Chugai, Pfizer, AbbVie, Merck, Mennarini, Janssen, Bristol-Myers Squibb, Novartis, and Eli-Lilly. He has received honoraria for speaking and attending advisory boards with Bristol-Myers Squibb, UCB Celltech, Roche/Chugai, Pfizer, AbbVie, Merck, Mennarini, Sanofi-Aventis, Eli-Lilly, Janssen, Amgen, Novartis, and Gilead. He has received honoraria from the educational groups Revalidaid and TREG Consultants. HC has received speaker fees for GSK and UCB, consulting fees for PTC Therapeutics, and grant funding from Pfizer. He is an advisory board member for AstraZeneca and Pfizer, and the Data and Science Monitoring Board chair for Horizon Therapeutics. AWM has received a research grant from Roche and has undertaken consultancy for AstraZeneca and Vifor on behalf of the University of Leeds in the field of vasculitis. JDI has received research grants from Pfizer, GSK, and Janssen. He has received consultancy fees (to his employer) from Anaptys Bio, Annexon Biosciences, AstraZeneca, BMS, Cyxone AB, Dragonfly, Eli Lilly, Galapagos NV, Gilead Sciences, GSK, Istesso Ltd, Janssen, Kenko International, Kira Biotech, Ono Pharma, Pfizer, Revelo Biotherapeutics, Roche, and Sanofi. He has received speaker fees from AbbVie and support for meeting attendance from Eli Lilly. KLH has received speaker fees from AbbVie and grant income from Pfizer and BMS. AB has received honoraria/grant funding from BMS, Galapagos, and Pfizer. No potential conflict of interest was reported by the remaining authors.

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## Supplementary material

Supplemental data for this article can be accessed online at https://doi.org/10.1080/03009742.2025.2497606.

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