PRE-TREATMENT ABSOLUTE MONOCYTE COUNTS ARE ASSOCIATED WITH bDMARD NON-RESPONSE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Abstract

Objectives

Previous published evidence has reported that increased absolute monocyte counts are associated with treatment non-response in patients with RA. This study investigated whether full blood count (FBC) components from routine clinical testing before treatment with a biologic DMARD (bDMARD) were associated with treatment non-response after three and six months.

Methods

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 EULAR non-response after three and six 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 characteristic (AUROC) curves.

Results

After three months of treatment, pre-treatment absolute monocyte count was the only FBC component found to be predictive of non-response (OR_{adj} 8.50, 95% CI 1.77 – 42.64, p=0.01), with an AUROC of 68.47%. After six months of treatment, again, the only FBC component found to be predictive of non-response was pre-treatment absolute monocyte count (OR_{adj} 12.31, 95% CI 2.03 – 79.55, p=0.01), with an AUROC of 65.18%. Both models including monocytes as a predictor were found to have superior performance to covariates-only models at both time-points (p=0.01).

Conclusion

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

[250/250 words]

Introduction

Patients with RA with inadequately-controlled disease on conventional synthetic DMARD (csDMARD) therapy can be escalated to biologic DMARD (bDMARD) therapy. However, bDMARDs are not a panacea and treatment response is variable; ≤40% of patients treated with TNF 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 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 modest studies have reported associations between blood-based B-cell, T-cell, NK-cell and monocyte composition with poorer outcomes(6-8). Others suggest neutrophils might 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 (FBC) 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 six months.

Methods

Ethical approval and informed consent

The Biologics in RA 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 ACR classification criteria) were recruited to BRAGGSS, a prospective multi-centre 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, hence why patients of a single ethnicity were initially recruited.

Each participant required an FBC measurement from ≤12 weeks prior to or two weeks after starting bDMARD treatment, and a 28 joint count DAS including serum CRP (DAS28-CRP) measured at baseline (pre-treatment) and after six months of treatment. The follow-up time-point of six months was chosen to reflect current UK bDMARD prescribing practice. Participants were recruited between 2009–2015 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 sub-components 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 CRP measured using ELISA 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 v.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 sub-components, 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 sub-components were imputed, total DAS28-CRP values were calculated at baseline and six months; EULAR response criteria(13) were calculated at six months.

The following pre-treatment FBC components (absolute values) were included in analysis:

- Haemoglobin, g/dL.

- Haematocrit, L/L.
- Mean corpuscular volume (MCV), fL.
- Platelets, $x10^9$/L.
- Neutrophils, $x10^9$/L.
- Lymphocytes, $x10^9$/L.
- Eosinophils, $x10^9$/L.
- Monocytes, $x10^9$/L.

Excluded components are stated in the Supplementary Methods.

The main outcome variable of interest was EULAR non-response at six 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, pre-treatment DAS28-CRP, RF and/or ACPA seropositivity, RA disease duration prior to commencing bDMARD and current smoking status. Secondary analysis of associations between FBC components and DAS28 sub-components 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 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 characteristic (AUROC) curve. Because performance was assessed using the same data used to build the models, the AUROC curve value was produced using 200 bootstrapped datasets. Performance was assessed using classification error (%false positives and negatives), accuracy (%true positives and negatives) and AUROC, and model fit was compared using the Akaike information criterion (AIC).

Results

Study participants

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 six months

34 participants (15.45%) were non-responders. The results of the univariable logistic regression with EULAR non-response are in Supplementary Table S6. The univariable linear regression of FBC components with DAS28 and its sub-components results are available in Supplementary Tables S1 – S5. Following backward stepwise logistic regression, the only FBC component significantly associated with non-response was monocyte count (OR_{adj} 9.56 per 10^9/L monocytes, 95% CI 1.61 – 59.86, p = 0.01; Table 2). In the univariable analysis, monocyte count was associated with CRP (β_{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 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 six 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 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 driving the association with poor EULAR response.

A strength of our study is that it is the largest to-date examining associations between pre-treatment 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 pre-treatment investigations lists 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 might require more complex and costly measurement.

Whilst the largest study of its kind, it remains under-powered, as evidenced by the wide confidence intervals for monocyte count in the final model, which could indicate over-fitting. Model predictive capabilities were likely 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 due to the original study design could mean that findings are not generalisable to more diverse populations. Steroid use data were only available in 7/220 participants due to the observational nature of this study, so unfortunately, analyses were not adjusted for this potential confounder. Similarly, no information was available on individual concurrent csDMARD agents, so analysis could not be limited to agents more likely to influence immunogenicity to bDMARD agents e.g. methotrexate.

Given that this study is under-powered, findings cannot be immediately transferred to clinical practice without validation in larger, independent cohorts. Due to 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 are driving the association between monocyte count and treatment non-response. This would require a more mechanistic experimental design to determine this.

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

In conclusion, in this longitudinal study of patients with RA, we demonstrate that pre-treatment 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 findings can be translated to clinical practice.

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Conflict of interest statement

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 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 Ltd, 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.

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Tables and figures

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, n (%)	170 (77.3) *0.0*	144 (77.4)	26 (76.5)
Age (years), median [IQR]	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), median [IQR]	10.0 [4.2, 18.5] *1.6*	9.2 [4.2, 18.6]	11.8 [5.1, 18.4]
Concurrent csDMARD, n (%)	183 (83.2)	156 (83.9)	27 (79.4)
DAS28[†], median [IQR]	5.5 [5.0, 6.1]	5.5 [5.2, 6.1]	5.0 [4.7, 5.5]
Tender joint count, median [IQR]	12 [8, 16] *7.5*	12 [8, 17]	10 [6, 14]
Swollen joint count, median [IQR]	7 [4, 10] *8.0*	7 [4, 10]	6 [2, 9]
Patient global health visual analogue score, median [IQR]	80 [65, 90] *8.0*	80 [69, 90]	70 [55, 80]
CRP, median [IQR]	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), n (%)	210 (95.5) *27.8*	178 (95.7)	32 (94.1)
Current smoker, n (%)	44 (20.0) *29.4*	39 (21.0)	5 (14.7)
Choice of bDMARD (n, %)			
Adalimumab*	54 (24.6)	50 (26.9)	4 (11.8)
Certolizumab*	15 (6.8)	14 (7.5)	1 (2.9)

Etanercept*	87 (39.6)	74 (39.8)	13 (38.2)
Golimumab*	6 (2.7)	5 (2.7)	1 (2.9)
Infliximab*	1 (0.5)	1 (0.5)	0 (0.0)
Total TNFi	163 (74.1)	144 (77.4)	19 (55.9)
Abatacept	15 (6.8)	12 (6.5)	3 (8.8)
Rituximab	23 (10.5)	14 (7.5)	9 (26.5)
Tocilizumab	19 (8.6)	16 (8.6)	3 (8.8)
	0.0		
Full blood count component, median, IQR]			
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 ($x10^9$/L)	289 [241, 356]	287 [238, 354]	300 [251, 352]
Neutrophils ($x10^9$/L)	5.1 [3.9, 6.6]	5.0 [3.9, 6.5]	5.3 [3.9, 6.7]
Lymphocytes ($x10^9$/L)	1.8 [1.4, 2.2]	1.8 [1.4, 2.2]	1.8 [1.5, 2.0]
Eosinophils ($x10^9$/L)	0.1 [0.1, 0.2]	0.1 [0.1, 0.2]	0.1 [0.1, 0.2]
Monocytes ($x10^9$/L)	0.6 [0.5, 0.8]	0.6 [0.5, 0.8]	0.7 [0.5, 1.0]

[†]Percentages of missing values are included for all time-points for DAS28 sub-components.

*Indicates TNFi agent.

Abbreviations: Biologic DMARD (bDMARD), conventional synthetic DMARD (csDMARD), inter-quartile range (IQR), mean corpuscular volume (MCV), TNF inhibitor (TNFi).

Table 2. Final logistic regression model of predictors of non-response following negative stepwise multivariable regression of all FBC components, after six months of treatment with a bDMARD.

Predictor	**OR_{adj} (95% CI)**	**p-value**
Monocytes, per 10E09/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*
Pre-treatment DAS28, per unit	0.34 (0.19 – 0.58)	1.54E-04*

*Indicates $p<0.05$.

Abbreviations: Biologic DMARD (bDMARD), confidence intervals (CI), conventional synthetic DMARD (csDMARD), full blood count (FBC), odds ratio (OR), TNF inhibitor (TNFi).

Figure 1 (please see separate image file for plots)

TITLE: Figure 1. ROC curves demonstrating model performance at predicting non-response.

LEGEND: 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 six months of treatment with a bDMARD. B) ROC curve for covariates-only model after six months of treatment with a bDMARD.

Abbreviations: Biologic DMARD (bDMARD), receiver operating characteristic (ROC).