Erratum

Erratum to “Predicting drug-free remission in rheumatoid arthritis: A prospective interventional cohort study” [J. Autoimmun. 105 (December 2019) 102298]

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Interestingly, neither its individual components (i.e. swollen/tender joint counts, patient global assessment) nor DAS28-CRP demonstrated predictive value in our study. In contrast, ACR/EULAR Boolean remission was not predictive of future DFR in the RETRO study [8]. It is possible that modifications to the ACR/EULAR Boolean construct, such as a relaxation of the patient global assessment threshold (which has been criticised by some as overly strict [40],[41],[42],[43],[44],[45],[46]), may improve its predictive utility in this setting; however, our limited sample size hinders further exploration.

It is possible that a longer duration of sustained remission prior to DMARD withdrawal may favour successful achievement of DFR. Higher rates of DFR are indeed observed with the use of modern treat-to-target DMARD regimens (where clinical remission is more likely to be achieved early in the course of disease) compared to historical treatment approaches [6], supporting this assumption. Furthermore, longer duration of DAS-defined remission was associated with higher rates of DFR following withdrawal of abatacept in the AVERT study [47], and lower mean disease activity prior to DMARD withdrawal was predictive of DFR in BeST [7]. In our study, the lack of a lead-in monitoring period before DMARD cessation prohibits a direct analysis of the value of remission duration in predicting DFR. Nevertheless, an indirect measure of remission duration – namely time since last change in DMARD therapy – is positively associated with achieving DFR, albeit at an insufficient magnitude to advance to the final integrative biomarker score.

Seronegativity for ACPA and RhF have previously been shown to be predictive of DFR [5],[7],[8],[9],[48], as observed for RhF in the clinical biomarker analysis of our study. In the RETRO study, combination of ACPA with the 12-cytokine multibiomarker disease activity (MBDA) score [49] further increased its ability to predict DFR vs. flare following DMARD cessation [50]. However, in our study ACPA and/or RhF status did not provide any additional predictive value beyond the five variables in the final composite biomarker score. We furthermore observe that IL-27 is associated with increased risk of flare following DMARD cessation. Indeed, IL-27 has been implicated in the pathogenesis of RA [51],[52],[53],[54],[55], though has also shown protective effects against experimentally-induced arthritis in murine models [56,57]. Our results suggest that further exploration of the mechanistic role of IL-27 in the context of arthritis flare may prove valuable.

Our composite biomarker score incorporates the expression of three genes within peripheral CD4+ T cells. The function of the FAM102B protein is unknown, although the paralogous FAM102A is known to be involved in oestrogen signalling [58], osteoclast differentiation [59], and cell membrane trafficking [60]. ENSG00000228010 is an antisense RNA gene to zinc finger 12 (ZNF12), a member of the Krüppel C2H2-type zinc finger family with evolutionarily-conserved function in the
regulation of developmental gene expression [61]. Interestingly, ZNF12 has been implicated as a causative gene in a quantitative trait locus influencing TNF-α production in vitro by human peripheral blood mononuclear cells in response to Candida albicans [62], supporting an immunomodulatory role of the gene. ENSG00000227070 is predicted to be a novel antisense RNA gene, though no published data exists as to its putative target (Ensembl genome browser release 95) [63]. To our knowledge, only one other study has explored differential gene expression within peripheral CD4+ T cells in the context of DFR in RA. However, this exploratory analysis of the U-Act-Early study focused on differential gene expression at the time of disease diagnosis using a network analytic approach [64], thus limiting a direct comparison with our results.

A striking observation is the lack of association of ultrasound biomarkers with patient outcome following DMARD cessation. However, to alleviate any potential concerns of referring clinicians, patients with any degree of power Doppler signal were excluded from DMARD cessation, thus preventing an assessment of this important ultrasound parameter. Furthermore, significant abnormalities may have been present outside of the seven joints included within the US17 scan. Nevertheless, a lack of predictive value of ultrasound in DMARD tapering and cessation was also observed by El Miedany et al. [48], who found no association between future flare and either greyscale or power Doppler abnormalities in an extended 40-joint scan protocol.

There are several limitations to this study, notably its small size, short duration of follow-up, and heterogeneity of DMARDs at enrolment. Over-fitting of the data is likely given that the number of candidate variables is greater than the number of study participants, and the impressive biomarker performance presented herein needs to be interpreted within this context. Indeed, it is now a priority to validate our findings in an external cohort, a crucial next step before considering application to clinical practice.

5. Conclusions

In summary, we describe the integration of variables across multiple domains (clinical, ultrasound, serological, gene expression) at an unprecedented resolution to predict DFR in RA. A composite biomarker score, based on only five baseline variables measured before DMARD cessation, had excellent predictive value for DFR at 6 months. If successfully validated in an external cohort, our biomarker score would hold promise in identifying those patients for whom drug withdrawal is appropriate, thus guiding an intelligent and personalised approach to DMARD therapy in RA remission.

Conflicts of interest

KFB, JDI, AGP and DWI are named as inventors on a patent application by Newcastle University relating to the prediction of drug-free remission in rheumatoid arthritis based on the results of this study. BT, AJS and AS have no conflicts of interest to declare.

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Appendix A. Supplementary data

The following are the Supplementary data to this article:

Multimedia component 1.

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