Many complex diseases are heterogeneous in their clinical presentation, severity and response to therapies. Understanding this heterogeneity may enable better targeting of treatments to the subgroups of patients most likely to respond—a concept known as stratified (or precision) medicine.

Stratified medicine was identified as a priority by the Medical Research Council (MRC) in 2011, and two consortia from the RA research community applied for funding. In both, the aim was to better predict treatment response in RA. The first reason for focusing on RA was that treatment practice is standardized in England through the National Institute for Health and Care Excellence (NICE) guidelines: MTX is usually the first-choice DMARD; patients who fail to respond to MTX and at least one other DMARD are eligible for biologic drugs, the most commonly prescribed being TNF inhibitor drugs (TNFi); those who fail to respond to first-line biologic therapy can then be switched to the biologic B-cell-depleting therapy rituximab (RTX) [1]. Second, there is a significant non-response rate to MTX (45% by 2 years), TNFi (25% by 6 months) and RTX (40% by 6 months) [2-4]. Third, introduction of early, effective therapy has consistently been shown to improve long-term outcomes, including joint damage, disability and employment [5]. Fourth, studies have shown that response to the first treatment given is the most important predictor of long-term outcome [6]. Finally, while biologics have transformed the treatment landscape of RA, the annual cost to the National Health Service was estimated in 2009 to be ~£560 M, compared with oral MTX, which costs less than £100/year/patient [7]. The identification of treatment response predictors would allow the allocation of patients to strata defined by the therapy they are most likely to respond to, early in the disease process.

One of the proposals aimed to identify biomarkers in the synovium that could be used as a filter for peripheral blood biomarkers to inform subsequent therapy choices using a prospective biopsy-driven randomized trial approach. The second proposal involved integrated analysis of peripheral blood collected from large cohorts of patients pre-treatment, who are then followed prospectively to assess response in order to identify genetic, genomic and proteomic predictors of response. Both RA proposals were invited to proceed to the full application stage, but the applicants were encouraged to consider whether a combined approach might be more powerful. Following discussion, it was apparent that the overall aims of the studies were similar and the approaches complementary; both recognized the importance of industry involvement and that a combined application would leverage greater benefits than either proposal alone. Hence, the Maximizing Therapeutic Utility in RA (MATURE) consortium was formed. This collaborative approach from the rheumatology research community, involving 12 academic centres and 9 industry partners, was one of the key factors that convinced the funders that the proposal had a high chance of success. Indeed, Arthritis Research UK partnered with the MRC to fund the application after successful competitive interview; MATURE was officially launched in June 2014. Industry partners include large pharmaceutical (Roche/Genentech, Pfizer, AbbVie, MedImmune, Janssen) and diagnostics companies (Beijing Genome Institute, Qiagen), and small medium enterprises (Protagen, Avacta Life Sciences). Their contributions span the funding of study drugs, funding of tests, in-kind generation of data, contribution of data and in-kind bioinformatics support.

MATURE comprises two parallel work-streams (supplementary Fig. S1, available at Rheumatology Online). In workstream 1, tissue-driven biomarkers and blood correlates will be investigated in a large synovial tissue biobank from 300 patients (biopsies pre-treatment and 6 months post-DMARD therapy), with associated clinical data collected as part of a previous MRC-funded initiative, Pathobiology of Early Arthritis Cohort (PEAC) [8]. In addition, a prospective biopsy-driven randomized clinical trial will test the hypothesis that discrete cellular and molecular signatures in the synovial tissue (pathotypes) will enrich for response to existing biologic therapies Stratification of Biologic Therapies for Rheumatoid Arthritis by Pathobiology (STRAP).

In workstream 2, large-scale blood-based screening will be undertaken on some of the largest collections and clinical datasets worldwide. Specifically, response to MTX, TNFi and RTX will be investigated in samples collected as part of randomized controlled trials and observational studies in which pre-treatment peripheral blood samples are available for multi-omic testing, including genome-wide genotyping, DNA methylation and expression profiling using array-based technology; RNA-seq in some samples
and a number of proteomic assays. Blood samples are also available at specified time points following treatment initiation in order to allow identification of pharmacodynamic markers of response [9].

Both workstreams are fully integrated through the multi-omic cross-cutting themes that converge in a large analytical and modelling package driven by bioinformatics/statistics experts to develop clinically useful algorithms and companion diagnostics to stratify patients early in disease.

A TranSMART data warehouse platform will be used to store, integrate and analyse the data generated. It has the advantages that it can accommodate phenotypic data as well as high-content multi-omic data; anonymized data can be uploaded by each centre using secure logins, and permissions can be altered to allow different levels of access to different consortium members, dependent on their contribution. A data sharing and security policy document has been developed to ensure that data can be accessed in an equitable, fair and secure manner.

In developing the proposal, the co-applicants worked with local and national patient groups, including INVOLVE, the National Rheumatoid Arthritis Society (NRAS) and Arthritis Care. The Chief Executive of the NRAS attended the final MRC panel interview and provided the patient’s

| Cohort name | Cohort | Biomedical resource | Access arrangements | Publications arising | Web-site |
|-------------|--------|---------------------|---------------------|---------------------|----------|
| MAximizing Therapeutic Utility in RA | Prospective longitudinal cohort of established RA with active disease about to start biologic therapy after failure of DMARD treatment; early RA patients about to start treatment with MTX | MTX: $n = 1500$
Anti-TNF: $n = 1000$
Rituximab: $n = 600$
Tocilizumab: $n = 100$
DNA RNA (peripheral blood)
Serum Subset with synovial tissue US data | Application documents and process on website | Current manuscript [9] |
| Pathobiology of Early Arthritis Cohort | All early arthritis; prospective longitudinal cohort with 3-monthly follow-up data | Total in cohort: $n = 300$
Synovial tissue
Synovial fluid
Serum
DNA (peripheral blood)
RNA (synovial tissue)
US data | Via steering committee | Kelly et al. Ann Rheum Dis 2015;74:611–7 [8]; Astorini et al. Curr Pharm Des 2015;21:2216–24 (review) [12]; Hymby et al. Arthritis Rheumatol 2015;67:2601–10 [13] |
| RA-MAP: Towards a Cure for RA | Prospective longitudinal cohort of early RA | Total in cohort: $n = 275$
Serum
Plasma
Peripheral blood mononuclear cells
Whole blood
RNA
DNA
Urine
X-rays
US data on a subset | Via steering committee | None, to date [10] |
| Scottish Early RA Inception Cohort | Newly presenting RA and undifferentiated arthritis; prospective longitudinal cohort with 6-monthly follow-up | On-going collection DNA RNA (peripheral blood)
Serum
X-ray | Via steering committee | Stalmach et al. PloS One 2014;9:e104625 [14]; Kronish et al., Arthritis Rheumatol 2016 (epub ahead of print) [15] |
In summary, better targeting of therapies to patients most likely to respond to them, earlier in the disease course, is a fundamental principle underpinning the work of the MATURA Consortium. Although the MATURA work focuses on RA, if successful, similar approaches could be applied to other complex rheumatic diseases for which there is a need for improved treatment response.

Supplementary data

Supplementary data are available at Rheumatology Online.

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