Article:
Melville, AR, Kearsley-Fleet, L, Buch, MH orcid.org/0000-0002-8962-5642 et al. (1 more author) (2020) Understanding Refractory Rheumatoid Arthritis: Implications for a Therapeutic Approach. Drugs, 80 (9). pp. 849-857. ISSN 0012-6667

https://doi.org/10.1007/s40265-020-01309-9

Understanding refractory rheumatoid arthritis: implications for therapeutic approach

Running head: Understanding refractory rheumatoid arthritis: implications for therapeutic approach.

Andrew R Melville[1], Lianne Kearsley-Fleet[2]*, Maya H Buch[2,3] and Kimme L Hyrich[†2,3]*

Affiliations:

[1]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom.

[2]Centre for Musculoskeletal Research, The University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom.

[3]National Institute of Health Research Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom.

**Andrew Melville and Lianne Kearsley-Fleet contributed equally to this review.*

Funding: No external funding was used in the preparation of this manuscript.

Conflict of interest: AM and LKF declare no conflicts of interest. MB has received research grants paid to her employer from Pfizer, Bristol-Myers Squibb, Roche, UCB and provided expert advice and received consultant fees from AbbVie, Bristol-Myers Squibb, Eli Lilly, EMD Serono, Pfizer, Roche, Sandoz, Sanofi and UCB. KH has received honoraria from Abbvie (paid to institution) and grant income from Pfizer, BMS and UCB (paid to institution).

Word count: ~~3292~~3469

†Corresponding author:
Professor Kimme Hyrich
Centre for Musculoskeletal Research
2.800 Stopford Building
The University of Manchester
Oxford Road, Manchester
M13 9PT United Kingdom
Kimme.hyrich@manchester.ac.uk

Abstract (250/250 words)

Refractory RA has emerged as an area of unmet need in a landscape of generally well-controlled disease. Whilst most patients are adequately treated on methotrexate and other first-line disease-modifying anti-rheumatic drugs (DMARDs), a proportion requires biologic (b) and targeted synthetic (ts) DMARDs, with a further subsection failing multiple agents. Recent observational studies have adopted working definitions of refractory RA based on number of failed DMARDs, with prevalence estimates of 6 – 21% depending on threshold and study population. Risk factors include treatment delay, baseline disease activity and function, female gender, smoking, obesity and lower socioeconomic status. Practical and conceptual challenges in defining refractory RA arise from limitations of disease activity scores used to assess response, with attendant misclassification risk of co-existent non-inflammatory pathology, and failure to capture additional outcomes, such as fatigue, that have variable treatment response. Time is an important factor in defining refractory disease; registry studies show that growing treatment options have resulted in rapid b/tsDMARD cycling and earlier refractory status, and refractory RA is itself a dynamic concept, evolving with each new therapeutic class. Whilst the biology underpinning refractory RA remains largely unknown, a general overview of biomarker studies and clinical trials old and new offers insights into prediction of response and treatment failure. Whilst the future holds promise, current data is insufficient to personalise or meaningfully sequence b/tsDMARDs. Therefore, avoidance of a refractory course is best achieved by following proven management paradigms (e.g. early diagnosis and treat-to-target), addressing modifiable risk factors, and considering enrolment in novel trials.

~~Rheumatoid arthritis (RA) is a common autoimmune disease affecting 1% of the adult population. Whilst many patients are adequately treated with methotrexate and other conventional synthetic (cs) disease modifying anti-rheumatic drugs (DMARDs), an estimated two-fifths of patients do not respond to methotrexate and many will go on to require a biologic (b) or targeted synthetic (ts) DMARD. For most patients, b/ts DMARDs offer the real opportunity for disease remission, but for a small but not insignificant proportion, disease control remains elusive despite trials of multiple different b/ts DMARDs. This review discusses the concept of refractory RA and our current understanding of this potentially unmet need in rheumatology.~~

Key Points:

- Despite tremendous progress in the treatment of rheumatoid arthritis (RA) over the past two decades in the era of targeted therapies, refractory disease has emerged as an area of unmet clinical need.
- There is currently no universally accepted definition of refractory RA, but various working definitions based on number of failed DMARDs have permitted initial insights into the scale of the problem and risk factors for a refractory disease course.
- A detailed mechanistic understanding of the biology underpinning refractory RA, or indeed response / non-response to targeted therapies, is lacking; tailoring of therapy at an individual level (which in theory might minimise the risk of sequential non-response) remains an aspiration.

1. Introduction: Rheumatoid Arthritis and Biologic Therapy

Rheumatoid arthritis (RA) is an autoimmune disease with a prevalence of approximately 1% of the adult population[1]. Whilst many patients are adequately treated with methotrexate and other conventional synthetic (cs) disease modifying anti-rheumatic drugs (DMARDs), an estimated two-fifths of patients fail to respond to these first-line treatments and ~~do not respond to methotrexate and may have to go on to~~ require a biologic (b) or targeted synthetic (ts) DMARD[2].

Since the success of the first tumour necrosis factor (TNF) inhibitors in the late 1990s, b/tsDMARDS have played a major role in transforming outcomes in RA, with positive effects on remission rates, joint damage/radiographic progression, function, quality of life and co-morbidities. The therapeutic options have exploded in recent years, with five different TNF inhibitors now available as well as therapies which modify other immune pathways, including interleukin inhibitors (IL6, IL1), anti-CD20 B-cell depleting agents, and T-cell co-stimulation (CTLA4) inhibitors. Most recently, intracellular-acting small molecule therapies have further expanded the treatment armamentarium, with the arrival of janus kinase (JAK) inhibitors (Table 1).

Table 1: Biologic and targeted DMARDs licensed by the European Medicines Agency (EMA) for rheumatoid arthritis (RA).

Tumour Necrosis Factor (TNF) inhibitors:
• Adalimumab • Certolizumab pegol • Etanercept • Infliximab • Golimumab
Interleukin-1 receptor antagonist:
• Anakinra
Interleukin-6 pathway inhibitor
• Sarilumab (receptor antagonist) • Tocilizumab (receptor antagonist)
Cell-targeted B-cell depleting agents:
• Rituximab (anti-CD20 Ig)
T-cell co-stimulation blockers:
• Abatacept (anti-CTLA4 Ig)
Janus kinase (JAK) inhibitors:
• Baricitinib • Tofacitinib

International guidelines recommend b/tsDMARD therapy after csDMARD failure (methotrexate monotherapy in most cases). In some countries, further stipulations prior to b/tsDMARDs exist, largely for health economic reasons; in the UK, for example, failure of at least two csDMARDs and a high disease activity score (28 joint count disease activity score (DAS28) > 5.1) are required. TNF inhibitors, as the first bDMARD to be introduced, continue to be the most commonly prescribed first-line bDMARD. This reflects clinician familiarity and abundant effectiveness and safety data; however,

randomised controlled trials (RCT) and (in the absence of head to head trials) network meta-analyses essentially suggest equivalent effectiveness across agents, and latest guidelines no longer recommend any hierarchical positioning[3–5].

In this review, we aim to provide an understanding of the emerging concept of refractory RA. We summarise the findings of recent observational studies on this subject, including definitions used, limitations thereof, and risk factors identified. In the absence of a detailed understanding of the biology underpinning refractory RA itself, we explore the scientific and wider clinical basis of response to therapy and treatment failure in general, ultimately outlining current and future implications for research and clinical practice.

2. Refractory disease

2.1. Extent of the problem and proposed definitions

Whilst targeted therapies (along with influential management paradigms including early diagnosis, early DMARD initiation, and treat to target) have led to improved outcomes for the vast majority of patients, an important subgroup continue with inadequately controlled disease, refractory to multiple drugs with different modes of action. Refractory RA remains under-represented in the literature, and a full appreciation of the individual impact and health economic burden is lacking, but it is increasingly recognised as an area of unmet clinical need[6].

There is currently no consensus definition for refractory RA. Indeed, it should be noted that, as the number of targeted therapies increases, the definition of what constitutes refractoriness continues to evolve. To illustrate this point, studies from the fairly recent past defined refractory disease based on failure of methotrexate alone[7], whilst most recent studies focus on multiple DMARD failures, including one or more b/tsDMARD.

In a recent observational study from Vienna, refractory RA was defined as failure to achieve low disease activity despite three or more DMARDs, of which one must be a bDMARD. Approximately 17% of a tertiary centre cohort met this definition, and 6% of a community hospital validation cohort[8]. Female gender, time to first treatment, and higher baseline disease activity predicted refractory disease in a multivariable model, with a 50% predicted probability amongst the most high-risk patients. Refractory patients also had a slightly younger age at onset (mean age 44 versus 51 years for treatment amenable patients). Known disease-specific factors associated with “severe” RA (i.e. predictive of radiographic progression), including sero-positivity for cyclic citrullinated peptide (CCP) or rheumatoid factor (RF), and baseline radiographic damage score, were non-significant in the model. In work published by the British Society for Rheumatology Biologics Register for RA (BSRBR-RA), among 13,502 patients starting their first bDMARD, 21% went on to start a third[9], consistent with an estimate extrapolated from RCT data[10]. H~~; h~~owever~~-~~, there is an argument for defining *(truly)* refractory RA as failure of multiple b/tsDMARD *classes*[10,11], as variation in key cytokine and cellular mechanisms driving pathogenesis and persistence, and/or redundancy in inflammatory pathway signalling, could explain single class failure. Therefore, another working definition in the BSRBR-RA study was failure of two classes of bDMARD (inadequate response or toxicity); e~~.~~ ~~E~~xcluding within-

class switches (TNF inhibitor to TNF inhibitor switches in particular were common prior to the introduction of alternative b/tsDMARDs), a lower percentage (6%) of bDMARD treated patients progressed to a third class[9]. This study also highlighted factors (measured at the start of their first bDMARD) associated with refractory disease including female gender, younger age, higher patient global assessment and HAQ, current smoking, obesity, and lower socioeconomic status.

Considering the range of therapies available for treatment of RA, it might be possible to simply define refractory RA as "resistance to multiple therapeutic drugs with different structures and mechanisms of action"[10]. Whether stopping therapy due to adverse events should be considered non-response (and count towards meeting a definition of refractoriness) is debatable, ultimately depending on whether the context (or study) calls for a more biological or pragmatic definition.

2.2. Challenges in assessing response (and ~~measuring disease activity and defining~~ non-response) to treatment

International guidelines for RA advocate a treat to target approach[4,5], based on monitoring of composite disease activity scores and intensification of therapy accordingly. Commonly used scores include DAS28[12], clinical disease activity index (CDAI)[13] and simplified disease activity index (SDAI)[14]; these encompass a range of subjective and objective clinical parameters, and have specific cut-offs to define remission, low, moderate and high disease activity (LDA, MDA, HDA) (Table 2). Remission is the modern target for newly diagnosed RA, achievement of which is associated with favourable short and long-term clinical outcomes[15], even compared with LDA[16], which is considered a suboptimal alternative/compromise. Non-response to treatment can therefore be defined clinically as failure to achieve an acceptable state of disease activity, i.e. at least LDA, within three to six months (primary non-response), or loss of control after an initial response lasting months to years (secondary non-response).

Table 2: Disease activity measures for rheumatoid arthritis.

Measurements (components)	Categories
DAS28[12] **(range 0-10)**	
• Tender joint count • Swollen joint count • Patient global assessment of health • ESR	Remission: <2.6 Low disease activity (LDA): >2.6 to <3.2 Moderate disease activity (MDA): >3.2 to ≤5.1 High disease activity (HDA): >5.1
CDAI[13] **(range 0-76**	
• Tender joint count • Swollen joint count • Patient global assessment of health • Clinician global assessment of disease activity	Remission: ≤2.8 Low disease activity (LDA): >2.8 to ≤10 Moderate disease activity (MDA): >10 to ≤22 High disease activity (HDA): >22
SDAI[14] **(range 0-86)**	
• Tender joint count • Swollen joint count • Patient global assessment of health	Remission: ≤3.3 Low disease activity (LDA): >3.3 to ≤11 Moderate disease activity (MDA): >11 to ≤26

• Clinician global assessment of disease activity • CRP	High disease activity (HDA): >26
Clinical disease activity score (CDAI); c-reactive protein (CRP); 28-joint disease activity score (DAS28); erythrocyte sedimentation rate (ESR); simplified disease activity score (SDAI).	

The use of composite scores to define treatment response, and by extension refractory RA, has its limitations. Subjective components are heavily weighted in the DAS28 formula; indeed, the tender joint count (which may be influenced by co-existent osteoarthritis or chronic pain) has double the weight of the swollen joint count. Another issue is the (un)feasibility of achieving low disease activity scores (particularly remission according to the strict ACR/EULAR definitions[17]) in long-standing disease, where damage, functional limitations and fatigue may have a major impact on patient global assessment[18]. There is a risk, therefore, that patients with non-inflammatory pathology might be misclassified as having active disease; switching b/tsDMARD therapy in this context is unlikely to improve symptoms, and perpetuation of this cycle could quickly amount to apparent refractoriness.

In theory, more objective measures, such as musculoskeletal ultrasound to confirm the presence of active synovitis, could aid assessment of response and avoid unnecessary treatment changes. Discrepancies between DAS28 scores and ultrasound activity are well-recognised[19]; indeed, in early RA it appears that only the objective DAS28 components (swollen joint count, CRP) correlate with presence of grey scale/power Doppler[20]. The use of ultrasound to validate ongoing refractory disease remains to be formally evaluated.

EULAR has recently (2019) set up a task force on "difficult to treat RA"[6], a concept that incorporates uncontrolled inflammatory disease, but also wider contextual factors such as chronic pain and fatigue, as well as co-morbidities, recurrent infections or other adverse events that limit treatment options. We would consider this a broader definition, rather than a synonym for refractory RA[21], which could be considered a (rare) sub-entity of demonstrable inflammatory aetiology. Nevertheless, it is well-recognised that many patients with "acceptable" disease activity scores have significant pain, fatigue, and functional disability[22–25]. Whilst some of these symptoms might have an inflammatory or RA-related biological basis (e.g. cytokine-mediated[26]), they often persist in spite of targeted therapy, and may be multifactorial. Understanding this disconnect is clearly of high relevance for clinical practice. It is also important to remember that treatment success ultimately depends not only on biological factors, but also wider contextual and psychosocial issues, health beliefs, and drug adherence[27].

2.3. Personalised medicine and predicting response to treatment for RA – elusive goals~~Predictors of response and reasons for treatment failure~~

The principles of personalised medicine (adopted from oncology in particular) have been influential in shaping the research landscape in rheumatology, leading to a wealth of biomarker studies (including genetic, transcriptomic, serum) conducted to identify ~~(~~often mechanistic~~)~~ predictors of response and non-response to therapy. Herein, RA is considered a syndrome of familiar clinical phenotype, but driven by distinct, treatment-targetable molecular mechanisms[28]. Ultimately personalised medicine would see a move away from clinical classification and trial-and-error prescribing, towards pathology-driven nosology and tailored therapy, thus reducing treatment failure. In general, results to date

(some of which are discussed below) have been insufficient to apply in practice, either accounting for modest variation in response and/or conducted in small numbers, or not taken through to validation. Research focussing on the biological basis of multi-DMARD refractory RA specifically is limited, but it is logical that sequential treatment failure will contribute to refractory outcomes.

2.3.1. Genetics and transcriptomic biomarkers

Genetic mutations (SNPs) have been extensively studied as predictors of response/non-response to b/tsDMARDs (particularly TNF inhibitors)[29], but small effect sizes and inconsistent reproducibility have limited their clinical utility[30–32]. Indeed, some associations may represent type 1 error. Interferon response gene signatures (detectable in peripheral blood by various methods) may also have relevance, with high scores predictive of non-response to rituximab in more than one study[33,34], independent of auto-antibody status, and producing an area under the receiver operating characteristic curve of 0.83 to 0.87, close to excellent (>0.90)[34]. Validation in large cohorts has not been performed.

~~Of several serum biomarkers studies, the ratio of soluble intercellular adhesion molecule 1 (sICAM1) to C-X-C motif chemokine 13 (CXCL13), proposed as a serum correlate of myeloid versus lymphoid dominant synovial pathology respectively, differentiated response to therapy in a phase 4 trial biomarker sub-study; high sICAM:CXCL13 ratio predicted response to anti-TNF therapy, whilst the reverse predicted response to anti-IL6R. This however has not been reproduced in other studies[34]. Interferon response gene signatures (detectable in peripheral blood by various methods) may also have relevance, with high scores predictive of non-response to rituximab in more than one study[35,36], independent of auto-antibody status, and producing an area under the receiver operating characteristic curve of 0.83 to 0.87, close to excellent (>0.90). Validation in large cohorts has not been performed.~~

2.3.2. Serological status and other serum biomarkers

Serological status ~~however~~ remains the most effective treatment stratifier at the disease level, and the only one used currently in routine clinical use. There is strong evidence from meta-analyses that rituximab is more effective in seropositive RA (CCP or RF positive, or both)[35,36]. Abatacept also appears more effective in seropositive patients, according to pooled registry data showing lower discontinuation rates[37]. These observations seem mechanistically plausible, given the modes of action of these agents (CD20+ B-cell lysis, and disruption of antigen presentation / T-cell-mediated B-cell help, respectively[38]).

Of several serum biomarkers studies, the ratio of soluble intercellular adhesion molecule 1 (sICAM1) to C-X-C motif chemokine 13 (CXCL13), proposed as a serum correlate of myeloid versus lymphoid dominant synovial pathology respectively, differentiated response to therapy in a phase 4 trial biomarker sub-study; high sICAM:CXCL13 ratio predicted response to anti-TNF therapy, whilst the reverse predicted response to anti-IL6R[39]. This however has not been reproduced in other studies[40].

2.4. Treatment failure – insights from clinical studies

Clinical studies in biologic-experienced patients offer further insights. Following inadequate response (IR) to TNF inhibition, superior response rates are ~~have been~~ seen with non-TNF inhibitor b/tsDMARDs compared with another TNF inhibitor[37], which, may suggest ~~alternative pathway~~ predominance of an alternative pathway medicating disease, or emergence of an "escape" pathway where loss of response has occurred. Reasonable responses to subsequent TNF inhibition are also well-described[41], however, meaning drug-specific issues (e.g. pharmacokinetics and bioavailability) undoubtedly contribute. Anti-drug antibodies, which have the potential to neutralise or increase clearance of bDMARDs, represent a well-publicised mechanism to explain non-response in some cases, but likely only a modest proportion[42,43].

Novel therapies targeting alternative cytokines (e.g. GM-CSF[44]) continue to be developed, and their impact remains to be seen. It is conceivable that some refractory RA disease may be driven by such mechanisms.

It may also be possible to learn lessons from targeted therapies that failed unexpectedly in RCTs of the past. Inhibitors of IL-1[45] and IL-17A[46] yielded disappointing results in RA, despite compelling pre-clinical supporting pathogenetic roles for both[47,48]. One reason for this may be the "population science" approach of conventional trial methodology, with selection of patients based on clinical classification criteria alone allowing marked heterogeneity at ~~a~~ molecular level, attendant variation in response, and too much "noise"~~, and inability~~ to detect responsive sub-populations.

2.4.1. A new era in RA trials – stratification by synovial tissue

If we are to gain better understanding of the biological basis for response / non-response to therapy (and more generally make p~~P~~rogress towards a molecular taxonomy of disease in RA) ~~continues, with~~ analysis of synovial tissue (the primary manifestation of disease and a rich source of potential biomarkers) is likely to play a key role~~element~~[49]. Synovial biopsy does not form part of standard clinical practice in RA currently, but the successful development of reliable, minimally invasive ultrasound-guided biopsy techniques for both small and large joints means this could be a realistic proposition in future if it would enhance therapeutic decision making[50].

A number of recent biopsy-mandated trials have been performed in RA at different stages of disease, namely early, treatment-naïve RA (PEAC)[49], csDMARD-IR (STRAP – ISRCTN 10618686), and TNF-IR (R4-RA – ISRCTN 97443826). Aims include stratifying patients according to distinct underlying histological patterns and molecular signatures (termed "pathotypes"), an approach which appears to offer additional prognostic information, and might enable prediction of response to different therapies and ultimately tailored decision making. ~~publications have focussed on stratification of RA by synovial tissue architecture and molecular signals, and the potential of this approach to predict response to therapy, in early, treatment-naïve RA (PEAC), csDMARD-IR (STRAP – ISRCTN 10618686), and TNF-IR (R4-RA – ISRCTN 97443826). STRAP and R4-RA are biopsy-mandated RCTs and represent a new era in RA trials.~~ Preliminary analyses of PEAC data ~~have~~ identified three distinct ~~disease "~~pathotypes~~"~~ (lympho-myeloid, diffuse-myeloid, fibroid/pauci-immune), with lymphoid and myeloid transcriptomes ~~ic signatures~~ predicting csDMARD response in treatment-naïve RA at six months (the former also predicting radiographic progression)[51]. In related analyses, patients of lympho-myeloid

pathotype were more likely to progress to bDMARD therapy by 12 months, and integration of pathobiological data with clinical parameters improved prediction of this outcome from 79% to 90%[52]. In TNF-IR synovitis, compared with treatment-naïve tissue, ~~B-cells were~~ enrichment of B-cells was seen~~ed~~ (present in 47% versus 35%), and whilst in early RA presence of B-cells correlated with signs of active disease detectable clinically, these were no longer apparent in TNF-IR[53]. All of these data suggest that tissue characterisation can add value to current practice of clinical assessment alone. Preliminary results from R4-RA suggest superior major response rates (CDAI improvement ≥ 50% and CDAI ≤10.1) with tocilizumab rather than rituximab in TNF-IR patients with B-cell poor synovitis[54]. Final analysis reports are awaited to clarify potential utility in clinical practice. Regarding refractory RA specifically, whilst it is well-established that biologic therapy alters the synovial cellular and cytokine environment in diverse ways[55], ~~and~~ relevant synovial tissue studies are awaited.

2.4.2. The ceiling effect – common mechanisms for inadequate response?

Remarkably similar RCT outcomes across targeted therapies (generally ACR20/50/70 response rates of approximately 60/40/20% after MTX-IR) beg the question whether a ceiling has been reached with current approaches to treatment. Hypotheses (which remain unproven) to explain this phenomenon include a "bottleneck" effect in cytokine signalling, ~~with~~ whereby all pathways ultimately converge~~ing~~ on the same key end mediators (~~particularly~~ principally TNFa and/or IL6)[56]. Alternatively, failure of resolution (distinct from absence of inflammation) may be a common mechanism underpinning residual disease activity; stromal cells, particularly fibroblasts, have an instrumental role in orchestrating and perpetuating synovitis, and direct targeting may represent a novel therapeutic avenue[57]. To this end, an early phase study of a seliciclib, a cyclin dependent kinase inhibitor (proposed to disrupt fibroblast proliferation, cytokine and matrix metallopeptidase~~s~~ release), is currently underway (ISRCTN 36667085). The fibroid RA pathotype identified above[51], with prevalent stromal cells and scanty immune cells, perhaps offers continuity to this narrative.

Evidence from the use of JAK inhibitors, which disrupt multiple cytokines simultaneously (including IL6, IFNg, GMCSF, IL12, IL23), provides further insights into refractory disease and ~~may~~ challenges the hypotheses above, as RCT outcomes ~~(ACR20 responses)~~[58] and real-world evidence[59] suggest ~~equivalent~~ effectiveness may be maintained in multi-biologic refractory cohorts.

2.5. Wider contextual factors in treatment failure

Importantly, wider contextual factors (some of which are modifiable) are known to ~~also~~ contribute to treatment failure. Smoking and obesity are associated with ineffectiveness of treatment and adverse drug reactions[60,61]. Smoking is thought to reduce clinical responses through the high concentrations of pro-inflammatory cytokines produced[62,63]; similarly in obesity, adipose tissue and adipokines lead to a pro-inflammatory environment[64]. Obesity may also influence exposure to therapies, particularly where dosing is not based on overall body mass. These factors can also be linked with social deprivation, alongside other factors such as comorbidities and suboptimal adherence, all of which can compromise treatment response[65]. Failure to respond to a treatment ought to imply adequate drug exposure in the first place, i.e. medication prescribed at the appropriate dosage, with full adherence. Research in adherence to bDMARD therapies has found that at least 15% of patients with RA do not take their bDMARD on the agreed day, with one-in-ten taking the drug over a week

before or after, or not at all. Amongst the 15% not taking therapy as prescribed, there was significantly less improvement in disease activity after six months[65]. In such cases, apparent 'non-response' may be explained by inadequate drug exposure, rather than disease-specific or drug-specific causes.

2.6. ~~Changes in current practice~~Changes in prescribing patterns over time – refractory disease or abundance of choice?

One challenge in studying refractory disease is that, by definition, in the absence of multiple treatment options, a patient cannot be classified as having multi-treatment resistant disease. This point must be taken into account when using longitudinal datasets to explore whether refractory disease is more or less common over time. Long-term registry studies, such as the UK BSRBR-RA (introduced above)[9], have found that the proportion of patients classified as having refractory disease has not changed significantly, but that since 2011 (the point of dichotomy within this analysis) patients were classified as becoming refractory much sooner. This is not surprising given the wider choice of therapies being used, within a treat-to-target era, and likely lower thresholds for tolerating higher disease activity levels over time. In general, over the course of the 21st century, patients with RA have been starting bDMARD therapies earlier in disease-course, with fewer numbers of previous csDMARDs, greater proportions of concurrent methotrexate, and ultimately reduced functional disability. It will be of interest to observe how the recent introduction of biosimilars[66], and the associated major cost savings, impact on the positioning and perception of biologic (and eventually targeted synthetic) DMARDs. Will we see a reduction in refractory disease with earlier targeted therapy, and/or will more routine use of what were once regarded precious commodities result in a lowering of thresholds for cycling?

3. Implications for ~~the patient and healthcare practitioner,~~ clinical practice and future perspectives

~~Refractory RA is an emerging concept and represents an area of unmet clinical need within a landscape of generally well-treated disease in the modern era.~~ Efforts to better understand and characterise refractory disease should ultimately be with a view to preventing it. In theory, prognostic biomarkers for a refractory course could, for example, stratify at-risk patients to earlier b/tsDMARD therapy, but this is currently without basis.

More broadly, whilst we know that responses diminish with successive lines of b/tsDMARD therapy[67] (which might suggest ~~perhaps suggesting~~ that initial choice of therapy is ~~might be~~ a crucial checkpoint on the path towards either well-controlled or refractory disease), we do not have meaningful data (with the exception of seropositivity) to better prioritize or sequence b/tsDMARDs. Observational studies addressing this question have major limitations, including confounding by indication and artefact (e.g. differential suppression of CRP by biologics targeting IL-6R). For the time being, therefore, the best healthcare practitioners can do to prevent refractory disease is to follow established treatment paradigms, such as early DMARD initiation, treat-to-target, and addressing modifiable lifestyle factors (particularly smoking and obesity).

~~Working definitions for refractory RA, based on arbitrary numbers of DMARD failures, have permitted preliminary observations on the scale of the problem, and tentative patient-specific and disease-specific associations. Conceptual and practical difficulties in defining refractory RA (including the limitations of disease activity scores and the challenges of disentangling inflammatory from non-inflammatory pathology) have been discussed above.~~ Looking to the future, a deeper understanding of the mechanisms underpinning persistent / drug-resistant disease might lead to optimisation of the use of existing treatments, or indeed novel targeted therapies. In this light, the study of refractory RA (as an extreme phenotype) might have value not only for affected individuals, but also for understanding inadequate response as a whole. Stratification trials (introduced in section 2.4.1)~~, such as STRAP and R4-RA, represent a novel era in RA trial design. Such studies~~ are likely to become increasingly sophisticated as the development and integration of new molecular technologies~~/~~ and analyses continue to gather pace. Whether we will see an era of truly tailored therapy, and reduced treatment failure, remains to be seen ~~(and in the meantime, b/tsDMARD prescribing will continue to be mostly dependent on individual preferences, restricted by cost and availability)~~, but healthcare professionals and patients should be encouraged to consider trial participation. On a related point, a re-evaluation of trial outcomes might be warranted going forward to maximise benefits for patients, with additional emphasis ~~a focus perhaps~~ on individual disease domains (such as pain and fatigue) rather than conventional composite disease activity scores~~composite scoring~~, thereby~~thus~~ taking ~~into~~ account of differential response profiles observed ~~differences in the impact of these~~ across b/tsDMARDs and potentially leading to form treatment tailoring according to symptomatology~~, and helping to maximise potential benefits to patients~~. In the meantime, b/tsDMARD prescribing will continue to be mostly dependent on individual preferences, restricted by cost and availability.

~~Finally, we should remain mindful of the relevance of the wider clinical and sociodemographic factors incorporated by the broader and related concept of "difficult to treat RA" (e.g. pain sensitization, co-morbidities, social determinants of health and access to care), some of which are likely beyond the power of current medical therapy to overcome.~~

4. Conclusions

Refractory RA is an emerging concept and represents an area of unmet clinical need within a landscape of generally well-treated disease in the modern era. Working definitions for refractory RA, based on arbitrary numbers of DMARD failures, have permitted preliminary observations on the scale of the problem, and tentative patient-specific and disease-specific associations. Conceptual and practical difficulties in defining refractory RA (including ~~the limitations of disease activity scores and the challenges of~~ disentangling inflammatory from non-inflammatory pathology, and the evolving nature of refractoriness with the passage of time and emergence of new lines of therapy) have been discussed above. Despite much interest in understanding and predicting response and non-response to targeted therapies, few research findings have made it into clinical practice, and tailoring treatment remains out of reach. Novel trial designs incorporating synovial tissue analysis show some promise. The molecular basis of true multi-drug failure, amounting to refractory disease, remains poorly understood. Amidst a focus on molecular medicine in the targeted therapies era, it is important to ~~Finally, we should~~ remain mindful of the relevance of ~~the~~ wider clinical and sociodemographic factors (including social determinants of health and access to care) that contribute to treatment failure and

may be ~~incorporated by the broader and related concept of "difficult to treat RA" (e.g. pain sensitization, co-morbidities, social determinants of health and access to care), some of which are likely~~ beyond the power of current medical therapy to overcome.

References

1. Humphreys JH, Verstappen SM, Hyrich KL, Chipping JR, Marshall T, Symmons DP. The incidence of rheumatoid arthritis in the UK: comparisons using the 2010 ACR/EULAR classification criteria and the 1987 ACR classification criteria. Results from the Norfolk Arthritis Register. Ann Rheum Dis [Internet]. 2012/09/05. 2013;72:1315–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22945499

2. Sergeant JC, Hyrich KL, Anderson J, Kopec-Harding K, Hope HF, Symmons DPM, et al. Prediction of primary non-response to methotrexate therapy using demographic, clinical and psychosocial variables: Results from the UK Rheumatoid Arthritis Medication Study (RAMS). Arthritis Res Ther. 2018;

3. NICE. TA375: Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed [Internet]. National Institue for Health and Care Excellence; 2016. Available from: nice.org.uk/guidance/ta375

4. Smolen JS, Landewe 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. Ann Rheum Dis [Internet]. 2017/03/08. 2017;76:960–77. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28264816

5. Singh JA, Saag KG, Bridges Jr. SL, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol [Internet]. 2015/11/08. 2016;68:1–26. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26545940

6. Roodenrijs NMT, De Hair MJH, Van Der Goes MC, Jacobs JWG, Welsing PMJ, Van Der Heijde D, et al. Characteristics of difficult-to-treat rheumatoid arthritis: Results of an international survey. Ann Rheum Dis. 2018;

7. Bingham SJ, Buch MH, Tennant A, Emery P. The impact of escalating conventional therapy in rheumatoid arthritis patients referred for anti-tumour necrosis factor-α therapy. Rheumatology. 2004;

8. Bécède M, Alasti F, Gessl I, Haupt L, Kerschbaumer A, Landesmann U, et al. Risk profiling for a refractory course of rheumatoid arthritis. Semin Arthritis Rheum. 2019;

9. Kearsley-Fleet L, Davies R, De Cock D, Watson KD, Lunt M, Buch MH, et al. Biologic refractory disease in rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Ann Rheum Dis [Internet]. 2018/07/08. 2018;77:annrheumdis-2018-213378. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29980575

10. Buch MH. Defining refractory rheumatoid arthritis. Ann Rheum Dis. 2018;

11. Fitton J, Melville A, Naraghi K, Nam J, Dass S, Emery P, et al. FRI0090 SINGLE CENTRE COHORT OF REFRACTORY RHEUMATOID ARTHRITIS ALSO IDENTIFIES A RARE SUBGROUP OF MULTIPLE TARGETED THERAPY CLASS NON-RESPONSE. Ann Rheum Dis. 2019;78:708.

12. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum [Internet]. 1995/01/01. 1995;38:44–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7818570

13. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther [Internet]. 2005/07/01. 2005;7:R796-806. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15987481

14. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatol [Internet]. 2003/02/22. 2003;42:244–57. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12595618

15. Combe B, Logeart I, Belkacemi MC, Dadoun S, Schaeverbeke T, Daurès JP, et al. Comparison of the long-term outcome for patients with rheumatoid arthritis with persistent moderate disease activity or disease remission during the first year after diagnosis: Data from the ESPOIR cohort. Ann

Rheum Dis. 2015;74:724–9.
16. Radner H, Smolen JS, Aletaha D. Remission in rheumatoid arthritis:Benefit over low disease activity in patient-reported outcomes and costs. Arthritis Res Ther. 2014;16.
17. Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis. 2014;73:492–509.
18. Baker KF, Pratt AG, Thompson B, Isaacs JD. Let's not fool ourselves. In RA, the ACR/EULAR remission criteria are not perfect! Ann Rheum Dis [Internet]. 2017;76:e12. Available from: https://ard.bmj.com/content/76/6/e12.long
19. Horton SC, Tan AL, Freeston JE, Wakefield RJ, Buch MH, Emery P. Discordance between the predictors of clinical and imaging remission in patients with early rheumatoid arthritis in clinical practice: Implications for the use of ultrasound within a treatment-to-target strategy. Rheumatol (United Kingdom). 2016;
20. Hensor EMA, McKeigue P, Ling SF, Colombo M, Barrett JH, Nam JL, et al. Validity of a two-component imaging-derived disease activity score for improved assessment of synovitis in early rheumatoid arthritis. Rheumatology. 2019;1–10.
21. Buch MH. Response to "Correspondence to viewpoint 'Defining refractory rheumatoid arthritis' by Buch" by Roodenrijs et al. Ann Rheum Dis. 2019;78:e106.
22. Hyrich KL, Watson KD, Lunt M, Symmons DPM, British Society for Rheumatology Biologics Register. Changes in disease characteristics and response rates among patients in the United Kingdom starting anti-tumour necrosis factor therapy for rheumatoid arthritis between 2001 and 2008. Rheumatol [Internet]. 2010/07/31. 2011;50:117–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20671021
23. Hamann PDH, Pauling JD, McHugh N, Shaddick G, Hyrich K, Maiden N, et al. Predictors, demographics and frequency of sustained remission and low disease activity in anti-tumour necrosis factor–treated rheumatoid arthritis patients. Rheumatology. 2019;
24. Kihara M, Davies R, Kearsley-Fleet L, Watson KDD, Lunt M, Symmons DPMP, et al. Use and effectiveness of tocilizumab among patients with rheumatoid arthritis: an observational study from the British Society for Rheumatology Biologics Register for rheumatoid arthritis. 2016/12/04. 2017;36:241–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27913894
25. Druce KL, Basu N. Predictors of fatigue in rheumatoid arthritis. Rheumatol. (United Kingdom). 2019.
26. Choy EHS, Calabrese LH. Neuroendocrine and neurophysiological effects of interleukin 6 in rheumatoid arthritis. Rheumatol. (United Kingdom). 2018.
27. Landewé RBM. Overdiagnosis and overtreatment in rheumatology: A little caution is in order. Ann Rheum Dis. 2018;
28. McInnes IB, Buckley CD, Isaacs JD. Cytokines in rheumatoid arthritis-shaping the immunological landscape. Nat. Rev. Rheumatol. 2016.
29. Criswell LA, Lum RF, Turner KN, Woehl B, Zhu Y, Wang J, et al. The influence of genetic variation in the HLA-DRB1 and LTA-TNF regions on the response to treatment of early rheumatoid arthritis with methotrexate or etanercept. Arthritis Rheum. 2004;
30. Plant D, Wilson AG, Barton A. Genetic and epigenetic predictors of responsiveness to treatment in RA. Nat. Rev. Rheumatol. 2014.
31. Cui J, Saevarsdottir S, Thomson B, Padyukov L, Van Der Helm-van Mil AHM, Nititham J, et al. Rheumatoid arthritis risk allele PTPRC is also associated with response to anti-tumor necrosis factor α therapy. Arthritis Rheum. 2010;
32. Pappas DA, Oh C, Plenge RM, Kremer JM, Greenberg JD. Association of rheumatoid arthritis risk alleles with response to anti-TNF biologics: Results from the CORRONA registry and meta-analysis. Inflammation. 2013;
33. Thurlings RM, Boumans M, Tekstra J, Van Roon JA, Vos K, Van Westing DM, et al. Relationship between the type I interferon signature and the response to rituximab in rheumatoid arthritis

patients. Arthritis Care Res. 2010;
34. Raterman HG, Vosslamber S, de Ridder S, Nurmohamed MT, Lems WF, Boers M, et al. The interferon type I signature towards prediction of non-response to rituximab in rheumatoid arthritis patients. Arthritis Res Ther. 2012;
35. Isaacs JD, Cohen SB, Emery P, Tak PP, Wang J, Lei G, et al. Effect of baseline rheumatoid factor and anticitrullinated peptide antibody serotype on rituximab clinical response: A meta-analysis. Ann Rheum Dis [Internet]. 2012/06/13. 2013;72:329–36. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22689315
36. Buch MH, Smolen JS, Betteridge N, Breedveld FC, Burmester G, Dörner T, et al. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis. 2011;
37. Gottenberg JE, Courvoisier DS, Hernandez M V., Iannone F, Lie E, Canhão H, et al. Brief Report: Association of Rheumatoid Factor and Anti-Citrullinated Protein Antibody Positivity with Better Effectiveness of Abatacept: Results from the Pan-European Registry Analysis. Arthritis Rheumatol. 2016.
38. Buch MH, Boyle DL, Rosengren S, Saleem B, Reece RJ, Rhodes LA, et al. Mode of action of abatacept in rheumatoid arthritis patients having failed tumour necrosis factor blockade: A histological, gene expression and dynamic magnetic resonance imaging pilot study. Ann Rheum Dis. 2009;68:1220–1227.
39. Dennis G, Holweg CTJ, Kummerfeld SK, Choy DF, Setiadi AF, Hackney JA, et al. Synovial phenotypes in rheumatoid arthritis correlate with response to biologic therapeutics. Arthritis Res Ther. 2014;
40. Tuckwell K, Gabay C, Sornasse T, Laubender RP, Wang J, Townsend MJ. Levels of CXCL13 and sICAM-1 correlate with disease activity score in patients with rheumatoid arthritis treated with tocilizumab. Adv Rheumatol (London, England). Advances in Rheumatology; 2019;59:54.
41. Smolen JS, Kay J, Doyle MK, Landewé R, Matteson EL, Wollenhaupt J, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor α inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet. 2009;
42. Kalden JR, Schulze-Koops H. Immunogenicity and loss of response to TNF inhibitors: Implications for rheumatoid arthritis treatment. Nat. Rev. Rheumatol. 2017.
43. Maneiro JR, Salgado E, Gomez-Reino JJ. Immunogenicity of monoclonal antibodies against tumor necrosis factor used in chronic immune-mediated inflammatory conditions: Systematic review and meta-analysis. JAMA Intern. Med. 2013.
44. Burmester GR, McInnes IB, Kremer J, Miranda P, Korkosz M, Vencovsky J, et al. A randomised phase IIb study of mavrilimumab, a novel GM-CSF receptor alpha monoclonal antibody, in the treatment of rheumatoid arthritis. Ann Rheum Dis. 2017;
45. Mertens M, Singh JA. Anakinra for rheumatoid arthritis: A systematic review. J Rheumatol. 2009;
46. Dokoupilová E, Aelion J, Takeuchi T, Malavolta N, Sfikakis PP, Wang Y, et al. Secukinumab after anti-tumour necrosis factor-α therapy: a phase III study in active rheumatoid arthritis. Scand J Rheumatol. 2018;
47. Kay J, Calabrese L. The role of interleukin-1 in the pathogenesis of rheumatoid arthritis. Rheumatol. 2004;43:iii2–9.
48. Gaffen SL. The role of interleukin-17 in the pathogenesis of rheumatoid arthritis. Curr. Rheumatol. Rep. 2009.
49. Orr C, Sousa E, Boyle DL, Buch MH, Buckley CD, Cañete JD, et al. Synovial tissue research: A state-of-the-art review. Nat. Rev. Rheumatol. 2017.
50. Kelly S, Humby F, Filer A, Ng N, Di Cicco M, Hands RE, et al. Ultrasound-guided synovial biopsy: A safe, well-tolerated and reliable technique for obtaining high-quality synovial tissue from both large and small joints in early arthritis patients. Ann Rheum Dis. 2015;
51. Humby F, Lewis M, Ramamoorthi N, Hackney JA, Barnes MR, Bombardieri M, et al. Synovial

cellular and molecular signatures stratify clinical response to csDMARD therapy and predict radiographic progression in early rheumatoid arthritis patients. Ann Rheum Dis. 2019;
52. Lliso-Ribera G, Humby F, Lewis M, Nerviani A, Mauro D, Rivellese F, et al. Synovial tissue signatures enhance clinical classification and prognostic/treatment response algorithms in early inflammatory arthritis and predict requirement for subsequent biological therapy: Results from the pathobiology of early arthritis cohort (PEA. Ann Rheum Dis. 2019;
53. Rivellese F, Humby F, Bugatti S, Fossati-Jimack L, Rizvi H, Lucchesi D, et al. B cell synovitis and clinical phenotypes in rheumatoid arthritis: relationship to disease stages and drug exposure. Arthritis Rheumatol. 2019;
54. Humby F, Buch MH, Durez P, Lewis M, Bombardieri M, Rizvi H, et al. A Randomised, Open Labelled Clinical Trial to Investigate Synovial Mechanisms Determining Response – Resistance to Rituximab versus Tocilizumab in Rheumatoid Arthritis Patients Failing TNF Inhibitor Therapy [abstract]. Arthritis Rheumatol. 2019;71 (suppl.
55. Ouboussad L, Burska AN, Melville A, Buch MH. Synovial Tissue Heterogeneity in Rheumatoid Arthritis and Changes With Biologic and Targeted Synthetic Therapies to Inform Stratified Therapy. Front Med. 2019;
56. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet. 2016.
57. Dakin SG, Coles M, Sherlock JP, Powrie F, Carr AJ, Buckley CD. Pathogenic stromal cells as therapeutic targets in joint inflammation. Nat. Rev. Rheumatol. 2018.
58. Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, Xie L, et al. Baricitinib in patients with refractory rheumatoid arthritis. N Engl J Med. 2016;
59. Fitton J, Melville A, Dass S, Emery P, Nam J, Buch M. THU0169 JANUS KINASE INHIBITORSDEMONSTRATE EFFECTIVENESS IN A REAL-WORLD MULTI-BIOLOGIC DMARD REFRACTORY RHEUMATOID ARTHRITIS POPULATION. 2019.
60. de Hair MJHH, Jacobs JWGG, Schoneveld JLMM, van Laar JM. Difficult-to-treat rheumatoid arthritis: An area of unmet clinical need. Rheumatol [Internet]. 2017/10/14. 2018; Available from: http://www.ncbi.nlm.nih.gov/pubmed/29029308
61. Hyrich KL, Watson KD, Silman AJ, Symmons DP, British Society for Rheumatology Biologics R. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatol [Internet]. 2006/05/18. 2006;45:1558–65. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16705046
62. Glossop JR, Dawes PT, Mattey DL. Association between cigarette smoking and release of tumour necrosis factor alpha and its soluble receptors by peripheral blood mononuclear cells in patients with rheumatoid arthritis. Rheumatol [Internet]. 2006/04/06. 2006;45:1223–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16585133
63. Chang K, Yang SM, Kim SH, Han KH, Park SJ, Shin J Il. Smoking and rheumatoid arthritis [Internet]. 2014/12/06. Int. J. Mol. Sci. 2014 p. 22279–95. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25479074
64. Daïen CI, Sellam J. Obesity and inflammatory arthritis: Impact on occurrence, disease characteristics and therapeutic response. RMD Open. 2015.
65. Bluett J, Morgan C, Thurston L, Plant D, Hyrich KL, Morgan AW, et al. Impact of inadequate adherence on response to subcutaneously administered anti-tumour necrosis factor drugs: results from the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate cohort. Rheumatol [Internet]. 2014/09/13. 2015;54:494–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25213131
66. Smolen JS, Goncalves J, Quinn M, Benedetti F, Lee JY. Era of biosimilars in rheumatology: Reshaping the healthcare environment. RMD Open. 2019;
67. Chatzidionysiou K, Lie E, Nasonov E, Lukina G, Hetland ML, Tarp U, et al. Highest clinical effectiveness of rituximab in autoantibody-positive patients with rheumatoid arthritis and in those for whom no more than one previous TNF antagonist has failed: Pooled data from 10 European registries. Ann Rheum Dis. 2011;