Transforming clinical trials in rheumatology: towards patient-centric precision medicine

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Abstract

Despite the success of targeted therapies in the treatment of inflammatory arthritides, the lack of predictive biomarkers drives a 'trial and error' approach to treatment allocation, leading to variable and/or unsatisfactory responses. In-depth characterization of the synovial tissue in rheumatoid arthritis, as well as psoriatic arthritis and spondyloarthritis, is bringing new insights into the diverse cellular and molecular features of these diseases and their potential links with different clinical and treatment-response phenotypes. Such progress raises the tantalizing prospect of improving response rates by matching the use of specific agents to the cognate target pathways that might drive particular disease subtypes in specific patient groups. Innovative patient-centric, molecular pathology-driven clinical trial approaches are needed to achieve this goal. Whilst progress is clearly being made, it is important to emphasize that this field is still in its infancy and there are a number of potential barriers to realizing the premise of patient-centric clinical trials.

Classical randomized controlled trials (RCTs) have been central to the successful development of conventional synthetic DMARDs (csDMARDs), biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs). The introduction of these drugs into clinical practice has revolutionized the treatment and outlook of major chronic inflammatory arthropathies, including rheumatoid arthritis (RA), psoriatic arthritis (PsA) and spondyloarthritis (SpA). Nevertheless, approximately 40% of patients do not respond at all to individual DMARDs if the response is measured using the composite American College of Rheumatology (ACR) clinical assessment tool. Indeed, in patients who previously had an inadequate response to csDMARDs, ~60% achieve a modest (20%) improvement in disease activity (ACR20 response) with bDMARDs or tsDMARDs, whereas 50% improvement (ACR50 response) is only attained, on average, in 40% of patients, and 70% improvement (ACR70) in merely 20% of patients1,2 .

These typical response rates have been repeatedly shown in multiple individual RCTs, at least in RA, for all existing bDMARDs and tsDMARDs used in combination with methotrexate in patients with an inadequate response to csDMARDs; they have also been confirmed in numerous meta-analyses and, more importantly, in head-to-head trials2–6 . Notably, this treatment response 'ceiling' is observed irrespective of the mode of action of the bDMARDs and tsDMARDs or of their diverse specific cellular, molecular and signalling targets, such as CD20, TNF, IL-6, CD80–CD86, GM–CSF receptor and the JAK–STAT pathway. Although emerging data suggest that a higher response threshold could be reached, breaking through the treatment response ceiling has proven particularly difficult.

This difficulty, together with the high cost and complexity of RCTs, has made bringing new drugs to the market extremely challenging; consequently, pharmaceutical companies have been reluctant to invest in large trials that might only yield response rates similar to those of existing drugs, and in some cases they have de-prioritized developing drugs for RA altogether.

This lack of investment in new therapies creates a substantial management problem, as only 20–30% of patients achieve a state of low disease activity (LDA) and even fewer achieve remission7 . Disease relapse or gradual loss of responsiveness over time after initial improvement (also known as secondary or acquired non-response) also contributes to the pool of patients with suboptimal outcomes8,9.

Advances in the cellular and molecular understanding of RA have been made in the past few years, with an appreciation of the heterogeneity of RA and of the probable existence of patient subgroups and disease sub-phenotypes10–12. This concept presents the opportunity to enhance drug response rates by matching specific targeted agents to cognate target pathways identified in such subgroups. Consequently, the rheumatology community needs to, in parallel, define the molecular traits of disease, develop integrated clinical and molecular pathology algorithms and apply these algorithms to deliver innovative trials. These developments will facilitate the more efficient evaluation of new drugs by reducing the number of participants required and the costs of current trials, potentially enabling the successful introduction of new drugs to address the unmet clinical needs. It is important to say, however, that a number of potential pitfalls and barriers exist that must be overcome to fulfil the premise of patient-centric clinical trials in rheumatology and precision medicine.

In this article, we discuss and review the ongoing unmet medical needs in inflammatory arthropathies, focusing mainly on RA, in the context of current clinical trial design and the difficulty of breaking through the treatment response ceiling. We then consider the potential for innovative molecular pathology-driven clinical trials, as well as the theoretical and operational challenges in implementing this novel approach, to achieve patient-centric precision rheumatology.

Unmet needs in RA

As already mentioned, although currently available DMARDs have revolutionized the treatment of RA, multiple RCTs have shown that approximately 40% of patients are non-responsive to therapy, with about one-third of patients having substantial disability that incurs costs for individual patients and for society13. Thus, extensive unmet needs and many issues remain to be addressed, as discussed below and summarized in Box 1.

Box 1 | Unmet needs in chronic inflammatory arthropathies

• Full understanding of the diverse pathogenetic mechanisms underpinning disease heterogeneity at the individual patient level is lacking.

• Disease is imprecisely defined, mainly on the basis of symptoms and signs, and molecular pathology is not included in management algorithms.

• Biomarkers currently used in diagnosis, prognosis, disease monitoring and response to therapy are insufficiently accurate.

• The specific pathways driving disease in different patients cannot be predicted; hence, targeted therapies continue to be used on a ‘trial and error’ basis.

• In conventional efficacy trials, a sizeable proportion of patients have an inadequate response to treatment (the ‘treatment response ceiling’), and the mechanisms of response (and/or non-response) and the optimal use and sequence of available treatments have not been established.

• Clinical trials need to recruit patient populations that enhance the likelihood of response spanning the disease course while synchronizing for disease stage (for example, early, established or late disease) and harmonizing for drug exposure at trial entry, to minimize additional disease heterogeneity caused by drugs with different modes of action.

Fundamentally, we have a limited understanding of the pathobiological events underpinning RA clinical heterogeneity and whether different treatments might be required for discrete molecular

subtypes and at different stages of disease. Although molecular pathology is increasingly informing tailored management, particularly in oncology (for example, with treatment decisions being guided by biomarkers such as HER2 (ref.14) and deficient mismatch repair/microsatellite instability15), in RA, the use of DMARDs follows an algorithm based mainly on clinical features, historical licensing and health economics rather than a rational, target pathway-driven approach16.

In addition, the lack of biomarkers to predict response to individual drugs for RA17 maintains the current trial and error practice whereby patients are cycled from one DMARD to the next, which leads to unnecessary exposure to potentially toxic drugs that have a low probability of success, delays disease control and allows progression of structural joint damage (which is associated with secondary disability) and wastes valuable health-care and societal resources.

Furthermore, although remission, or at least LDA, should be achievable through use of a treat-to-target approach in RA, many patients do not reach this target18. Whether this failure occurs because of delays in the escalation of therapy or in changing to an alternative, more efficacious DMARD, or because of a specific refractory disease phenotype, or a combination of both factors, is unclear. Accurate measurement of response and remission status can be complicated by the inherent limitations of composite disease activity scores, which are higher in patients with concomitant non-inflammatory conditions and low pain threshold19–21. Finally, as most patients who reach a state of LDA or remission remain dependent on medication22, drug-free remission remains relatively aspirational, highlighting the need for new therapies to achieve this goal.

Critically, we need to understand how individual therapies that target different molecules and have distinct modes of action achieve similar efficacies. Also essential to know is whether a patient who does not respond to anti-TNF therapy (still the predominant first-line bDMARD) would have responded to an alternative bDMARD targeting an alternative pathway (for example, IL-6 receptor blockade with tocilizumab or B cell depletion with rituximab). In other words, we need to know whether clinical responses to different therapies are elicited in the same, different, or overlapping patient populations.

We also need to better understand the types of non-response, including loss of responsiveness over time23. An interesting hypothesis postulates that blockade of a specific pathway, through phenotypic plasticity, leads to ‘resistance escape’ via the emergence of an alternative pathway, as has been reported for the IL-17 axis following anti-TNF therapy24. Additional causes of loss of response that have not been systematically investigated in clinical practice or tested in appropriately designed trials include immunogenicity, which has been reported in as many as 50% against some anti-TNF monoclonal antibodies and biosimilar agents25. Despite the strong evidence that immunogenicity affects therapeutic response to TNF inhibitors, the evidence related to other bDMARDs is less impressive and absent for tsDMARDs. Moreover, a study found non-response with high levels of synovial TNF expression despite anti-TNF therapy, suggesting that insufficient target blockade in the disease tissue may play a part in inadequate therapeutic response26. Thus, anti-drug antibodies and insufficient tissue targeting may both contribute to non-response. Finally, it is worth considering that in a large proportion of patients (up to 50% in some series) ‘loss of response’ might be attributable to non-adherence27. Whilst multiple mechanisms can lead to non-response or loss of response, addressing these factors is important to complement tailored therapy based on molecular pathology.

It is clear that a number of unmet needs persist in RA and that every effort must be made to investigate and enhance our understanding of disease pathogenesis in the context of targeted

therapies and the mechanisms of response and non-response to these therapies. Clinical trials have an important role in addressing such unmet needs, as discussed in detail below.

Current clinical trial designs

Conventional clinical trials have been vital in the successful evaluation and introduction of DMARDs into clinical practice, which has transformed the lives of millions of people with inflammatory arthropathies. Classical two-armed, parallel group RCTs have been instrumental in determining the efficacy and safety of these drugs as well as underpinning the stringent regulatory documentation required by licensing authorities. The Outcome Measures in Rheumatology (OMERACT) initiative established international consensus on core outcome measures for inflammatory arthropathies, such as the ACR response criteria, disease activity scores and clinical disease activity indices, which have been accepted by regulatory authorities as the current gold standards, although as discussed above, they have weaknesses that could be improved by integrating biological end points.

As reviewed in detail elsewhere28, the classical RCT design provides a clear comparison with the principal purpose of establishing whether a difference exists between an experimental treatment and an existing alternative and determining the risk–benefit profile of the former. Single and/or double blinding, together with the random allocation of patients with similar characteristics (determined by strict eligibility criteria) to the experimental group and the control group, minimize factors that might introduce bias and influence outcomes, so that any differences observed between the two groups can be considered genuine. A classical RCT design, therefore, represents the gold standard for providing the methodological rigour needed for the evaluation of the efficacy and safety of an experimental agent in comparison with existing alternatives.

However, as well as major strengths, traditional efficacy RCTs have clear limitations, as summarized in Box 2 and discussed in detail elsewhere28. Here, we focus on the evolutionary journey of trial designs in RA (summarized in Fig. 1), and in inflammatory arthritis in general, which must follow the advances in the understanding of disease pathogenesis and definition of clinical subtypes in order to address the above described unmet needs. A major reason why it is essential for rheumatology clinical trial designs to evolve is that all conventional RCTs over the past 10–15 years in patients with an inadequate response to csDMARDs, regardless of the therapeutic target or mechanism of action of the investigational drug, have struggled to surpass the typical ACR20, ACR50 and ACR70 response rates of 60%, 40% and 20%, respectively

Box 2 | Strengths and limitations of conventional trials

Strengths

• Conventional clinical trials have been instrumental in rheumatology for demonstrating the safety and efficacy of conventional synthetic DMARDs (csDMARDs), biologic DMARDs and targeted synthetic DMARDs, the successful development of which transformed the lives of millions of patients with inflammatory arthropathies.

• Conventional randomized clinical trials (RCTs) are methodologically very robust and still represent the gold standard in drug development.

• The development and validation of clinical assessment tools used in clinical trials have been crucial in ensuring regulatory approval of effective DMARDs and their introduction into routine practice in multiple disease indications. Limitations

• Recruitment and analysis strategies for conventional RCTs assume that the target population is homogeneous (for example, with respect to response to csDMARDs, number of tender and swollen joints, erythrocyte sedimentation rate, C-reactive protein levels and/or antibody status) without considering the diverse pathogenetic factors underpinning disease heterogeneity or the mechanisms underlying treatment failure.

• Conventional efficacy trials are not aligned with current rheumatoid arthritis practice (such as treat-to-target principles) or generalizable to 'real-life' populations in which patients have comorbidities.

• Conventional RCTs require a large number of patients and are becoming increasingly costly as their failure often occurs late in the drug development pathway.

A better understanding of the basis for this failure to break through this treatment response ceiling is vital to facilitate the development of new drugs that do not fall into the usual '60–40–20' response pattern and thus improve patient care. Currently, the biological mechanisms underlying the ceiling effect are not fully understood. The so-called bottleneck hypothesis proposes that current therapies target different upstream events of pathways that ultimately converge into only a couple of common final effector pathways, for example, TNF and IL-6 production1 . Alternatively, the 'diverse endotype hypothesis' proposes that multiple common pathways targeted by current therapies are prevalent in a large proportion of patients with inflammatory arthropathies, whereas in a minority of patients the disease tissue (synovium) is characterized by different cellular and molecular patterns, which elude current drug mechanisms of action10,11,29.

The testing of these two hypotheses requires an approach different from the classical RCT in terms of the study design, as the clinical development programme for targeted therapeutics essentially followed that for csDMARDs (which act on multiple, rather than specific, pathways), and in terms of the study population, as currently patient recruitment is agnostic with regard to the involvement of the pathway targeted by the study drug. For example, the design of classical efficacy trials assumes that the treatments under investigation are applicable to anyone with the relevant clinically defined condition, such as RA, PsA or SpA. It is abundantly clear, however, that each of these clinically defined disease entities encompasses discrete subpopulations of patients characterized by heterogeneous pathobiological as well as clinical phenotypes.

These trial designs also assume that the potential therapeutic effect is greater than the effect of the natural variation, as reflected by the placebo response. If the placebo response is high, it will diminish the therapeutic effect. This natural variation is not random but is determined by substantial biological heterogeneity; thus, the inclusion of patients with molecular subtypes that lack the target of the therapeutic agent under investigation will complicate interpretation of the trial results. In particular, the chances of showing a statistically significant effect of a targeted therapy in a traditional comparative trial enrolling unselected participants diminishes if the prevalence of the target of that therapy is low, as for example was the case for RCTs of secukinumab (an IL-17 inhibitor) in RA30. IL-17 is expressed in the synovial tissue at substantial levels in only 20–30% of patients31 (C.P., unpublished observations); unsurprisingly, therefore, in the aforementioned trial30, ACR20 response rates at 24 weeks were lower with secukinumab 150mg than with the active comparator abatacept (30.7% and 42.8%, respectively). Interestingly, however, secukinumab 150mg was superior to placebo (ACR20 response rate 18.1%), although the secukinumab 75mg dose was not (ACR20 response rate 28.3%). Thus, although the development of this agent was abandoned for the treatment of RA, as it would not outperform competitors on the market even at the high dose, there is no doubt that in some patients IL-17 inhibition was beneficial30.

Additional limitations of classical RCTs include the fact that they are not aligned with current practice in RA management (that is, treat-to-target principles), as patients in the control arm of an RCT usually continue to receive unchanged background treatment instead of therapy that is escalated according to clinical status. To address this issue, an increasing number of trials now incorporate a 'rescue' or 'escape' treatment arm32. Also, the strict eligibility criteria of RCTs mean that the study populations are not representative of 'real-life' patients, in whom various comorbidities (such as obesity, cardiovascular and respiratory diseases, infection and malignancy) are often present during treatment; trial outcomes thus lack generalizability33.

To reflect real-life practice, pragmatic studies have become more popular. However, current trials cannot establish the mechanisms of response (or non-response) for any of the available targeted therapies. Additionally, the optimal use and sequence of these therapies remain uncertain, including the choice of first-line bDMARD for patients who are naive to or unresponsive to methotrexate, second-line bDMARD for patients who are naive or unresponsive to methotrexate, and second-line bDMARD for patients who did not adequately respond to a first-line bDMARD. Thus, although conventional clinical trials have indisputably been indispensable in the successful expansion of the therapeutic armamentarium in rheumatology, innovative clinical trials that go beyond demonstrating efficacy are very much needed. These should include, for instance, trials specifically designed to address mechanisms of response and non-response, optimize the use of existing therapies, recruit patient populations likely to achieve remission or considerable therapeutic response (for example, ACR50) spanning the disease course, while synchronizing for disease stage (for example, recruiting patients with similarly early, established or late disease) and harmonizing for previous drug exposure at trial entry, to minimize additional disease heterogeneity caused by drugs with different mechanisms of action. This will be discussed in the next section.

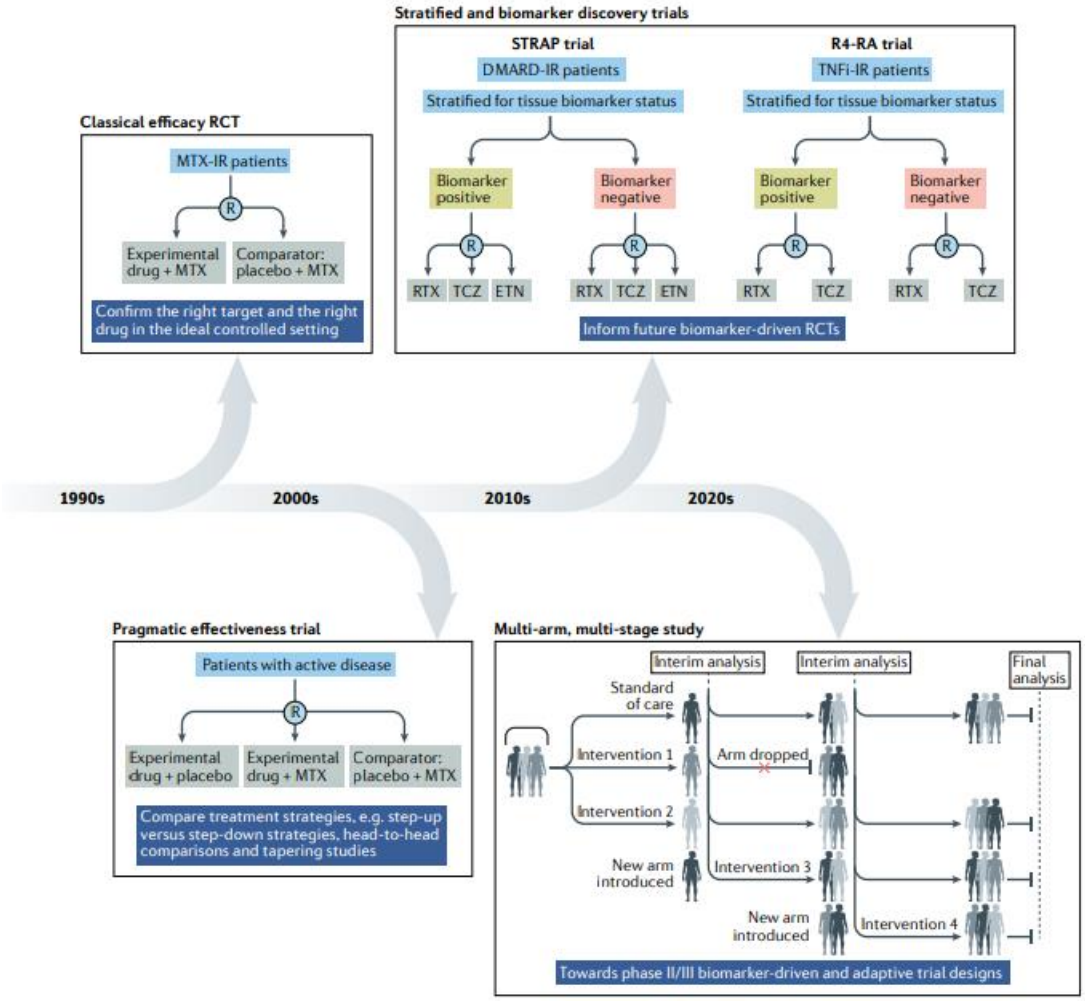

Fig. 1 | Evolution of trial design in rheumatoid arthritis. *Trial design in rheumatoid arthritis (RA) has evolved alongside advances in clinical paradigms, biotechnology and understanding of disease pathogenesis. The conventional efficacy trial is designed to test a therapeutic intervention in the ideal controlled setting, in which bias is minimized and the patient population is homogeneous, to confirm whether the target is clinically relevant and the drug designed to disrupt the target is efficacious. Efficacy trials in the 1990s enabled the introduction of biologic DMARDs. Pragmatic effectiveness trials aim to test how well an intervention performs in a 'real world' setting. In RA, such studies have been used to compare different treatment strategies, such as step-up (treat-to-target) versus step-down strategies, head-to-head comparisons and tapering studies, and to determine the optimal use of therapeutic options including conventional synthetic DMARDs, biologic DMARDs and targeted synthetic DMARDs. In stratified and biomarker discovery trials, the inclusion of biomarker-defined patient subgroups affords the opportunity to improve the performance of interventions. The first such trials in RA are applying synovial tissue-based biomarkers to stratify patient populations, which are then randomly allocated to multiple treatment arms; the treatment outcomes across biomarker-positive and biomarker-negative groups can then inform the next era of trials in RA, namely biomarker-driven trials. The STRAP and R4-RA trials, for example, stratified patients on the basis of synovial tissue infiltrate being B cell-rich or B cell-poor, although every patient was randomized to one of the arms of the trial. A multi-arm, multi-stage trial design can be used to compare multiple drugs, as an open master protocol allows multiple treatments to enter or exit the trial over the course of the study. Investigators can make adaptations following pre-specified interim analyses, such as dropping ineffective treatments or even adding new, emergent treatments. These trial designs, fully adopted in oncology, are beginning to emerge in the treatment of inflammatory arthritis. ETN, etanercept; IR, inadequate response; MTX, methotrexate; R, randomization; RCT, randomiz controlled trial; RTX, rituximab; TCZ, tocilizumab; TNFi, TNF inhibitor.*

Towards precision rheumatology

In oncology, an enhanced understanding of the molecular pathology of the disease tissue has driven the development of therapies that target discrete molecular subclasses of tumours. Demonstration of the clinical utility of this approach, however, also required the implementation of innovative clinical trial strategies to enable targeting of specific pathways expressed in discrete subsets of patients with the same tumour type; for example, 'umbrella' trials that compared the effects of treatment on HER2+ and HER2– breast cancer and 'basket' trials that assessed treatment effects in HER2+ tumours across multiple types of cancer (including breast, gastric or pancreatic cancer)34. Also, in 2018 pembrolizumab was approved for use in patients with deficient mismatch repair/microsatellite instability-high tumours regardless of cancer origin, as this biomarker predicted response to anti-PD1 receptor antibody treatment15. Similarly, the rheumatology community will need to engage with regulatory authorities to shift the paradigm of current clinical trial design to potentially achieve a similar clinical impact with pathology-driven trials.

Although the processes of cancer and arthritis are clearly distinct, the in-depth characterization of the synovial tissue of patients with early-stage, DMARD-naive RA, that is, before the modification of pathology by therapeutic intervention10,11, has highlighted the importance of diverse cellular and molecular features in specific subsets of patients and their potential link to different clinical and treatment-response phenotypes. These findings require confirmation in independent early arthritis cohorts and in patients with established and late-stage RA following therapy, as well in other forms of inflammatory arthritis, but they nevertheless raise the tantalizing prospect of enhancing response rates in rheumatology by matching the use of targeted agents to the cognate target pathways that might drive specific subtypes of disease in distinct patient groups.

Biomarkers in trial design

A long and exhaustive search for peripheral blood biomarkers in RA has been largely disappointing and a 2016 systematic review concluded that the added predictive value of these biomarkers is low17. An important difference, however, has emerged between seropositive (that is, positive for anti-citrullinated peptide antibodies (ACPAs) or rheumatoid factor) and seronegative patients with RA; for example, a meta-analysis of four placebo-controlled trials of rituximab found that seropositive patients responded better to rituximab than seronegative patients, with a modest but significant difference between the groups35. The APIPPRA study, in which ACPA-positive individuals who had inflammatory symptoms but who did not fulfil the criteria for RA were randomly allocated to receive either abatacept or placebo, is conceptually a biomarker-driven trial but in pre-RA. Similarly, in the PRAIRI study, individuals positive for both ACPA and rheumatoid factor but without arthritis were randomized to receive either rituximab treatment or placebo36. In a PsA study, 64 patients underwent randomization to receive standard bDMARD therapy (n=38) or strategic bDMARD treatment (n=26) allocated on the basis of peripheral T helper cell phenotype, which was determined by flow cytometry and classified into four types (TH1-high, TH17-high, TH1/TH17-high and TH1/TH17-low); the strategic treatment in stratified patients had significantly higher efficacy than standard bDMARD therapy37.

Although efforts continue to identify peripheral blood biomarkers, the focus of biomarker discovery is shifting to the joint disease tissue (synovium). Numerous biopsy-driven observational studies that enrolled patients before starting bDMARD therapy have suggested that certain synovial tissue signatures are associated with treatment response to anti-TNF38,39, anti-IL-6 receptor40 or B cell depletion therapy41,42. It is worth mentioning, however, that the clinical value of these latter

studies remains uncertain, as the results have not been confirmed in independent controlled studies.

In an attempt to address this acute need, international consortia (involving 19–27 centres across the UK and Europe) have undertaken the first two biopsy-driven RCTs in patients with an inadequate response to csDMARDs (the STRAP trial43) or anti-TNF therapy (the R4-RA trial44). These RCTs were made possible by the development of a minimally invasive, safe and well-tolerated ultrasound-guided procedure that enables the collection of high-quality synovial tissue from both large and small joints of most patients45,46. In these trials, following ultrasound-guided synovial biopsy, patients were randomized (1:1) to receive either rituximab or tocilizumab (R4-RA), or 1:1:1 to receive etanercept, rituximab or tocilizumab (STRAP). The primary hypothesis is that patients with B cell-poor synovial infiltrate will have a lower response to rituximab than to tocilizumab or etanercept.

The full results of these RCTs are pending but the trials have been specifically designed with the aim of validating the clinical utility of synovial signatures identified in the Pathobiology of Early Arthritis cohort10–12, testing the original hypothesis that expression levels of prevalent drug targets in the disease tissue are associated with clinical response to cognate-targeted bDMARDs, for example, levels of synovial B cells and response to rituximab, and to carry out hypothesis-free discovery assays to identify new therapeutic targets in patients resistant to the above medications.

Although biopsy-driven RCTs at the multi-centre level have been shown to be feasible by STRAP and R4-RA, confirmatory evidence of their clinical utility and of biomarker validation is still pending and should be replicated through classical RCT designs and variations thereof and/or innovative designs such as umbrella or basket trials, which are discussed in the next section.

Innovative study designs

Many innovative biomarker-driven trial designs have been developed, notably in oncology47,48. These trial designs can be categorized as adaptive or non-adaptive depending on whether the protocol is adjusted on the basis of interim data analyses. The choice of design is dependent on the nature of the biomarkers and the experimental treatments being assessed in the study; some designs require definitive and rapid assessment of the biomarker and knowledge of its prevalence, as randomization and sample size estimation are contingent on biomarker results, whereas other designs enable assessment of multiple biomarkers and/or experimental treatments in biomarker-defined subgroups or the whole study population. Some of these trial designs reflect current practice in oncology, in which biomarker development and assessment is integrated into drug development, and might not be applicable to inflammatory arthropathies, in which the focus is on discovering and testing biomarkers for established treatments. A full review of all these trial designs is beyond the scope of this article, but we discuss designs with potential relevance to rheumatology.

Emergent biomarker-driven RCT designs.

Figure 2 illustrates several variations of biomarker-driven RCTs available for defining and testing precision-medicine strategies that are relevant to rheumatology. A biomarker-strategy design evaluates the ability of a biomarker to identify a treatment-responsive subgroup. Individuals are randomized to take either conventional tests or a biomarker test (with or without conventional tests), and all test-positive individuals then receive either the experimental treatment or the control treatment and response rates are evaluated (Fig. 2a).

A biomarker stratification RCT can be used when there is evidence that the experimental treatment is more effective in a biomarker-positive subgroup than in a negative biomarker-defined subgroup, to determine whether the experimental treatment is of no benefit in biomarker-negative individuals. In this type of trial, individuals are stratified into biomarker-positive and biomarker-negative subgroups, then randomized either to the experimental or to the control treatment group; this stratification ensures a balance of biomarker-positive and biomarker-negative individuals across treatment groups (Fig. 2b).

Umbrella and basket trial designs. Umbrella trials and basket trials (Fig. 3) are being planned and/or conducted in RA and other inflammatory arthropathies. In an umbrella design (Fig. 3a), individuals with a single disease, for example, RA, are stratified into different groups on the basis of biomarker positivity and multiple therapies are tested, with each therapy assigned to the group positive for the respective biomarker of interest. A basket trial (Fig. 3b) enrols individuals with multiple diseases that share one or more biomarkers; sub-studies might be carried out in disease-defined or biomarker-defined subgroups.

As mentioned above, although the processes of cancer and arthritis are clearly very different, evidence suggests that, by analogy, the expression of a therapeutic target in the synovium might favour treatment response, and its absence would probably favour non-response. For example, early studies in the development programme demonstrated that TNF expression levels in synovial tissue from patients with RA were associated with better response49.

Although the results of such small studies must be interpreted with caution, this hypothesis could be efficiently tested by use of an umbrella trial design (Fig. 3a), whereby selecting patients expressing high levels of a particular target could enrich response rates to the cognate-targeted DMARDs in comparison with standard of care. Additional support for this approach comes from post hoc analysis of the ADACTA trial50, which demonstrated that rates of ACR50 response to treatment with tocilizumab and adalimumab increased markedly when patients were stratified using the peripheral blood biomarkers CXCL13 and soluble ICAM1 as surrogate markers of synovial pathology.

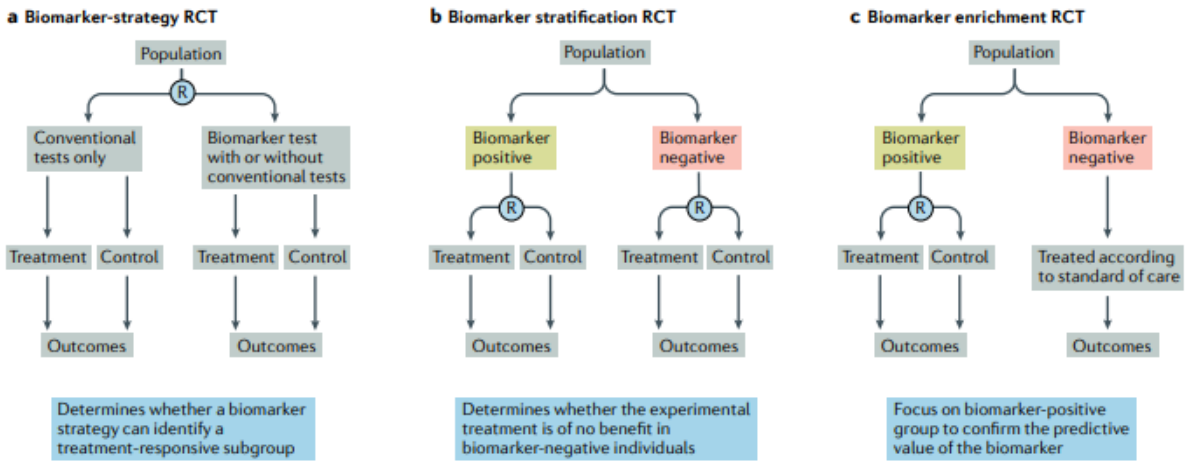

Fig. 2 | ***Emergent biomarker-driven trial designs.*** *Biomarker-driven randomized controlled trials (RCTs) are based on a single or a combination of biomarkers that are anticipated to predict a drug's effect within a given disease group. a| Biomarker strategy trial design. This trial design first randomly allocates individuals to undergo either a biomarker test or conventional test. Both biomarker-positive and conventional test-positive individuals receive the experimental treatment and the control treatment and response rates are evaluated.*

This type of trial provides evidence of the ability of a biomarker to identify a treatment-responsive subgroup. b | Biomarker stratification RCT. When evidence exists that the experimental treatment is more effective in a biomarker-positive subgroup than in a biomarker-negative subgroup, a biomarker stratification RCT can be used to investigate whether the experimental treatment is of no benefit in biomarker-negative individuals. Following stratification into biomarker-positive and biomarker-negative subgroups, individuals are then randomized to either the experimental or the control treatment group. Stratification is used to ensure a balance of biomarker-positive and -negative individuals across treatment groups, and only individuals with valid biomarker results enter the trial. c | Biomarker enrichment trial. In a biomarker enrichment trial, only biomarker-positive patients are randomized, in order to compare the experimental treatment with the control treatment in this particular biomarker-defined subgroup. The biomarker-negative subgroup is treated according to the standard of care and can provide control data. R, randomization.

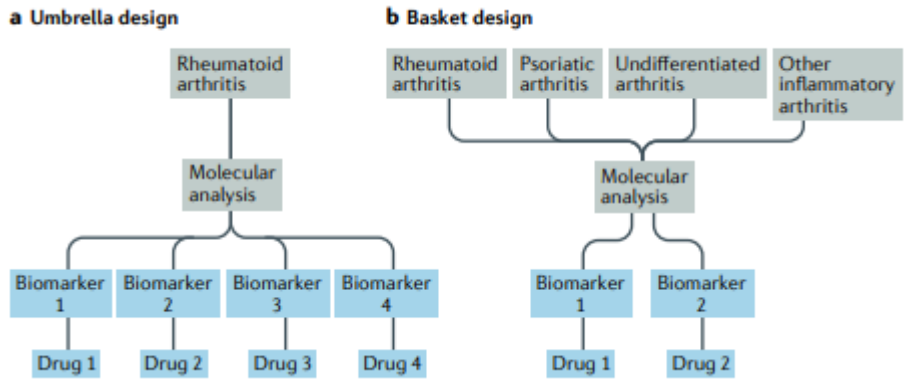

*Fig. 3 | **Biomarker-driven trial designs.** Similar to multi-arm, multi-stage trials (see Fig. 1), biomarker driven umbrella and bucket trials use an overarching master protocol, which can be predicated on molecular analysis that is driven by potential treatment-predictive biomarkers. Whilst biomarker-driven randomized controlled trials evaluate single biomarkers, umbrella and basket trials can evaluate multiple biomarkers and therapies simultaneously. a | Umbrella design. In an umbrella trial, individuals with a single disease (in this example, rheumatoid arthritis) are stratified into different biomarker-positive groups and multiple therapies are tested, with each therapy assigned to the corresponding putative predictive biomarker. b | Basket design. A basket trial evaluates a single therapy in multiple diseases that share a common biomarker. For example, a group of patients with rheumatoid arthritis, psoriatic arthritis, undifferentiated arthritis or inflammatory arthritis can form a 'basket'. Substudies of disease and biomarker subgroups might also be included.*

Another exciting opportunity would be to use a basket trial design (Fig. 3b) to test the hypothesis that some specific pathways are important to pathogenesis, at least in some patients, across different nosological entities, such as RA, ankylosing spondylitis (AS) and PsA, and that the same agent could be effective across multiple disease indications by targeting those pathways. Support for this notion comes from not only the oncology field, where, for example, trastuzumab has been shown to be effective in several different cancer types when patients were selected for high levels of HER2 expression51, but also from the rheumatology literature52. For instance, it is well established that TNF inhibitors are effective in subsets of patients across a number of chronic inflammatory arthropathies including RA, AS and PsA52 (Table 1). Although TNF inhibitors are already licensed for use in these diseases, confirmation of their efficacy in a molecular pathology-driven basket trial might not only enrich for treatment response but also, importantly, provide proof of concept to support similar hypothesis-testing of novel developmental compounds or other existing targeted DMARDs.

Notably, the response profiles from RCTs of bDMARDs other than TNF inhibitors have been variable across inflammatory arthropathies and, in some cases, unexpected. For example, whereas IL-6 inhibitors are effective and licensed for the treatment of RA53, the results in AS have been

disappointing54. Conversely, IL-17 inhibitors are approved for the treatment of PsA and AS but not for RA55. Similarly, the IL-12–IL-23 inhibitor ustekinumab is an approved treatment for PsA but is ineffective in RA56, and, despite positive results in a pilot study in AS57, both ustekinumab and risankizumab (IL-23 inhibitor) failed to show a significant benefit in RCTs58,59. These results have led to the conclusion that the IL-6 pathway is not important in the pathogenesis of SpA and, conversely, that the IL-23–IL-17 pathway is not relevant in RA, which could reflect differences in pathobiology at the primary site of disease (the synovium in RA and the enthesis in AS)60. As already discussed, however, in clinical trials, some patients with SpA did respond to IL-6 inhibition61 and some patients with RA did respond to IL-17 inhibition55, but the nature of the trial design, which included participants with potentially low expression levels of the therapeutic target at the primary disease site, would inevitably lead to an overall negative group-level response.

Thus, as illustrated in Fig. 3b, pathway-driven basket trials that recruit patients on the basis of their molecular characteristics, for example, prevalent TNF or IL-17 signatures, irrespective of the clinical diagnosis, could result in a positive outcome when treatment allocation is guided by molecular pathology. In addition, and potentially of extreme relevance, basket trials might revolutionize drug development, not only in terms of showing efficacy but also with regard to gaining regulatory approval, as efficacy could be proven in multiple disease indications in a single trial, in contrast to the current (very expensive) paradigm of having to perform multiple trials for each disease indication.

Adaptive trial designs. Whereas the study designs discussed so far would be suitable for validating existing potential biomarkers against cognate-targeted therapies, the early development of entirely novel biomarkers against entirely novel targeted agents might be better served by adaptive designs, in order to reduce the overall number of participants while reducing the exposure to potentially ineffective new drugs.

In an adaptive multi-arm, multi-stage (MAMS) clinical trial (Fig. 4), multiple treatments can be tested in multiple biomarker-defined populations simultaneously, and pre-specified interim analyses during the course of the study may lead to changes in the study protocol. Molecular analysis can be used to determine the biomarker status within a population with a single type of arthritis or various types of arthritis (such as RA, PsA and undifferentiated arthritis), and each biomarker-defined subgroup of patients is allocated to a suitable substudy. As a result of interim analysis, a substudy can be stopped owing to lack of efficacy of the drug under evaluation or a successful substudy can be extended to include more patients; another substudy might be further subdivided into additional substudies, according to profiles of responders and non-responders.

Table 1 | **Effects of biologic DMARDs in inflammatory arthritis**

Drug	Rheumatoid arthritis	Psoriatic arthritis	Ankylosing spondylitis
TNF inhibitors	+++	+++	+++
IL-6 inhibitors	+++	+[70]	–[54]
IL-17 inhibitors	+[71]	+++	+++
IL-12–IL-23 inhibitors	–[56]	+++	–[57–59]

+++, approved treatment and positive effects in phase III trial; +, not approved but limited efficacy in phase II or III clinical trials; –, negative results from phase II or III clinical trials.

Challenges with innovative trials As discussed above, molecular pathologydriven trials represent an exciting prospect with the potential to transform the development pathway of drugs for inflammatory arthropathies; however, it is important to stress that the field is still in its infancy, and

numerous potential pitfalls and barriers exist, as briefly discussed in this section and summarized in Box 3.

First, with particular regard to biomarker-driven studies, it is important to state from the outset that molecular pathology-driven classification of disease subpopulations is not an established methodology in clinical practice and will require validation. A new classification based on molecular pathology has potential repercussions for the accuracy of patient selection and, consequently, on the outcome. In addition, the heterogeneous nature of disease characteristics has implications for achieving 'faithful' and reproducible disease phenotyping through relevant biomarkers and molecular pathology of the synovial tissue. Moreover, it is possible that the patient molecular profile could change during the disease course or be influenced by concurrent factors including age, sex, environmental factors, comorbidities and/or concomitant medications.

Importantly, synovial tissue biomarkers are still at an early stage of development and confidence must be established in their ability to accurately identify the treatment-responsive subpopulation, which is particularly relevant, for example, in biomarker-enrichment trial design.

Likewise, the precision and reproducibility of the biomarker assay method must be established to ensure that the chosen biomarker can accurately distinguish biomarker-positive and biomarker-negative patients. Also, for the design of trials that will feasibly evaluate both patient selection and drug efficacy it is essential that the metrics to assess effectiveness are accurate, particularly if the studies will be small. Thus, assessment metrics and tools used to evaluate outcomes could require adjustment, as current methods have been validated to reproducibly measure clinical modifications following therapeutic intervention in RCTs, but might not necessarily be able to reliably estimate specific biological changes.

Second, with regard specifically to adaptive trial designs, a number of methodological and statistical issues need to be considered (summarized in Box 3). An in-depth discussion of these issues is beyond the scope of this article, but it is enough to say that caution is advisable and that it is important to define the trial and data analysis plan as much as possible in advance, in order to avoid potential operational biases, as per FDA recommendations62. Also, in adaptive trials, the risk of introducing a type I error (a false-positive finding) is substantial, owing to changes in sample size that could lead to an inappropriate interpretation of the results, and treatment effect estimates that are used to make decisions at each stage of an adaptive trial might be based on small datasets, potentially leading to a type II error (failure to detect a true treatment effect); both types of error could lead to the selection of an incorrect adaptation63.

Third, there are a number of practical, perception-related and operational barriers to delivering precision medicine driven by molecular pathology, which will require considerable effort to overcome. For example, flexible funding will be necessary, and protocol updates and amendments could be frequent. Shipment and tracking of samples as well as monitoring and assessment of biomarkers are important logistical issues. Patients might have concerns over multiple experimental treatment options, and recruitment and dropout rates could be unpredictable. Importantly, trial administration is complex; thus, substantial infrastructure support is required.

One important barrier is that the molecular characterization of the diseased tissue requires a synovial biopsy and many rheumatologists still question the feasibility, acceptability and safety of this procedure. These issues have been addressed by studies showing that synovial biopsy is safe, well-tolerated and associated with a very low risk of complications45,64. Nonetheless, it will take

time to change perception, although, paradoxically, patients with RA who have participated in biopsy-driven studies have become advocates to reassure fellow patients as well as clinicians65.

An OMERACT adaptive trial design special interest group has been convened to address methodological barriers and obtain global consensus on how best to conduct adaptive design trials in RA66. Also, even if international, multi-centre trials have resulted in many rheumatologists receiving training in performing ultrasound-guided synovial biopsies, global education and training on a sustained basis are necessary; in this context, EULAR has endorsed the establishment of synovial biopsy courses that will continue to provide the appropriate level of education to ensure high standards and dissemination of this procedure. In the USA, the Rheumatoid Arthritis Synovial Tissue Network (REASON) and the Accelerating Medicines Partnership are multi-centre collaborations that are using tissues obtained by synovial biopsy to study disease pathogenesis and identify biomarkers to predict response to treatment67–69.

Ultimately, until the clinical utility of a molecular pathology-driven approach is established and its cost-effectiveness demonstrated, existing core paradigms in rheumatology drug development are unlikely to change.

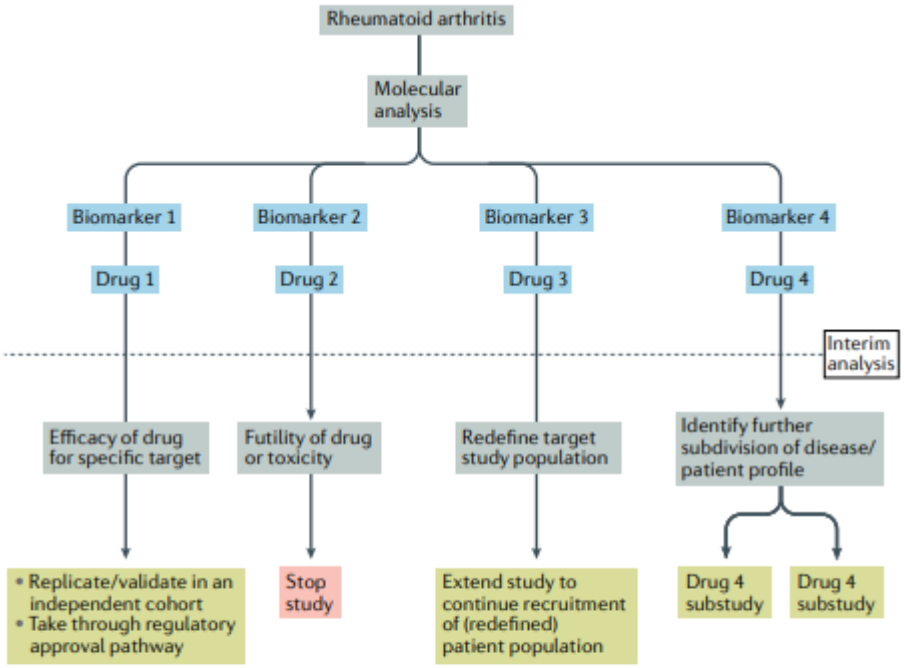

Fig. 4 | **Biomarker-driven adaptive trial design.** Biomarker-driven randomized controlled trials and umbrella and basket trials can be quite large, with no ability to evolve the study design or treatments, whereas a biomarker-driven adaptive trial design combines the concepts of biomarker-driven studies with the multi-arm, multi-stage format and can be used to study multiple biomarkers in a population (in the example shown, patients with rheumatoid arthritis). Adaptations can be made during the course of the study on the basis of pre-defined interim analyses of outcome within the biomarker-defined subgroups including dropping a biomarker-defined subgroup, redefining the target study population or identifying further subdivision of the biomarker-defined subgroups disease or patient profiles with regard to the respective drug under evaluation. Adapted from REF.[51], Springer Nature Limited.

Box 3 | Challenges with innovative clinical trials

Challenges with biomarker-driven studies

- Ensuring that the correct patient subpopulation is selected for the study
- Inaccurate phenotyping owing to the heterogeneity of disease characteristics
- Factors such as age, sex, environment and concomitant disease and/or medications also contribute to variability in the population profile and affect the accuracy of phenotyping
- Confidence in the accuracy of synovial tissue biomarkers for identifying the treatment-responsive population remains to be established
- The precision and reproducibility of the biomarker assay method must be established to ensure that the chosen biomarker can accurately group patients
- Assessment metrics and tools used to evaluate outcomes might require adjustment, in order to reproducibly measure specific biological variations Methodological and statistical challenges
- Risk of operational bias (for example, from selection bias, the choice of assessment method, treatment modification, change in the target population, change between original hypothesis and final statistical plan or setting of the stop–go decision)
- Simulation modelling is required to generate a robust sample size calculation
- The best outcome measure for modelling and interim analyses needs to be determined
- For precision medicine, the primary end point of a trial should reflect a clinically relevant level of improvement corresponding to standard of care (such as a treat-to-target approach)
- For basket trials, the primary end point needs to be valid for all conditions included in the study
- Statistical analyses need to be pre-specified to avoid introducing a type I error (a false-positive finding)
- Incorrect adaptation based on an inaccurate estimate of treatment effect could lead to a type II error (that is, failure to identify a valuable therapy) and potentially the inappropriate termination of a drug development programme

Conclusions

Although pharmaceutical companies continue to produce a rich pipeline of novel therapeutics, the complexities and extraordinary costs of conventional trials have limited their development. The rheumatology community needs to develop an alternative strategy with innovative trials that will facilitate the development of novel drugs to address unmet treatment needs (for example, patients with disease refractory to existing medications), while reducing the number of participants required in each trial and reducing the costs associated with performing single trials in multiple disease indications. Naturally, changing existing core paradigms of drug development in rheumatology will require demonstration of the clinical utility and real advantage of using innovative trial approaches. Nonetheless, exploiting advances in the understanding of the molecular pathology of the diseased tissue could drive the development of therapies that target discrete molecular subtypes of disease, using innovative patient-centric trial designs (such as umbrella, basket and adaptive trials) that enrich treatment response.

This development might also lead to a shift from the concept and practical challenge of 'finding the patient for the trial' to 'finding the trial for the patient', through the establishment of broad frameworks and systems that integrate closely with health-care delivery in order to accelerate progress and realize the true promise of precision medicine.

In conclusion, the development of innovative patient-centric molecular pathology-driven clinical trials could optimize the allocation of existing targeted therapies and increase response rates above the current '60–40–20' pattern, facilitate the development of new drugs and transform the clinical and regulatory approval pathway. The use of such trials will also limit the number of participants who are exposed to compounds to which they are unlikely to respond. Thus, despite the considerable challenges and difficulties associated with the development of patient-centric molecular pathology-driven trials in rheumatology, innovative trial designs represent an opportunity for the community to accelerate the next phase of the therapy revolution for patients with inflammatory arthropathies.

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