The introduction of anti-TNF drugs for RA has transformed the outlook for patients and they are now an accepted part of clinical practice [1]. Their use has spread to several other related inflammatory disorders. There are five anti-TNF agents licensed for use in RA in Europe, with even more to come, and several other biologic agents for RA are also available including abatacept, rituximab and tocilizumab. As the number of agents and their clinical indications increase, the need for a robust evidence base to inform rational clinical decisions also increases. These agents are expensive, and need to demonstrate their cost effectiveness.

The evidence base for their appropriate use lies predominantly in industry-funded clinical trials. Companies design studies to meet the regulatory requirements and the pivotal pre-licensing Phase III trials for anti-TNF agents in RA needed to show that the biologic is superior to MTX in RA patients who have failed on that drug [2–4]. There is no requirement to show relative benefit within drug class, but companies are aware of an increasingly competitive marketplace.

Third party payers seek evidence not only on effectiveness and safety, but also on cost effectiveness. Thus, bodies such as the National Institute for Health and Clinical Excellence (NICE) in the UK have attempted to reach judgements on the relative value of the use of biologics in RA and related disorders, to inform, for example, their sequence of use [5], but the evidence base for such decisions is limited.

The accumulated clinical trial evidence addresses only some of the important questions raised by patients and clinicians: still uncertain are issues such as (i) what is the optimal order of use of agents? (ii) Once started and disease control achieved, can these drugs be stopped? (iii) How far can data from one indication be extrapolated to similar disorders? Given the variable natural history of these chronic conditions, and the availability of alternative cheaper co-therapies that can be used in combination, the list of potential questions exceeds the resources available to address them.

Investigator-led trials must address these questions. Public and charitable funders are willing to support such trials, but with limited money; the questions have to be prioritized. Money is not the only scarce resource: there is a limited pool of expertise to plan, run and interpret trials, and for rarer disorders or rare variants of common disorders, even the number of patients available to participate in trials is constrained. In the UK, the major funders of RA research, Arthritis Research UK and the National Institute for Health Research (NIHR), work together in commissioning trials or responding to requests from investigators. Given the issues above, they co-sponsored a workshop in April 2010 bringing together patients, clinicians, clinical academics, regulators, NICE and industry to address how to prioritize questions on the use of biologic agents in the rheumatic diseases.

The messages from patients were clear: they seek answers that might improve their treatment and that of their fellow sufferers, and are willing to accept the consequent responsibility of entry into trials. Patients seek a personalized approach in terms of drug choice and sequence for their disease; we do not yet know how to achieve this. Clinicians share the same concerns, but are worried about costs and toxicity, and need the evidence to inform best practice. Early use of biologics can change disease course, but this is neither affordable nor necessary for all, and even so many years after the introduction of these agents, we still do not know which patients would benefit from this aggressive early approach. Clinicians also feel under pressure to use biologics off-label for other severe autoimmune diseases, but worry about the evidence. Clinicians are keen to participate in research, but are often discouraged by regulatory hurdles around clinical trials.

Regulatory bodies such as the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK license drugs on the basis of efficacy (defined as can it work?) and an acceptable risk/benefit ratio. Increasingly, regulators seek stakeholder views (http://www.ema.europa.eu/htms/human/humanguidelines/efficacy.htm) on what are the most relevant approaches to the use of agents such as biologics, to inform the licensing process, in particular to reflect common use in considering drug safety—few of the workshop attendees were aware of this consultation. In general, however, regulators respond to the evidence presented to them, but do not lead on its acquisition.

The regulators’ remit is not to consider effectiveness (defined as does it work in practice?) or cost effectiveness (what benefits at what price?), though these are increasingly demanded by third-party payers. Bodies advising on cost effectiveness of drugs, such as NICE,
are consequently aware that they have to use immature evidence in reaching their judgement on the appropriate use of drugs, and need both patient experience and professional practice to inform the decision making. NICE can highlight where the evidence base is lacking, and can encourage further research in important areas.

Increasingly, industry also appreciates that licensing without a prospect of payer approval is of limited gain; there is increased acceptance that the future lies with industry responding to a joint regulator/payer view of the world [6], an increasing focus on personalized medicine and that in routine practice disease outcomes do not always reflect the experience from Phase III trials.

The funders’ views were based on the constituencies they serve: either a patient and research community (ARUK), or the patient and wider NHS (NIHR). There is a greater emphasis for research to be needs led, which should drive the science and not the other way round.

The challenge, therefore, is bringing together these expressions of goodwill. Studies on efficacy alone cannot be a priority for investigator-led trials even in orphan indications. Expressions of willingness by the key players to agree a common path that provides answers for the use of the drugs in the real world have yet to be translated into action. Given the choice of agents and the consequent greater choice in therapeutic paths, investigators have to respond to users, particularly the expressed desire for personalized medicine, and translate those aspirations into tractable priorities for future clinical trials.

Acknowledgements

The opinions expressed in this article are the authors’ own, but we acknowledge the contribution to these ideas from the attendees at the joint Arthritis Research UK/Health Technology Assessment workshop, and are especially grateful for the contribution of Mathew Homfray, member of Arthritis Research UK Research Stakeholder Committee; Prof. David L. Scott, President, British Society for Rheumatology; Dr Gopalan Narayanan, Medical Assessor Chairman of the Medicines and MHRA; Prof. Peter Littlejohns, Clinical and Public Health Director, NICE; and Dr Ravi Rao, Rheumatology Cluster Head (Actemra) Roche Pharmaceuticals and Sir Alasdair Breckenridge, MHRA.

Disclosure statement: The authors have declared no conflicts of interest.

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