Biomarkers in rheumatology: promise and pitfalls

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"Magnificent promises are always to be suspected"
– Theodore Parker (1810–1860)

Recent advances in the development of novel immunomodulatory therapies for various autoimmune conditions have revolutionized both clinical practice and research in rheumatology. The improved efficacy achieved, for example, with macromolecule TNF inhibitors in rheumatoid arthritis (RA), has certainly increased our expectations as regards the outcomes of therapy. Disease remission for RA patients is not only desirable, but is considered attainable. With ever-expanding numbers of targeted therapies approved for the clinic and more in development, key unmet needs increasingly arise. The success of biologic agents in rheumatology has spawned considerable research into additional potential targets and agents. For new drugs in early phases of development, is there a way to define whether they have reasonable efficacy, acceptable tolerability, and are worthwhile of further study without large and long clinical trials? With the surfeit of putative therapies in the pipeline, there are neither the resources nor the patients to test each one. Invariably, solutions to such questions include discussions of biomarkers. For example, is it possible to know which specific patients are the most appropriate candidates for which particular agents? The newer agents have presumably distinct mechanisms of action, and while some patients have tremendous responses to treatment, others fail to respond. Being able to define the subset of patients most likely to achieve benefit and least likely to experience toxicity to a given type of agent *a priori* would be a tremendous aid in optimizing treatment. This is particularly important for the syndrome-like rheumatic diseases. To date, biomarkers in rheumatology have been like the local football club right before the start of the season – full of fantastic promises for ultimate success. Unfortunately, as data emerges, disappointment seems to inevitably follow. What underlies the letdown?

What are biomarkers?

Some of the disappointment regarding biomarkers in rheumatology derives from false expectations, which in turn relate to a lack of understanding as to what biomarkers are exactly, and how they should be used. Biomarkers are objectively measured indicators of the status of a biologic process or disease. They may define various aspects of pathogenesis, activity, response to therapy or outcome of disease. Biomarkers that are not 'approved' outcome measures are often termed 'intermediate biomarkers'. An intermediate biomarker that correlates directly with specific outcomes may be considered a surrogate marker – a term with regulatory connotations. Examples of surrogate markers include bone mineral density as an indicator of risk for insufficiency fractures, and $CD4^+$ T-cell counts as an indicator of the status of HIV infection. Such powerful markers can be used to assess what the impact of therapy is likely to be on key clinical outcomes that would otherwise take a long time period and large numbers of patients to establish. Not all biomarkers reach the stringent requirements to be a surrogate marker. However, this is not to imply they have no value. Parenthetically, even surrogate markers may be imperfect, as has been observed in the case of certain drugs that effectively lowered cholesterol levels but did not decrease the development or sequelae of atherosclerotic disease.

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Is a given biomarker valid?

The history of rheumatology is rife with examples of investigators, toiling in their own laboratories using the latest immunologic techniques to develop assays and disease models for hypothesis testing in the clinic. In some cases, suggested associations from such initial endeavors evaporated when testing in diverse patient populations failed to confirm the original observations, or the assays themselves could not be replicated. Such examples highlight the need for validation of biomarkers. The term 'validation' – much like biomarker – is sometimes misunderstood. From a technical standpoint, validation implies strict def-

10.2217/17460816.3.4.303 © 2008 Future Medicine Ltd ISSN 1746-0816

initions of precision and reproducibility. Internal and external standards, linearity of the assay and stability over time (i.e., is the same answer obtained today, in a month, or in a year with the same samples) are also essential, as well as reproducibility by multiple laboratories. Too often, the need for strict technical validation is ignored and investigators prematurely test methods in a therapeutic trial. From a clinical standpoint, validation implies rigorous prospective assessment in heterogeneous patients with various levels of disease activity and severity. The chance of linear relationships between biomarkers and complex clinical outcomes may be low. Thus, a careful analysis of how the putative biomarker performs in a number of diverse studies is needed. Also, retrospective analyses that determine whether a biomarker 'predicts' clinical response, while not uncommonly reported in the literature, are useful to generate hypotheses but not to prove utility. We must select a biomarker in advance and then prospectively test the hypothesis under many clinical conditions. The true value of a new biomarker lies in its ability to shorten the time needed to determine whether an agent will likely be effective – that is, be truly predictive. Biomarkers that merely reflect contemporaneous clinical measures would be of limited value.

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Are rheumatic diseases suitable for biomarkers?

Most rheumatic diseases may be considered to be syndromes. Thus, patients with RA may have a common constellation of clinical signs and symptoms that may result from disparate genetic, hormonal, environmental and other factors. This substantial heterogeneity poses significant difficulties as regards the utility of biomarkers. In addition, questions arise as to the optimal source of material for rheumatic conditions. As systemic immune conditions, peripheral blood might be expected to be a relevant source of cells and secreted products that could serve as biomarkers. However, in conditions such as RA, an argument could be made that the central target organ is the synovium, and that relevant biomarkers are most likely to come from joint tissue. Of course issues of accessibility, cost and other factors are also operative.

Many companies assume that a biomarker-based study will speed up drug development in chronic rheumatic diseases. On the contrary, the process may be slowed due to the time and effort required for proper design, execution and analysis. Experimental medicine groups and clinical development groups within industry experience constant tension between them; the former prolongs the development process in order to eliminate or prioritize compounds, while the latter pushes management to move directly to clinical end points so that they can get the 'answer' sooner, albeit at greater expense and potential toxicity to patients.

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How useful is a given biomarker in the clinic?

Not infrequently, scientific publications herald data concerning the promise of some new biomarker for rheumatic diseases. Such findings are typically considered worthy of publication when they are statistically significant. However, there is a tremendous gap between statistical significance and clinical relevance. This is especially true for powerful new techniques, such as whole-genome scans, and large-scale proteomics. The sheer volume of analyses performed and data generated virtually guarantees that some association will reach the level of statistical significance. But in the clinic, the bar is much higher. When interacting with an individual patient, only data that substantially alters the pre-test likelihood of a given outcome will be of any value. This is expressed as a likelihood ratio. While statistically significant associations are of interest, unless they are quite robust they cannot have a meaningful impact on clinical decision-making.

The future of biomarkers in rheumatology

What is the way forward for the use of biomarkers in RA? Clearly, an understanding of the potential utility of a given biomarker, including its limitations, is important. While not every putative biomarker will be a surrogate marker, it

may be of value, for example, in defining particular subsets of patients. In addition, researchers need to keep an open mind about potential biomarkers. The dramatically different patterns of clinical response to current rheumatic disease therapies suggest critical differences among our patients with the same diagnosis. In fact, it may be that diseases such as RA are final common pathway syndromes and the true value of a biomarker approach is in the stratification of patients. In the future, outcome measures may require combinations of markers requiring a systems analysis approach. Biomarkers may be used as a component of personalized medicine. Finally, to be of value to the clinician, biomarkers must be validated and readily available across the globe.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utiliized in the production of this manuscript.

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