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The convergence of clinical research and clinical care

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A striking change in the field of rheumatology has been highlighted by the approval of another biologic agent, abatacept, for the treatment of rheumatoid arthritis, and by the ongoing clinical trials of a variety of biologic therapies in other diseases, including systemic lupus erythematosus (SLE, discussed in the Review by D Isenberg and A Rahman in this issue of *Nature Clinical Practice Rheumatology*). Until recently, nearly all therapeutic interventions in rheumatic diseases, such as rheumatoid arthritis and SLE, were empiric. We had insufficient information about either the pathogenesis of the diseases or the mechanism of action of the medicines to gain much insight into disease processes from the results of therapeutic interventions. The causes and precise pathogeneses of diseases such as rheumatoid arthritis and SLE still elude us, and the salient mechanism of action of drugs such as gold salts, hydroxychloroquine, methotrexate, and cyclophosphamide in these diseases is also unknown. As a result, laborious pragmatic clinical trials have been necessary to develop regimens that optimized the clinical benefit and minimized toxicity. These trials were largely built on previous clinical observations, rather than on physiologic or pharmacologic insight. Evidence from the trials could therefore tell us about the clinical impact of a particular agent in a specific disease, but could not reveal much about how the disease process was influenced and how this resulted in the clinical benefit.

All of this changed with the introduction of biologic drugs. For the first time, we had highly specific agents that each targeted a particular molecule. The newly available biologic treatments are not merely expensive disease-modifying antirheumatic drugs, but are precisely targeted therapies that neutralize a particular molecule or cell. Although the primary questions for clinicians remained, "Does it work?" and "Is it safe?", the application of biologic agents afforded the opportunity for fundamental questions about human pathophysiology to be addressed for the first time. What role does tumor necrosis factor play in rheumatoid arthritis? Is interleukin-1 an essential mediator of rheumatoid inflammation? What is the role of T cells or B cells in rheumatoid arthritis or in SLE? Can patients in whom a specific cytokine or cell is dominant be prospectively recognized?

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This has completely changed the scientific basis of rheumatology and, in a subtle but potentially profound way, the practice of rheumatology. Clinical care has become potentially synonymous with clinical research because every time a clinician administers a biologic drug, he or she is asking whether the precise target of the biologic treatment has a role in disease pathogenesis in that patient. The data derived from all of these clinical encounters could potentially provide essential information on the physiologic basis of various rheumatic diseases that could point the way to more effective application of biologic agents and greater benefit for the patients. The challenge is to develop a means to collect and collate this information.

In this issue of *Nature Clinical Practice Rheumatology*, T Pincus discusses the need for "practice-based evidence" to complement information from clinical trials. This, he feels, could be done in academic practices and in prominent clinical practices and might supplement the data obtained from traditional formulaic controlled clinical trials, to give a more complete and balanced view on the likely clinical impact of new therapeutics. Although it is laudable, maybe this approach does not go far enough. Perhaps the goal should be to consider a way to mine data in a more broad clinical arena, so that as much information as is practically possible can be collected and analyzed to permit a full understanding of the impact of targeted therapy of rheumatic disease.

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Competing interests
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