Safety and efficacy of biologics, and the future direction of rheumatoid arthritis therapy

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■ **How did your education/training lead to your interest in rheumatology?**

When I was in medical school, I was most interested in internal medicine. During my internal medicine residency, it became clear to me that I found the field of rheumatology most interesting and most stimulating. I think it was the combination of long-term management of patients – so that we, as rheumatologists, become the primary providers for that aspect of their medical care – and the fascinating science of rheumatologic diseases. At the time that I was considering a career in rheumatology, we had little to offer our patients but methotrexate and cyclophosphamide, but the explosion of therapies in our field in the past 15 years has confirmed for me that I made the right decision and has made it even more satisfying to take care of these patients. While I have always considered myself a clinician, I did spend several years in the laboratory during my fellowship, an experience that has proven invaluable in my clinical career, by providing me with the tools to understand and assess the biologic pathways and biologic therapies central to these diseases.

■ **How have registries monitoring biologic therapies in rheumatoid arthritis contributed to our knowledge of the safety of these drugs?**

In any clinical development program, the number of patients exposed to a new drug is necessarily limited by expense and practicality, and is frequently just a small fraction of the number of patients exposed to the drug in its first year of clinical availability. In addition, subjects participating in clinical trials are typically a unique population, with more disease activity and fewer comorbid conditions than those who may be treated in clinical practice. Registries accomplish two major goals: they provide numbers, which allow for the identification of rare safety signals and better precision on the true risk of both rare and more frequent events; and they provide safety data on the more heterogeneous population of patients treated in clinical practice, which gives clinicians more information on the risks of adverse events they may see in the clinic.

■ **Various kinase inhibitors are currently in late-stage clinical trials in rheumatoid arthritis. How do you think these agents will fit into our treatment paradigm?**

We have been waiting for many years for the advent of oral agents that are as effective as parenteral biologics in rheumatoid arthritis (RA), and these kinase inhibitors finally seem to offer that promise. Where they will fit in our treatment paradigm, however, will depend on a number of factors, including cost, safety profile and the appeal of the convenience of oral dosing for our patients. It seems extremely unlikely that these agents will ever supplant methotrexate as our first-line therapy for RA, given the safety, efficacy and low cost of this drug. However, in the right circumstances, I think these kinase inhibitors will be considered to be an alternative to our current biologics, perhaps even TNF inhibitors. I presume that this will not happen immediately, as the need for alternative therapies is not so

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great that clinicians will forego their usual caution about the safety of new agents. However, as safety data accumulates, perhaps in the very registries we discussed above, these agents are likely to move earlier in the treatment algorithm. Ultimately, the cost of these agents will be an enormous factor in this decision, and one that will become increasingly important given the overall cost pressures in healthcare these days.

■ **Besides kinase inhibition, what are the other emerging therapeutic approaches for treating RA?**

The kinase inhibitors are likely to be the most exciting step forward in RA therapy in the next few years. There are other promising targets, including GM-CSF and IL-17, though it is too early to know how much clinical value these agents will have. There are a variety of agents in development that target the same pathways as some of our existing therapies, including IL-6 and T-cell costimulation. While it is nice to have options, I'm not sure these will add a great deal to our armamentarium. I am perhaps most intrigued by studies looking at therapeutic approaches, such as the ability to taper or withdraw biologic therapy, rather than specific new therapies. I am very hopeful that these studies will provide us with the tools to manage our RA patients more efficiently and more cost effectively.

■ **What would be the potential impact of biosimilars entering the RA market?**

If nothing else, these agents will provide the market pressure to keep the costs down on the branded products. How much uptake we will see with the biosimilars will depend upon a number of factors, including data to confirm that they have similar efficacy and safety to existing products and their cost. Given the cost of the development programs that will be necessary to get these biosimilars approved, and the high cost of manufacturing of biologic agents, I'm actually not certain that biosimilars will enter the market at an acquisition cost that will be low enough to drive their widespread use.

■ **In your opinion, how do you feel future clinical trials assessing the efficacy of RA treatments should be designed to obtain optimal clinical information?**

In a word, we need comparator trials. Trials to date have provided us with solid data on the efficacy of individual agents, but they don't really help us determine which agents are best for which patients. We need comparative efficacy trials that can guide us in specific clinical situations – inadequate response to methotrexate or inadequate response to a TNF inhibitor, for example. A number of trials, including BeSt, TICORA and CAMERA, have shown us that, in patients with active disease, modifying therapy in response to disease measurements, rather than sustained treatment with a single approach, leads to the best outcomes. Now we need trials that will help us manage those patients who have achieved and maintained remission, so that we can learn how to adjust therapy appropriately in these patients as well. Finally, I remain hopeful that our continued search for reliable biomarkers in current and future trials will eventually yield fruit, and that we will eventually have tools that can guide us on selecting between available agents in a manner that is more scientific than trial and error.

Financial & competing interests disclosure

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