Roy Fleischmann

Adjunct Professor of Medicine, University of Texas Southwestern Medical Center; Co-Medical Director of Metroplex Clinical Research Center, Dallas, Texas, USA

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Q1 Can you start by telling us a bit about your journey into rheumatology and what initially inspired you to specialize in this field, and what continues to drive your passion for research and patient care?

There are probably two main reasons. The first is that during medical school and my post-medical school training, the most dynamic professors I encountered were rheumatologists. They were deeply interested in the diseases they treated and very passionate about their work. Their enthusiasm was contagious, and I found myself drawn to the field because of them.

The second reason, and perhaps the more important, is personal. My favorite aunt had rheumatoid arthritis. She was treated in the 1950s, 60s, and 70s with steroids and gold salts, which were the standard therapies at the time. Unfortunately, her disease progressed to the point where she ended up in a wheelchair, and she passed away in her early 50s, likely due to complications from both the disease and the steroids. That personal connection drove my interest in a pursuit of a fellowship in rheumatology.

During my fellowship, I was trained in clinical trials, which aligned with my goal of finding better medications. At the time, we had very few effective treatments, and my goal was to contribute to developing therapies that were safer and more effective than gold salts or corticosteroids. Over the past 40 years, we've made significant progress in this area. While we're not perfect, we're certainly a long way from where we were in the 1970s and 80s.

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Q2 You've been instrumental in the development of therapies for rheumatoid arthritis and other rheumatic diseases. What do you see as the most significant advancement in this field over the past decade?

That's an interesting question, and it takes us quite a long way back. When I started practicing, the main treatments for rheumatoid arthritis were gold salts, steroids, and non-steroidal anti-inflammatory drugs. These were often toxic and not particularly effective.

I finished my training in 1974 and started practicing in 1975. In 1977, I attended an American College of Rheumatology (ACR) meeting in Boston, where a former co-fellow introduced me to methotrexate. At the time, it was being used off-label, about 10–12 years before it was FDA-approved for rheumatoid arthritis. By 1980, I had most of my patients on methotrexate, and somewhere between 15–25 mg of folic acid a week, and the results were significantly better. That was one major advancement.

Then, in the early 1990s, I was approached to work on trials for TNF inhibitors, starting with etanercept. These drugs were a game-changer, far more effective than methotrexate alone. From there, I became involved with other biologics, all of which were excellent but not perfect.

In the late 2000s, we started seeing the introduction of JAK inhibitors, which I believe are somewhat more efficacious than biologics, though they come with safety considerations. Most recently, CAR-T cell therapies have shown dramatic results, although they're still in the early stages and very expensive.

So, over the years, we've gone from having almost no effective treatments to a wide range of options that significantly improve patient outcomes.

Q3 Could you share with us some of the key findings from the SELECT-BEYOND study, particularly regarding the long-term efficacy and safety of upadacitinib in patients with rheumatoid arthritis?

There are two key studies involving upadacitinib that I think are noteworthy: SELECT-BEYOND and SELECT-COMPARE. Let's start with SELECT-BEYOND, which involved patients who had failed biologics and were subsequently treated with JAK inhibitors like upadacitinib. The study demonstrated that these patients could respond well to JAK inhibitors, which was a significant finding.

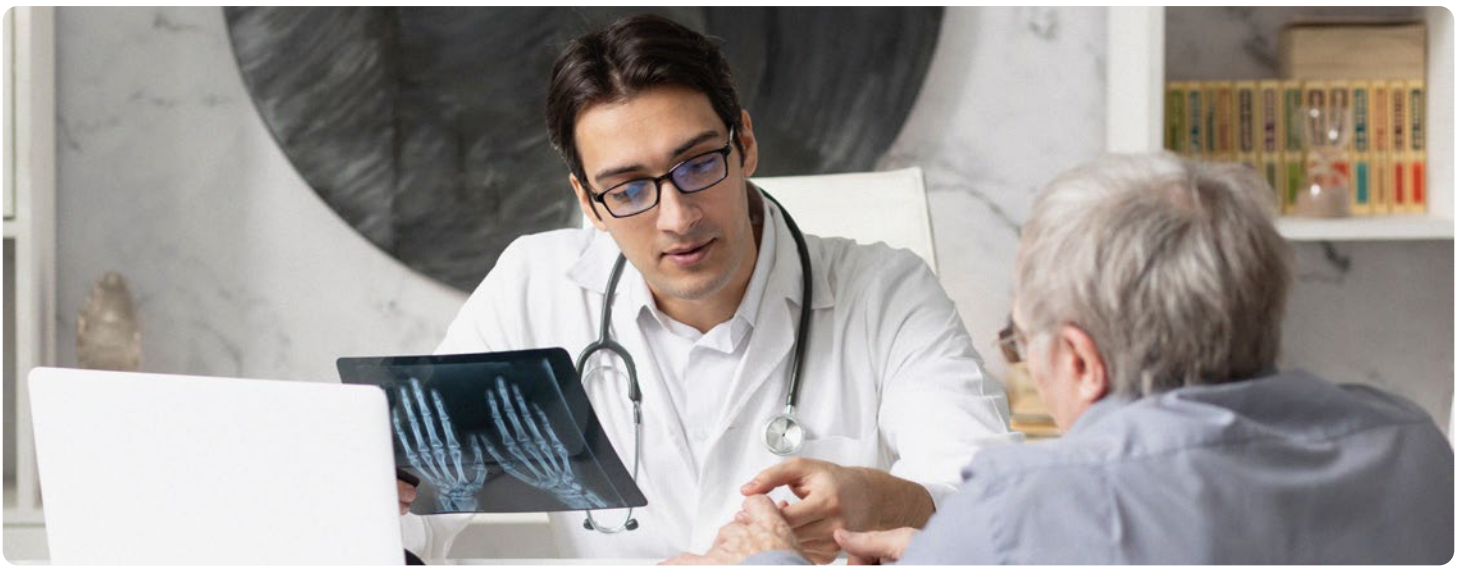
However, I believe SELECT-COMPARE is the more impactful study. In this trial, we directly compared the efficacy and safety of upadacitinib, a JAK inhibitor, with adalimumab, which is probably the most widely used TNF inhibitor worldwide. The trial showed that upadacitinib was actually more efficacious than adalimumab.

This finding is particularly important because it challenges the traditional treatment paradigm. Typically, after methotrexate failure, clinicians turn to TNF inhibitors as the next step. However, the SELECT-COMPARE results suggest that, in an ideal world where cost and access aren't barriers, upadacitinib might be the better option for patients who don't respond to methotrexate.

Of course, it's not a perfect world. Factors like cost and safety profiles play a significant role in clinical decision-making. While the efficacy of JAK inhibitors like upadacitinib is promising, safety concerns, such as cardiovascular risks and venous thromboembolism, must be considered, especially in patients with preexisting risk factors.

One of the key takeaways from the trial and subsequent analyses, including comparisons with findings from the ORAL Surveillance trial, is that patient selection is critical. For example, patients without significant cardiovascular or venous thromboembolism risk factors tend to do well on JAK inhibitors, while those with these risks require careful monitoring and mitigation strategies, regardless of the therapy used.

In practice, SELECT-COMPARE highlights the potential of JAK inhibitors as first-line treatments after methotrexate failure. It also reinforces the importance of tailoring treatments to individual patients' risk profiles to optimize outcomes while minimizing safety concerns.



Q4 What factors do you think are most critical in determining whether a patient responds well to targeted therapies such as JAK inhibitors?

That's a really great question, one we don't have an answer for yet. Two major unmet needs in rheumatology are predicting who will respond to which therapy safely and treating the patients who don't respond to any available therapy.

Right now, we don't have reliable tests or predictors to determine the best medication for a new patient. It's trial and error, which can be frustrating for both clinicians and patients. This is an area where AI might help in the future by analyzing vast amounts of data to identify patterns and predictors of response.

Q5 How do you see technologies like AI and machine learning influencing rheumatology research and practice in the coming years?

AI is an exciting but challenging tool. One of the risks is 'garbage in, garbage out': if the data fed into AI models isn't robust, the results won't be reliable. That said, AI has the potential to analyze complex datasets that even the smartest human minds can't process entirely. For example, AI could help identify which patients are likely to respond to specific therapies or uncover new mechanisms of action for drug development. However, we need to approach it cautiously to ensure the outputs are meaningful and actionable.

Q6 What are the biggest challenges in bringing new therapies from research to clinical pra ctice, and how do you think these can be addressed?

The challenges are multifaceted. First, the development pipeline itself is incredibly demanding. It begins with preclinical experiments, which are conducted in test tubes and animal models, typically rodents. These models are meant for understanding whether a particular mechanism might work, but they are not perfect, as rodents are not people.

Of the thousands of compounds tested preclinically, only a small fraction, maybe 10%, make it to Phase I clinical trials, and even less progress to Phase II. By Phase III, where safety and efficacy are rigorously evaluated, perhaps 1% of the original compounds remain. That is an enormous drop-off.

This is where AI could help by analyzing preclinical data and narrowing the field. Instead of starting with 1,000 compounds, you might start with 50 that are more likely to succeed, reducing costs and increasing efficiency.

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Another challenge is running clinical trials. Finding the right patients has become increasingly difficult, especially for diseases like rheumatoid arthritis. When I started trials in the 1990s, it was relatively easy to enroll patients because we had so few effective therapies. Now, with 16 approved medications, many of which are available as generics or biosimilars, it is harder to find patients who meet the ethical and clinical criteria for participating in trials. If you cannot find patients, you cannot conduct trials, and if you cannot conduct trials, you cannot bring new therapies to market.

There is also the challenge of designing trials. Protocols must be written carefully to answer a

single, clear question about a drug's effectiveness and safety. However, some protocols try to answer too many questions, which can dilute the results and make it harder to draw conclusions.

Finally, there is the issue of regulatory approval and cost. Even when a drug shows promise, the expense of developing it, often upwards of a billion dollars, makes pharmaceutical companies cautious, especially when competing against well-established therapies.

Addressing these challenges requires better trial designs, innovative technologies like AI, and possibly new regulatory approaches to streamline the process. But at the end of the day, the biggest challenge is finding ways to ethically and efficiently test therapies while ensuring they meet the highest standards of safety and efficacy.

Q7 Are there any emerging drugs or therapeutic approaches that you believe hold promise?

Yes, there are several interesting developments on the horizon. At the recent ACR meeting, there was a report on an anti-CD40 ligand, which showed promising results. Another area generating interest is vagus nerve stimulation, a device-based therapy. While it didn't show very dramatic efficacy, it could be an option for patients who, for some reason, cannot or will not take biologics or injectable therapies or for patients who have failed all approved therapies. Thus, this might fill a niche for some patients. There are also ongoing trials with programmed cell death protein 1 (PD-1) antagonists and CD40 inhibitors, as well as new JAK inhibitors.

The most exciting area, in my opinion, involves CAR-T cell therapy and T cell engagers. These are highly sophisticated and expensive treatments, but the results so far have been dramatic, particularly for patients who haven't responded to many other therapies. It's likely that these therapies will become increasingly important, although their complexity and cost remain significant hurdles.

Another challenge is finding pharmaceutical companies willing to invest the enormous resources, often over a billion dollars, required to develop new drugs. The bar is very high because we already have many effective therapies. However, there's still a subset of patients, around 20%, who don't respond to any current treatment. For them, these emerging approaches could be life-changing.

So, while progress continues, we're constantly balancing innovation with practicality. It's crucial to keep pushing for new treatments, especially for those patients who remain unresponsive to existing therapies.

Q8 With emerging treatments, how can clinicians balance the benefits of innovative therapies with potential long-term risks?

This balance should be addressed in clinical trials. Phase III trials should compare new therapies to existing ones, not just placebos, to assess how well they work relative to what's already available.

For safety, we need long-term prospective studies with large patient populations, similar to the oral surveillance trial. These studies provide critical insights into risks that might not appear in smaller trials.

For clinicians, the key is to stay informed by reading the latest clinical trial data, not just reviews or meta-analyses, and applying those findings to patient care. It's a challenging but essential part of advancing the field and improving outcomes for patients.