Rheumatology in 2006
Crossroads or Crisis?

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Abstract
Rheumatology has made remarkable advances in patient treatment in the past decade related to the impressive array of new drugs that have been approved or are undergoing clinical trial. While this situation should engender optimism for the future, concerns about sustaining momentum have been raised. These concerns relate to uncertainty in the research agenda for major diseases such as osteoarthritis and fibromyalgia, lack of informatics systems to allow accurate assessment of risks and benefits of new treatments, and a paucity of clinical trials in rheumatoid arthritis aimed at sustained remission or cure. Fortunately, the opportunities for the future remain very bright because of burgeoning research in biomedicine and outcomes assessment as well as progress in developing personalized medicine to individualize treatment better.

The past decade has witnessed a remarkable transformation in the field of rheumatology as new treatment approaches have dramatically improved patient outcomes. The progress has been startling, with 5 biologic agents approved for the treatment of rheumatoid arthritis (RA) during this time. In systemic lupus erythematosus (SLE), a wide array of promising new agents is under investigation. In view of the impressive progress in RA treatment and the strong pipeline of drugs in SLE, the future of rheumatology appears very bright. Indeed, I can think of no other time in the history of rheumatology when progress has been so rapid and the number of treatment options has exploded so greatly. This phenomenon is not unique to rheumatology. As in other fields of medicine, two trends are converging: a short time interval between the introduction of new therapies and an almost simultaneous entry into the market of new agents that share the same mechanism.

While this situation should engender great excitement and optimism, there are nevertheless reasons for concern. At a recent conference, I heard an eminent investigator declare that clinical research in rheumatology was in crisis. To say the least, the audience was surprised, but this expert, whose credentials are impeccable, went on to explain cogently the reasons for his assessment. I can quibble with the word “crisis,” since it is used too often, but I cannot quibble with this expert’s views. I, too, think that rheumatology may be approaching a crossroads, if not a crisis.

Why this view, especially as the biomedical research engine continues to fill the pipeline for new agents to test? I think that, in this circumstance, a SWOT analysis can be insightful. A SWOT analysis is a framework often used by business modelers for evaluating the state of an organization. Simply stated, a SWOT analysis enumerates Strengths, Weaknesses, Opportunities and Threats. As an analytic tool, it provides guidance for the future and is often the first step in the creation of a strategic plan.

A SWOT analysis is an ambivalent undertaking. First, no one likes to point to weaknesses in an organization. More neutral terms (eg, “shortcomings” or “areas for improvement”) may be preferred, but a blunt term like “weakness” has a way of focusing attention. Second, a SWOT analysis engenders discomfort because of the seemingly subjective way in which attributes are conceptualized or categorized. A leadership style can be called a Strength if it is thought to provide stability or a Weakness if it is thought to slow innovation or discourage dissent. The difference between a Threat and an Opportunity may also be in the eye of the beholder.

Risking the dangers inherent in a SWOT analysis, I will forge on. Without a careful appraisal of the state of rheumatology in 2006, I think trouble for our specialty may be ahead. Certainly, medical practice is becoming a much more competitive and cost-driven business and, unless plans are made for the future,
our field will miss out on opportunities, with ultimate loss to our patients.

**Strengths**

Strengths are the easiest category to discuss. Rheumatology is a vibrant and expanding field, riding the crest of excitement following major advances in the treatment of RA and osteoporosis, in particular, and a promising pipeline of drugs in SLE. These advances require ever-growing knowledge and sophistication and reinforce the value of specialty care and the need for rheumatologists. In this regard, some of the new biologic agents require infusions, necessitating an infrastructure for their administration that a general physician most likely cannot provide. Furthermore, immunology is booming, powering a strong tide that is raising all ships, including that of rheumatology. Coupled with outstanding investigators in patient outcomes, the field of rheumatology is poised for further advances in the treatment of immune-mediated and inflammatory disease. Furthermore, the patient and professional groups for rheumatology are providing strong advocacy and financial support to keep the momentum going.

**Weaknesses**

It is too bad that Weaknesses is the second phase of the SWOT analysis since, after the giddiness of the Strengths category, it is a downer, a veritable wet blanket on the initial excitement. Probing weakness can be painful. It is a cause of self-reflection and provides a dose of reality. It is the bad medicine that must be swallowed.

A real weakness in rheumatology concerns the slow progress in some of the most common debilitating diseases. Notably, among prevalent conditions, osteoarthritis is proving to be an enormous challenge. Pathogenesis remains obscure, model systems are lacking, and biomarkers have yet to be developed despite great effort. While the number of patients with this disease is rising as the population grows older, rheumatology unfortunately does not have much new to offer beyond a more informed valuation of the risks and benefits of nonsteroidal anti-inflammatory drugs (NSAIDs).

Research on fibromyalgia is also lagging, reflecting in part the field’s uncertainty about the validity of this diagnosis as well as its ambivalence about its role in patient management. However rheumatologists may regard fibromyalgia, it is part of their specialty. I believe that rheumatologists can provide great service to patients by assuring more informed and precise diagnoses as well as formulating relevant research questions to take advantage of advances in neurobiology and neuroimaging. Given the number of patients with this condition and the associated burden of illness, it is a weakness of rheumatology that it is not more involved in investigation.

Finally, in a way that may seem surprising, I think that the research agenda in RA is not as strong as it should be. Indeed, I can detect weakness. This weakness does not relate to puzzlement about pathogenesis or lack of biomarkers, nor does it relate to a sluggish pipeline of new agents or targets to explore. Rather, I think that the weakness relates to the current focus on clinical trials designed to allow regulatory approval of new drugs and efforts to fulfill “unmet needs” that, in this country, are likely to be decreasing.

The current trial designs are based on establishing efficacy of a new agent in patients with active disease who have “failed” current therapy, which is usually defined as conventional small molecule disease-modifying antirheumatic drugs (DMARDs). In this design, methotrexate is the anchor drug, with patients with an inadequate response to this drug continuing its use while randomized to a new agent or placebo. Efficacy can be assessed by various measures of clinical response as well as radiographic assessment. The difficulty with this approach and the source of the crisis is that, in the United States, fewer and fewer patients meet entry criteria for trials, meaning that patients studied are a small minority in this country or live overseas. While globalization of clinical trials is a welcome event, trials outside of the United States may involve types of patients that are not representative of the patients that most clinicians see here. (Of course, there are ethical issues in the performance of clinical trials in countries where the drugs will be too expensive to use, but that is another issue.) Furthermore, as new biologic therapies enter the market, patients eligible for such trials will represent the most resistant groups, whose prior history of immune modulation may confound interpretation of safety and efficacy.

Such trials will no doubt continue on the hope that a uniquely effective DMARD will be found. If such trials are the mainstay of the agenda of clinical research in RA, however, a broader universe of exciting and transformative research may not occur. Clearly, current therapy is successful. Remissions occur, radiographic progression can stop, and disability can be prevented. The important issues at present are to find the best way to achieve these goals in the shortest time possible with the least costs in terms of side effects as well as financial outlays.

New methodology is needed to design trials aimed at remission. Furthermore, more boldness is needed in scientifically testing combinations of agents that can permanently block disease progression. Unless rheumatology as a field strives to cure RA or induce sustained remission in a more decisive way, the field will be weakened.

For rheumatology to move forward, it should also eliminate the distinction between small molecule and large molecule drugs and develop a terminology more informative than “targeted therapies.” All drugs are targeted, and it is essential that research determine exactly what each of the effective agents does alone and in combination. After two decades of use, the mode of action of methotrexate remains unknown. It is a sign of weakness of the field that the target action of a highly effective agent receives scant attention.

**Opportunities**

Identifying Opportunities is also easy. Modern biomedical research is providing a host of powerful genetic, genomic, biomarker, and imaging modalities to characterize disease at
the level of the individual patient. “Personalized medicine” will be possible and will provide better margins of safety and efficacy as new diagnostic and “theragnostic” tests come on line.\(^4\) Rheumatology should seize this opportunity, which will require cooperation via networks as well as the more widespread utilization of outcome measures in office practice.\(^5\) In this way, the largest amount of data can be assembled for predictive modeling. Measures such as the Disease Activity Score (DAS), Health Assessment Questionnaire (HAQ), and Simplified Disease Activity Index (SDAI) should become routine parts of patient follow-up so that, in a big computer somewhere, clinical data will be amalgamated with genomic and genetic data to provide new ways to choose therapy.

Threats

The category of Threats is another downer, but as in the case of the Weaknesses category, it cannot be escaped. If the Vioxx situation should have taught rheumatologists one lesson, it is that the landscape of risks and benefits is forever shifting and changing and that small increases in certain adverse events can have colossal impact when considered over the whole treated population. Fortunately, TNF blockers appear to be quite safe drugs, but with continued use and extension into other populations around the world, the safety profile may change. Vigilance is essential, with a constant search needed for signals that may indicate either an uptick or upsurge of any side effect.

As patients receive new agents sequentially, a “one-two punch” situation may take place, with one biologic agent setting the stage for another’s knockout blow. Current data indicate that biologic agents together may have an increase in the frequency of infection. Is it possible that two in succession may carry the same increased risk? In the enthusiasm to improve patient outcomes and explore new approaches, rheumatologists must remember the risk entailed in these ventures and assure that aggressive treatment is justified by unacceptable disease activity as measured by an objective score.

At present, an ever increasing number of patients in all fields of medicine are receiving medications whose goal is the prevention of conditions in which the actual risk to the individual may be small. Thus, an intervention may cut in half the likelihood of a condition for a particular person, but that decrease may translate into a reduction from a chance of 2 in 1000 to 1 in 1000. Framing choices in terms of absolute versus relative risk can produce very different decisions. In this regard, a patient and physician may view risks of disease and risks of treatment very differently. Thus, even a very small risk of cancer may deter a patient from starting certain biologic agents, although the physician may be accepting of an event that appears remote at best. In rheumatology, the prevention of osteoporosis, a serious and debilitating condition in some patients, is an important and worthwhile goal but will undoubtedly occur at a cost. Slowing or even inhibiting bone turnover to decrease osteoporosis may have detrimental effects in other situations such as healing of micro- or macro-fractures.\(^5\)\(^7\) The occurrence of jaw osteonecrosis, while a rare event, may be a warning of the dangers of bisphosphonates. These dangers should be weighed carefully and clearly defined, so that the use of a valuable class of medicines can go forward. Otherwise, rheumatology will lurch from one round of litigation to the next.

Another threat to rheumatology is the lack of organized systems for risk assessment of new drugs. The United States, as a decentralized health care system, does not have the informatics systems needed to do longitudinal studies to determine in the real world the true benefits and risks of new drugs. Furthermore, while pharmaceutical companies are supposed to perform postmarketing studies to address such issues, these studies are frequently delayed or neglected. Coupled with the difficulties in performing clinical research in less common diseases,\(^5\) the gaps in knowledge on treatment may grow, leading to pervasive empiricism. In a health care environment, in which subspecialties will compete for shrinking dollars, information will be essential to assure that rheumatology patients get appropriate care and that expensive drugs are targeted to those most in need.

Conclusion

Despite weaknesses in infrastructure and growing threats on the horizon, rheumatology should prosper in the future. Importantly, the field needs to be cooperative, assertive and imaginative. It also needs to be a bit wary since great advances of the past decade may have been a matter of luck. Hopefully, rheumatologists will recognize that a crisis is a time to gather strength and not bemoan weakness, and to turn threats into golden opportunities.

References