PERSPECTIVE

Non-Biological Complex Drugs

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Assuring patient-centred care: engaging patients with rheumatoid arthritis in disease monitoring and pharmacovigilance

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With the advent of complex therapies in the form of biologicals, emerging biosimilars and non-biological complex drugs, monitoring for treatment related benefit and the potential for adverse effects is as critical as monitoring for signs and symptoms of rheumatoid arthritis disease progression. With a focus on strengthening patient and provider education and engagement, patients can be successfully engaged in the long-term monitoring of their disease and play a vital role in the determination of adequate treatment response or treatment failure.

Keywords: Biological therapy, patient engagement, pharmacovigilance, treatment response

Introduction

Despite years of research the clues and keys to understanding autoimmune diseases continue to elude us. Today, more than 50 million Americans live with autoimmune syndromes and women represent nearly three quarters of this group. Researchers note that worldwide, autoimmune diseases affect 8% of the population, 78% of whom are women [1]. While cures for the multiple autoimmune syndromes remain a research goal, the past 15 years has seen the development of a number of new complex treatments for autoimmune conditions. As a result of the development of biological and non-biological complex drugs, patients now receive significant symptomatic relief for multiple autoimmune diseases. Access to safe and effective biological therapies has been especially effective in protecting joint function and strengthening quality of life for those patients with rheumatoid arthritis (RA). Without question, biologicals have served as a major benefit for patients. However, these complex drugs have also been accompanied by new health threats and economic challenges [2].

Challenge of biologicals and follow-on products

In the US, the personal retail cost of biological therapy can range from as little as US$25 a month to as much as US$3,000 a month depending upon insurance coverage. Extensive direct-to-consumer marketing of these drugs, through television and other media has enhanced adoption of these therapies and created significant revenue streams for pharmaceutical companies. In 2007, Americans spent US$40.3 billion on biological drugs [3] and in 2008, 28 per cent of sales from the pharmaceutical industry's top 100 products came from biologicals; by 2014, that share is expected to rise to 50 per cent [4].

While small molecule drugs have well-defined structures and can be thoroughly characterized, biologicals represent a different category of therapies developed from an array of genetic proteins from living cells [5]. As complex proteins, biologicals are large in structure, difficult to manufacture and highly sensitive to environmental changes. While pharmaceutical companies throughout the world have patented and closely protected their manufacturing processes, recent regulatory changes in the US have mirrored decisions within the European Medicines Agency (EMA) to provide a pathway for the development of follow-on biologicals or biosimilars. Although it is hoped that the development of biosimilars will increase access, decrease personal costs and extend therapeutic benefits to patients, it is important to remember that unlike simple chemically synthesized drugs, no two biologicals or biosimilars will be identical. Just as biological products have produced both benefits and unforeseen immunogenic adverse reactions, newly marketed biosimilar products share this same potential.

As the development of biologicals and biosimilars and new non-biological complex drugs (NBCDs) proceeds, it is important to review and strengthen the processes utilized by clinicians and patients to select and monitor the therapeutic and potential adverse effects of these therapies. In particular, there is a need to increase engagement of patients with RA in efforts to refine and reach consensus on the definitions of the important clinical concepts of 'inadequate response' and 'treatment failure'. Recent collaborations among US and European scientists and physicians have created a consensus definition for disease remission in RA [6]. Nevertheless, more work is needed to incorporate patient input in efforts to determine the characteristics that contribute to the need to stop/start or change therapies.

Rheumatoid arthritis treatment challenges

For many patients the diagnosis of RA is difficult to manage. While there is relief that the joint pain, loss of movement, fatigue and other symptoms finally have a clinical label, new concerns often immediately emerge as patients learn of the many side effects and potential adverse reactions associated with biological treatment choices. Fear of the disease and fear of treatment frequently become intertwined. Indeed a recent study conducted by the American Autoimmune Related Diseases Association (AARDA) noted that as many as 30 per cent of patients with autoimmune diseases never fill their prescriptions [7]. Lack of trust and limited communication between the patient and the prescribing physician as well as expensive treatment costs were cited as contributing

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factors to non-adherence. Facing the lack of trust and communication, compounded with economic challenges, patients may sometimes fail to report that they have avoided or stopped taking a prescribed medicine. Thus, a determination of 'treatment failure' by a physician may simply be the result of failure to take a medicine as prescribed. In addition to communication issues, patient adherence to therapy is often influenced by the method of drug or treatment administration. For RA patients receiving biologicals, the challenge of self-injection can complicate treatment delivery especially for the many patients who admit to 'needle-phobia'. Thus, the decision to switch therapy may be influenced by the patients' reaction to the method of administration.

Development of guidelines specific to switching medications

The selection of biological therapy and the determination of the need to switch biological treatment is a significant issue for patients with RA even if the new therapy is within the same drug classification. With the advent of biological and complex drug therapies, and the promise of new biosimilar therapies that may be less expensive, the decision to switch medications must be balanced against all known potential risks. While the treatment decisions determined through patient/provider communication should be strengthen and always honoured, the growing opportunity for new, potentially better, less expensive and less invasive therapies often complicate and confound final treatment selections. Healthcare providers and patients on biological medications readily note that the therapeutic benefit achieved from initial response to a biological product may seem to attenuate over time. Without specific biomarkers for many autoimmune diseases including RA, it has been difficult to classify or describe universal characteristics that may be associated with determination of 'treatment failure' or 'inadequate response'. In some instances, patient frustration with the delivery mechanisms associated with biologicals, e.g. infusion and injection, may contribute to reports of 'inadequate response' and 'treatment failure'. As new biosimilars are developed with new device delivery tools influencing patient acceptance, the challenge of sorting the reasons for switching treatment will continue to grow [8]. As a result, patients may sometimes be unnecessarily switched, or consider the original therapy a failure when, in actuality, the original treatment was performing as biologically expected. In a study published in *Arthritis Research & Therapy*, researchers analyzed published clinical outcomes of biological treatment among RA patients with an inadequate response to tumour necrosis factor α (TNF-α) inhibitors [9]. Their analysis revealed that for patients with prior exposure to TNF-α inhibitors, the likelihood of a response to subsequent treatment with biological agents was diminished. Indeed a diminished response to a TNF-α inhibitor biological seemed to be correlated to the number of previous TNF-α inhibitor treatments a patient may have received. Within the class of biological products for treatment of RA, analysis also revealed that within a short 15-month period, more than a third of patients switched among more than one biological therapy [10]. In order to support the determination of the right course of treatment for patients, increased emphasis is needed on the development of detailed assessment tools and communication strategies to engage patients as equal partners in post-licensing pharmacovigilance.

Engaging patients in treatment selection, disease monitoring and pharmacovigilance

Pharmacovigilance is the science of collecting, monitoring, researching and evaluating information from healthcare providers and patients on the benefits and potential adverse effects of all drugs including biologicals. However, for the most part pharmacovigilance has most often been a process assigned to providers and manufacturers with little formal input from patients. While physician and other healthcare providers remain focused on improving patients' health, the ability to accurately measure disease and treatment progression is frequently confounded by the multiple clinical assessment, global health and combined laboratory monitoring tools available to monitor RA disease [11]. As assessment and evaluation of disease, treatment progress or problems is largely determined at periodic monthly office visits, long-term day-to-day patient directed assessment of disease or treatment status is largely missing. Within an autoimmune disease, such as RA, where symptoms may widely fluctuate between healthcare visits without clear explanation, patient monitoring for disease progression and treatment effect can offer valuable input particularly as the decision to change therapy is considered. In addition, while there remains an array of disease modifying antirheumatic drugs (DMARDs) and biologicals for selection, detailed patient-based data could positively influence the selection of the right drug/biological for the right patient at the right time. Indeed, with the absence of comprehensive patient-based input some investigators note that physician-based determinants were more likely to influence treatment choices than patient report of symptom change [12].

With the advent of patient-centred care it is now time to maximize the influence of the patient in assessment of symptom progression and subsequent treatment decisions. While periodic physician evaluation of global health and patient joint signs and symptoms has served as a primary resource for selection of therapy, new research supports the need to include ongoing patient assessment and report of joint signs and symptoms in the overall assessment of disease and determination of therapy. The benefits of patient engagement in disease assessment and management were recently described in the journal *Rheumatology* [13]. With appropriate instruction from nurse specialists in rheumatology, patients were accurately able to self-assess joint signs and report symptoms to complete the widely adopted rheumatologic Disease Activity Score (DAS28). Through comprehensive patient engagement and health education over a period of six months, DAS28 assessments completed independently by patients achieved significant congruence with DAS28 assessments completed by rheumatology healthcare professionals. Patients in this study also reported improved understanding of their disease.

With the expected development of new follow-on biological medications, and the emergence of NBCDs in simple pill form, the lure of a 'better benefit' will be enticing for both patients and providers. However, in order to protect patients, the determination of interchangeability among biologicals and complex drugs must include not only thorough safety and efficacy studies but also plans to engage patients in ongoing monitoring of not only disease-based symptoms but also the potential side effects and adverse reactions of associated treatments. Recent studies note that while clinical assessment collected during office visits might recommend the need to add or switch therapy, many patients reported satisfaction with their current therapy and expressed no desire to change [14]. As the growth of new RA therapies continues,

concerns related to switching therapies will need to be addressed.

Conclusion

International collaboration among physicians and scientists has recently improved efforts to accurately assess disease activity and remission among RA patients. Despite this effort, dissatisfaction remains with regards to the sensitivity and specificity of validated RA disease assessment tools among both clinician and patient groups. In particular, patient groups have advocated for the expansion of RA clinical assessments beyond joint counts and global health status to include assessment of significant clinical aspects of RA disease such as fatigue and sleep [15]. Just as recent efforts within OMERACT (Outcome Measures in Rheumatology) and the US-based PROMIS (Patient-Reported Outcomes Measurement Information System) project, have been designed to include the patient's perspective [16], renewed attention is needed to develop evidenced-based tools to engage RA patients in personal, day-to-day, home monitoring of disease and treatment parameters. Over the past decade studies have affirmed that long-term chronic disease management is improved when patients are engaged. Indeed the expectation for home monitoring of signs and symptoms is an essential component of the treatment plan for patients with hypertension and diabetes. Personal self-monitoring of blood pressure and glucose levels as well as diet and exercise are a widely expected and become points for discussion and dialogue between patient and provider. These targeted measures are linked to treatment selection and disease monitoring and strengthen patients' investment in their personal health and overall plan of care. Without validated tools to assist in long-term self-monitoring, patients with RA may likely remain passive partners in their care. As the complexity of RA care grows with the advent of biosimilars and NBCDs, the determination of treatment failure or inadequate response warrants an increased focus on involvement of the patient in both disease and treatment pharmacovigilance. Indeed, while the medical community often assumes it is the best source for data regarding adverse treatment response, the US Food and Drug Administration (FDA) recently noted that voluntary and spontaneous reports from patients and consumers serve as the principal mechanism for detection of serious adverse events [17]. As payment and policy issues impact access to quality care, regulatory authorities will need to encourage the development of patient-focused assessment tools to assure that patients are not only involved in monitoring the progress of disease signs and symptoms but are also thoroughly prepared to monitor for the myriad of both positive and negative treatment effects. As complex drugs and biologicals are developed we must continue to develop strategies to maximize patient engagement to assure the highest standards for safe quality care.

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Dr Wyatt is a retired nurse practitioner and health educator with more than 35 years of clinical nursing practice. In 2004, she was diagnosed with rheumatoid arthritis (RA) and osteoarthritis. Having lived with these chronic illnesses, Dr Wyatt is uniquely attuned to the needs and challenges facing patients. Dr Wyatt is a recognized international speaker, author and a staunch advocate for patient rights and safety. She is currently a volunteer member on the Board of Directors of the National Arthritis Foundation and a member of the National Advisory Council of the Agency for Healthcare Research and Quality of the US Department of Health and Human Services.

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