RHEUMATOID ARTHRITIS IN A POLICY PERSPECTIVE

A REGISTRY FOR RESEARCH AND BETTER TREATMENT OF ALBERTANS

MARCH 2015

IHE INSTITUTE OF HEALTH ECONOMICS ALBERTA CANADA

McCaig Institute for Bone and Joint Health

UNIVERSITY OF ALBERTA

UNIVERSITY OF CALGARY

Institute of Health Economics

The Institute of Health Economics (IHE) is an independent, not-for-profit organization that performs research in health economics and synthesizes evidence in health technology assessment to assist health policy making and best medical practices.

IHE Board of Directors

Rheumatoid arthritis in a policy perspective: A registry for research and better treatment of Albertans

INSTITUTE OF HEALTH ECONOMICS
ALBERTA CANADA

Institute of Health Economics
1200 – 10405 Jasper Avenue
Edmonton AB Canada T5J 3N4
info@ihe.ca

www.ihe.ca

ISBN 978-1-926929-41-5 (print)
ISBN 978-1-929929-42-2 (online)

Authors

Deborah A. Marshall, Associate Professor, Department of Community Health Sciences, University of Calgary; Canada Research Chair, Health Systems and Services Research; Arthur J.E. Child Chair, Rheumatology Outcomes Research

Egon Jonsson, Executive Director & CEO, Institute of Health Economics

Liam Martin, Division of Rheumatology, Department of Medicine, University of Calgary

Dianne Mosher, Division Head, Division of Rheumatology, Department of Medicine, University of Calgary

Karen V. MacDonald, Research Associate, Department of Community Health Science, University of Calgary

Acknowledgements

We would like to thank the following:

Alberta Biologics Council, Project Steering Committee

- Kirsten Garces, Value and Access, Senior Manager, AMGEN Canada Inc.
- Cynthia Schurman, Provincial Affairs Manager, AbbVie Corporation
- Derek Badger, Government Affairs Manager, Janssen Inc.
- Egon Jonsson, CEO, Institute of Health Economics
- Allison Hagen, Director of Finance, Institute of Health Economics

Arto Ohinmaa, Associate Professor, School of Public Health, University of Alberta

Glen Hazlewood, Clinical Assistant Professor, Cumming School of Medicine, University of Calgary

Table of Contents

Executive Summary

Rheumatoid arthritis (RA) is a chronic autoimmune disease for which there is no cure. It affects approximately 0.9% of the population in Canada, and about 30,000 Albertans may have the disease.[1, 2] Early diagnosis and intervention, together with a treat-to-target strategy where a goal is defined and therapy is adjusted until the goal is achieved, are essential to success in controlling the disease effectively.[3] Most RA patients are first treated with conventional disease-modifying anti-rheumatic drugs (DMARDs) and, if they continue to exhibit moderate to high disease activity after three months of treatment, then a biologic therapy is introduced.[3] Timely and targeted care with conventional or biologic therapies is important and has been shown to increase the chance of disease remission at one year.[4, 5] This, together with the introduction of biologic therapies, has significantly advanced the ability to control RA and avoid joint damage and disability.

No guidelines are currently in place for selecting a specific biologic agent from the different biologic agents available on the market, or for switching from one agent to another. Little comparative effectiveness data is available—as required increasingly for health technology assessment and coverage and reimbursement decisions—about the use of these therapies in routine clinical practice to compare the effectiveness of one approach for managing RA to other approaches.[6-10]

Comparative effectiveness data would also inform other important issues related to clinical practice patterns and models of care, including:

- the optimal time to initiate biologic therapy;
- whether biologic agents can be stopped temporarily in patients achieving disease remission;
- how biologic agents compare with combination DMARD therapy; and
- best treatment strategies in patients who do not respond adequately to initial therapy.[3]

A comprehensive RA registry in Alberta would generate the comparative effectiveness data required to guide best clinical practice in these critical areas. Disease registries allow us to compare the performance of different therapies in routine clinical practice. Registries can serve many purposes including:

- understanding the natural history of a disease;
- determining the clinical effectiveness and cost-effectiveness of healthcare therapies and services;
- measuring and monitoring safety and harm;
- measuring the quality of care; and
- supporting clinical decision-making.[8]

Over the past two decades, clinicians, the research community, and policy-makers in a number of countries worldwide have developed and implemented their own national/regional RA biologic therapy registries to monitor patients over time.[11] As RA treatment guidelines recommend an earlier, aggressive treatment approach and subsequent entry biologics (SEBs) are introduced, the need for such registries in Canada is becoming more apparent. A need also exists for comparative effectiveness studies, which require high quality data collected longitudinally from the RA patient population over the continuum of care in routine practice.

Alberta has the opportunity to vault to the forefront of capturing data and generating evidence on RA therapies, helping solidify its position as a leading Canadian centre of research and innovation in arthritis prevention and treatment. The Alberta Biologics Pharmacosurveillance (ABioPharm) registry collects data on all biologic agents available to its population base, but data collection does not begin until the start of biologic therapy. Applying our experience with the ABioPharm biologics registry as a base, Alberta can build a registry of all RA patients that is sustainable and would be the first in Canada to capture data on patients along every point in the continuum of care. An RA registry in Alberta would serve as a "learning system" resource, capable of changing over time in response to new technologies, better treatments, and shifting patient demographics in the province.[12] Given the high rate of comorbidities in the RA population and the disease's negative impact on productivity, a resource with this capability would generate important health, social, and economic gains for Alberta.

Recommendations

To seize this opportunity, Alberta needs to take the following steps:

Funding Support

- ✓ Commit to long-term funding of an RA patient registry with a funding model involving multiple partners that could include the pharmaceutical industry.

Operational Changes

- ✓ Include in the registry all patients referred to a rheumatologist who are diagnosed with RA and follow these patients longitudinally, including those being treated with DMARDs and biologic therapies.
- ✓ Improve the processes of applying for biologic therapy insurance coverage and securing payment, to reduce the onerous and time-consuming paperwork required of rheumatologists.
- ✓ Provide consistent and appropriate support and education to patients who are receiving biologic therapy.

Evidence Generation

- ✓ Structure the RA registry to collect data at all stages of the continuum of care, beginning with patient referral to rheumatological care and continuing through treatment, remission, and long-term monitoring of patients. Include epidemiological data, such as geographic location, occupation, and work setting, to help further our understanding of the impact of RA in Alberta.
- ✓ Use the improved quality and breadth of data from an expanded registry to measure rheumatological care against performance benchmarks in each of the six dimensions of healthcare quality, including safety, accessibility, effectiveness, efficiency, acceptability, and appropriateness. Use the outcomes as a "learning system" to drive continuous improvement in care.
- ✓ Analyze registry data on a scheduled basis and report the findings on safety and access to therapies:
    - safety data with a special focus on adverse reactions to drugs, immunogenicity, and rapid response to drug recalls; and

- appropriateness data to ensure biologic therapy is administered according to provincial treatment protocols.

- ✓ Continue to support investigator-initiated research, with the required ethics approval and privacy protection, in areas that inform clinical practice and public health policy. Include as priorities the analysis of data to address research questions in the areas of:
  - the current burden of illness associated with RA in Alberta and projected needs for associated healthcare services in the future;
  - measurement of RA patient outcomes and healthcare system performance outcomes;
  - alternative models of care for early diagnosis and management of RA patients (for example, centralised intake and specialized clinics);
  - implementation of personalized therapeutic approaches (that is, precision medicine) to improve RA patient outcomes; and
  - comparative effectiveness and cost-effectiveness of alternative therapeutic pathways in the context of routine clinical practice.

Partnerships

- ✓ Work with Alberta Health Services and its Bone and Joint Health Strategic Clinical Network to put in place systems for quickly moving data from an RA registry into knowledge, and moving knowledge into better clinical care practices.
- ✓ Continue collaboration between the divisions of Rheumatology at the Universities of Alberta and Calgary to increase knowledge, using data from the RA registry, about the risks and benefits of biologic therapy and other RA therapies, and to support the future sustainability of the registry.
- ✓ Participate in collaborations among RA registries, in Canada and internationally, to update treatment guidelines, develop standardized outcome measures and similar patient follow-up practices, and increase study power when analyzing rare events, exposures, and diseases.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease for which there is no cure. It affects approximately 0.9% of the population in Canada, and about 30,000 Albertans may have the disease.[1, 2]

RA occurs when the immune system, which normally fights off pathogens, becomes over-active and begins attacking the tissue in the lining of the joints.[13, 14] The joints become sore, inflamed, and stiff. Damage to joint cartilage and bone can begin as soon as six weeks from disease onset. Without treatment to control the inflammation, the joints can be severely and irreversibly damaged and deformed, causing significant permanent disability. The immune attack brought on by RA can spread to the tissue in the lining of internal organs such as the eyes, lungs, and heart. Inflammation in the arteries increases the risk of mortality.[13, 14]

The disease affects people at all ages, but more than half of all new cases are diagnosed in people between ages 40 and 70, a highly productive period of life.[14] It occurs three times more often in women than in men, and is twice as prevalent in the aboriginal population as in the general population.[15] The life expectancy of people with RA is 10 years less than that of the general population in Canada, and the mortality rate is approximately 30% higher than that of the general population of the same age and sex.[1]

Up to half of people with RA who do not receive adequate treatment or do not respond to treatment will be unable to work within 10 years of symptoms first appearing.[1] Those who continue to work will eventually experience a decline in productivity as work absenteeism increases and on-the-job output falls.[16, 17] Loss of productivity is brought on by the limitations imposed by pain and reduced joint mobility, as well as the onset of comorbidities such as depression, cardiac disease, internal organ damage, and osteoarthritis.[16, 17] The burden of disease can also spread to family members, who are called upon to provide increasing levels of care for people with RA whose independence diminishes as their disease progresses.[18]

In Canada, in 2010, the total annual economic burden of RA was estimated to be $5.7 billion, suggesting an annual economic burden of approximately $800 million in Alberta.[2] This amount includes both the direct and indirect costs of RA. Direct costs comprise all healthcare costs incurred to treat RA and comorbidities, of which hospital admissions to treat joint damage and deformity are the largest component. Indirect costs include loss of productivity due to diminished capacity while at work, temporary absence from work, or permanent elimination from the work force.[19] The incidence, prevalence, and economic burden of RA are expected to increase as Alberta's population grows and people live longer.

Conventional Drugs and Biologics

Until the late 1990s, disease-modifying anti-rheumatic drugs (DMARDs) were the most effective treatment available for RA. Treatment with DMARDs alters the body's general immune response in the hope of reducing the immune system's attack on the joints.[3] Methotrexate is considered the "anchor" DMARD for treating rheumatoid arthritis, since its benefits to patients significantly outweigh the risk of drug toxicity.[3, 20] Other DMARDs may be used in combination with methotrexate, or as an alternative for people who cannot tolerate methotrexate or who experience inadequate benefit from the drug.[3]

A new class of treatment emerged in 1998 with the introduction of the first targeted biologic therapy for RA in Canada. Unlike DMARDs, biologic therapies for RA alter specific immune responses associated with the disease. Targeted tumour necrosis factor (TNF) was the first class of biologic agent proven effective in treating rheumatoid arthritis. TNF-alpha is a cytokine, or protein, that allows the cells to send signals to each other.[14] Cytokines play a fundamental role in the processes that cause RA inflammation. Anti-TNF biologic agents work by inhibiting TNF-alpha, to reduce the inflammatory response. Other classes of biologic agent were subsequently introduced, targeting different aspects of the immune system to control joint inflammation.[14]

Early diagnosis and intervention, together with a treat-to-target strategy where a goal is defined and therapy is adjusted until the goal is achieved, are essential to success in controlling the disease effectively.[3] Timely and targeted care is important and has been shown to increase the chance of disease remission at one year.[4, 5] This, together with the introduction of biologic therapies, has significantly advanced the ability to control RA and avoid joint damage and disability.

Early diagnosis and intervention together with a treat-to-target strategy are essential to success in controlling RA effectively.

In Canada, early intervention combined with the treat-to-target methodology is a central feature of the national guidelines developed by the Canadian Rheumatology Association for treating RA, and has informed the Inflammatory Arthritis Models of Care developed by the Arthritis Alliance of Canada.[3, 21]

Unfortunately, the delivery of care in Canada has not matched the advances in RA therapy. The shortage of specialists competent in assessing RA means that the disease is often not recognized during its early stage. This leads to lost opportunity for early intervention by a rheumatologist and suboptimal delivery of RA care.[22-24] Thus, timely access to appropriate therapy remains one of the greatest challenges facing health service planners.[22-24]

A delay of more than three months between symptom onset and start of therapy reduces the chance of attaining disease remission by 50% and increases the chance of progressive joint damage by 30%.

Lost opportunity for early intervention to control inflammation can have significant negative consequences. The optimal time in which to initiate RA treatment is in the three months following the onset of symptoms.[25-28] A treatment delay of more than three months reduces the chance of attaining disease remission by 50% and increases the chance of progressive joint damage by 30%.[29] A recent German study by Huscher et al. found that increased direct costs related to treatment were largely offset by reduced hospitalization rates and reduced work disability, with no substantial change in overall costs of RA patients.[30] Furthermore, given the availability of improved treatment strategies with conventional DMARDS as well as clinical practice trends to earlier treatment initiation, Huscher et al. do not anticipate net cost increases for RA treatment in the future.[30]

Treatment Options

The Canadian Rheumatology Association (CRA) has developed RA treatment guidelines and recommendations, the first of which is to make disease remission the treatment goal.[3] When remission proves unattainable, the CRA recommends a treatment goal of low disease activity while minimizing disability and joint damage, and improving quality of life.[3] The CRA guidelines call for conventional DMARDs as the first line of treatment, reflecting the effectiveness of these conventional drugs in many patients.[3] DMARD therapy is recommended as soon as possible following the onset of symptoms. The guidelines emphasize the importance of commencing DMARD therapy within three months of symptoms first appearing, to avoid permanent joint damage caused by inflammation.[3]

Patients with active RA should receive at least one DMARD, with or without low-dose oral corticosteroids.[31] Methotrexate is the preferred DMARD owing to its proven efficacy, high tolerability by patients, and relatively low cost. Combination therapy is recommended when methotrexate alone is inadequate.

The CRA recommends introducing biologic therapy when patients continue to exhibit moderate to high disease activity after three months of treatment, with at least two DMARDs taken separately or in combination.[3] No guidelines are in place for selecting a specific biologic agent from the different biologic agents available on the market or for switching safely from one agent to another. The absence of guidelines in this important area reflects a lack of comparative effectiveness data on the different biologic agents available. Comparative clinical effectiveness research—required increasingly for health technology assessment and coverage and reimbursement decisions—compares the effectiveness of one approach for managing RA to the results of other approaches.[6-10]

The Medicare Modernization Act of 2003 demonstrated the movement of payers to collect and use comparative effectiveness data in coverage decisions.[32] As a major payer for healthcare services, the Centres for Medicare and Medicaid Services subsequently published *Coverage with Evidence Development,* a document focused on and offering guidance about the need for comparative effectiveness data to inform national coverage decisions for new health technology. In support of these policy changes, agencies such as the Agency for Healthcare Research and Quality (AHRQ), through its Effective Health Care Program,[10] and the Patient-Centered Outcomes Research Institute (PCORI)[33] conduct research on the "outcomes, comparative clinical effectiveness, and appropriateness of health care, including prescription drugs" to generate and translate such knowledge into practice. Similar directions are being pursued in Canada.

In the future, the availability of comparative effectiveness data would also inform other important issues related to clinical practice patterns and models of care, including:

- the optimal time to initiate biologic therapy;
- whether biologic agents can be stopped temporarily in patients achieving disease remission;
- how biologic agents compare with combination DMARD therapy; and
- best treatment strategies in patients who do not respond adequately to initial therapy.[3]

A comprehensive RA registry in Alberta would generate the data required to guide clinical practice in these critical areas. Disease registries allow us to compare how different therapies are performing in routine clinical practice. Registries serve many purposes including:

- understanding the natural history of a disease;
- assessing treatment adherence and persistence over time;
- determining the clinical effectiveness and cost-effectiveness of healthcare therapies and services;
- measuring and monitoring safety and harm;
- measuring the quality of care; and
- supporting clinical decision-making.[8]

Clinicians, the research community, and policy-makers in many countries worldwide have developed and implemented their own national/regional RA biologic therapy registries to monitor patients over time.

Over the past two decades, clinicians, the research community, and policy-makers in a number of countries worldwide have developed and implemented their own national/regional RA biologic therapy registries to monitor patients over time.[11] As RA treatment guidelines recommend an earlier, aggressive treatment approach and subsequent entry biologics (SEBs) are introduced, the need for such registries in Canada is becoming more apparent.

Cost and Cost-Effectiveness

Three biologic therapies whose major uses are for RA accounted for $73.5 million of drug expenditures in Alberta during the 2012-2013 fiscal year, and were among the top four drug expenditures in the province.[34] Seven biologic therapies for RA were available in Alberta at the beginning of 2014.[35] These biologic therapies are included in the Alberta formulary, which lists the drugs covered under the provincial drug benefit plan.[35]

At the lowest dose recommended by Health Canada, the annual cost of these biologic therapies ranges from approximately $12,400 to $20,500.[31] Costs can increase substantially with an escalation of dosage, exceeding $39,000 per year for the recommended high dose of the most expensive biologic therapy. The cost of DMARD therapy ranges from approximately $1,000 to $2,000 annually.[31]

In contrast with DMARDs and other conventional drugs, which are manufactured from chemicals, biologic agents are produced through the metabolic activity of microorganisms or extracted from living tissues, mostly of animal origin.[36] Participants at Canada's Public Policy Forum pointed out that manufacturers need to be vigilant in controlling raw materials and in product purification and testing, to ensure their biologic agents are not modified by exposure to and contamination by viruses and pathogens.[36] The difficult manufacturing processes contribute to the cost of biologic therapies. Treatment costs are also higher for biologic therapies that must be delivered by intravenous infusion in a hospital day medicine facility or in a clinic by a registered nurse, as compared to therapies that are self-administered subcutaneously or orally.

From a public policy perspective, the cost of different therapies for RA must be balanced with the social, physical, and economic benefits derived from them for patients and families living with RA, that is, value for money. These benefits include, but are not limited to, relief from pain and suffering, improvements in quality of life, avoidance of other healthcare costs to treat RA and its numerous comorbidities, reduced loss of productivity, and reduced premature mortality.

The cost of biologic therapy is not directly comparable with the cost of treatment with DMARDs, since they are applied in different patient populations: those who respond to conventional treatment, and those who do not. Typically, and consistent with the evidence, biologic therapy is available only after patients have not responded adequately to treatment with DMARDs.[3]

The high cost of biologic therapy for RA has made it the subject of numerous cost-effectiveness analyses with mixed findings.[37-43] At willingness-to-pay thresholds of $50,000 to $100,000 per quality adjusted life year, biologic therapy is generally considered cost-effective for patients who do not respond to initial treatment with DMARDs.[37, 43] No data are available for comparing the cost-effectiveness of biologic therapies based on their different mechanisms of action.

From a public policy perspective, the cost of different therapies for RA must be balanced with the social, physical, and economic benefits derived from them for patients and families living with RA, that is, value for money. These benefits include, for example, relief from pain and suffering, improvements in quality of life, avoidance of other healthcare costs to treat RA and its numerous comorbidities, reduced loss of productivity, and reduced premature mortality.

Numerous shortcomings exist in most of the cost-effectiveness studies conducted to date.[42] For example:

- Data used in the studies were derived primarily from short-term randomized controlled trials conducted over months rather than years, despite the chronic nature of RA. Most studies acknowledged that the lack of long-term data made it difficult to project cost-effectiveness with certainty.
- Studies were not based on comparative effectiveness data, and thus study findings were often not valid for general clinical settings.
- Studies were not based on data from head-to-head treatment comparisons.
- Studies often omitted relevant outcomes for RA patients, such as employment and morbidity.
- Indirect costs were rarely examined, even though they are major contributors to the overall burden of illness and adherence to treatment.[42]

Economic modelling has also been made challenging by the complexity of treatment strategies using different combinations and sequences of DMARD and biologic therapies, and by the significant changes in RA treatment over the last 10 to 15 years. These changes make it challenging to interpret findings based on combining the results of trials conducted during this period.

A need exists for scientifically reliable studies based in routine clinical practice settings to explore:

- various RA treatment sequences, treatment adherence and persistence, and associated patient outcomes over the long term in routine clinical practice settings;
- whether biologic agents can be temporarily stopped in patients who achieve disease remission; and
- best treatment strategies in patients who do not respond or have limited response to initial therapy.

Studies of this type require high-quality data collected longitudinally from the RA patient population over the continuum of care in routine practice.

Coverage of Biologic Therapy Costs

In Canada, governments and private, employer-sponsored insurers cover most drug costs.[44] The federal, provincial, and territorial governments offer varying levels of coverage with different eligibility requirements, premiums, and deductibles.[44] Publicly funded drug programs generally provide coverage for those most in need, based on age, income, and medical condition.[44] In particular, these drug plans provide coverage for at-risk and vulnerable population groups, such as seniors, social assistance recipients, and aboriginal populations.[44]

Most provinces and territories also have special programs for population groups that require more enhanced coverage for treating disease or conditions associated with high drug costs, including patients who require biologic therapy for RA.[45]

The cost of biologic therapy for RA patients in Alberta is mostly covered through private insurance, government drug plans, or a combination of these. Alberta government coverage of the cost of biologic therapy for RA is by special authorization for a fixed period, based on the patient meeting Alberta Health criteria.[45] Patients must reapply through their physician for coverage beyond each authorized period, demonstrating clinical benefit from the biologic therapy received. Coverage is provided to those patients who demonstrate continued clinical benefit.

Rising drug costs remain an issue that affects ease of access to biologic therapy under public and private plans, decisions about listing them on the provincial formulary, and strategic planning for drug development by manufacturers. There is a clear role in public policy for economic modeling that examines the impact of biologic therapies from the viewpoints of clinical effectiveness and cost-effectiveness. Equally important is the need to consider innovative policy strategies, which include not only cost considerations but also value for money, particularly strategies that improve access to and ensure appropriate use of these therapies, as governments and payers struggle to manage biologics in a financially sustainable manner.

Province-to-Province Differences in Access to Biologic Therapy

Access to biologic therapy differs from one province or territory to the next in Canada.[35] As of June 2014, Alberta and four other provinces list seven approved biologic therapies for RA in their formularies, with other biologics under development. Five provinces and two territories

currently list eight biologic therapies, and one territory lists just five.[35] Each jurisdiction also conducts its own review of drugs to determine which will be listed in its formulary.

Decisions about whether a SEB can be prescribed as a substitute for its originator drug should be informed by high-quality comparative effectiveness data.

Some provinces and territories cover the entire cost of biologic therapy for RA when the patient does not have private insurance coverage, while others require the patient to pay a portion of the cost through a co-pay formula.[46, 47] Among private insurers, even wider variations exist in terms of eligibility criteria and out-of-pocket costs to plan members.[46] Yet more eligibility criteria exist under the federal government's Non-Insured Health Benefits plan, which provides supplementary health benefits, including drugs for First Nations and Inuit populations.[48]

In the absence of head-to-head comparative data, selecting from the biologic therapies available is influenced by physician and patient preference, method of administering the drug, and risks, such as infections and malignancies. In some areas of Canada, costs to the patient, such as co-payments under private medical plans, also influence the biologic therapy selected.

The eligibility criteria for biologic therapies vary by province. Similarly, the approved duration of biologic therapy for RA, after which a patient must be assessed for treatment effectiveness, differs significantly across the country, ranging from three months to one year. As a result, access to biologic therapy for RA in Canada is affected by where the patient resides, together with the patient's clinical response to the therapy.

This varying access, despite the known clinical benefits of early diagnosis and treatment of RA, may expose some patients to significantly increased risk of joint damage. Greater effort needs to be made to reduce wait times, bottlenecks, and other barriers to treatment so that the risk of permanent joint damage can be reduced or eliminated. This effort would be facilitated by a provincial registry in Alberta that captures long-term data on RA patients, beginning with their entry into rheumatological care and continuing through treatment, remission, and long-term monitoring.

Future Treatment Options – Subsequent Entry Biologics

Patent protections on the first generation of biologic therapies for RA have begun to expire, giving rise to follow-on versions known as subsequent entry biologics (SEBs).[49] SEBs will increase market competition, which is expected to reduce the cost of biologic therapies.

SEBs are just starting to enter the market in Canada. In March 2010, Canadian health authorities published a framework for approving SEBs for sale.[49] On 15 January 2014, two SEBs received notice of compliance from Health Canada for multiple indications, one of which was for RA, making them the first of their type authorized for sale in Canada.[49-52]

When more SEBs eventually enter the market in Canada, the demands of controlling variability and safety during the production process will increase. As indicated above, the sophisticated production processes used in manufacturing biologics are sensitive to even minor changes in source material, equipment, or facilities, which can cause significant differences in the final product and can affect the degree of similarity between a SEB and its originator product.[36]

Since provincial governments have exclusive authority in Canada to designate drug similarity, the responsibility for deciding whether a SEB can be prescribed as a substitute for its originator drug falls ultimately upon provincial policy-makers. These decisions should be informed by high-quality comparative effectiveness data on biologic therapies. These data are not currently available in Canada. As the number of companies producing biologic agents—originator drugs or SEBs—increases, and the number of new or modified drugs entering the Canadian marketplace grows, issues of variability and complexity will have implications for clinical practice, public policy, and regulatory oversight.

Canada's Public Policy Forum convened a select group of leading health experts in November 2013 to explore regulatory and policy issues around SEBs in the country.[36] These experts concluded that the concept of similarity is central to most policy and practical discussions of SEBs because changes in the structure of these agents and their originator products, together with the potential for immunogenicity and adverse reactions, make it difficult to assess whether one can be interchanged or substituted for another. They called for clear rules on the following questions:[36]

- How closely should a SEB mimic its reference product?
- Can patients who experience a bad outcome with a SEB use the originator product in its place?
- How might regulators differentiate the SEB from the originator product, particularly with regard to adverse reactions and immunogenicity?
- What happens if the originator drug is removed from the market?

Another important issue requiring close examination by both policy-makers and clinicians, but not explored in the Public Policy Forum meeting, is the safety, timing, and method of switching SEBs. "Can SEBs be switched safely and, if so, when and how?" is a question that will need an answer in both policy and practice as a range of these products becomes available in Canada.[36]

The health experts convened by Canada's Public Policy Forum suggested that strong post-market and clinical data will be required to set clear rules on SEBs.[36] But they also found that data collected by manufacturers and patient groups in Canada are often limited and incomplete, and many policy-makers have found it difficult to define, through regulation, the minimum amount of clinical data necessary to make safety and efficacy determinations. The Public Policy Forum found that a number of steps need to take place in all provinces and territories to respond to these challenges, including investing in data collection and data-sharing platforms. Some participants suggested establishing a requirement for post-market data collection before SEBs enter the market and become potentially harder to track.[36]

Subsequently, in May 2014, the Institute of Health Economics convened a symposium on biologic therapies. The goals of the symposium were to promote a discussion about the future of biologic therapies and SEBs for managing RA, and to determine how Alberta can ensure its leading role for best outcomes for RA patients. Key stakeholders and experts presenting at the symposium and in attendance included patients, clinicians, researchers, health policy-makers, industry representatives, and private payers. The main topics of discussion were:

- the changing landscape of RA patient management;
- a report on the Alberta Rheumatoid Biologics Pharmacosurveillance Program (ABioPharm);

- the implications of biologic therapies from multiple perspectives (patient, public payer, private payer);
- Health Canada's policies on biologic therapies and SEBs;
- health technology assessment perspectives from the Canadian Agency for Drugs and Technology in Health; and
- the role of surveillance and longitudinal data collection in the current regulatory environment.

The health experts suggested that a provincial registry in Alberta that captures data longitudinally on RA patients across the continuum of care, beginning with entry into rheumatological care and continuing through all phases of treatment, remission, and long-term monitoring of outcomes, and including information about new and established treatments, is needed to inform best clinical practices and policy-making for the appropriate management of RA. A registry of this kind in Alberta would support evidence-based clinical practice and public policy related to the optimal utilization of RA therapies, including originator biologic therapies, SEBs, and future therapies as they become available. It was also suggested that such a registry should be considered for implementation nationally.

The Role and Value of Registries

Registries collect data that can be analyzed to measure the safety, effectiveness, and cost-effectiveness of medical products and services over the long term and in the context of routine clinical practice.[8, 53] This information contains powerful evidence that can continuously, or in an almost live-streaming fashion, inform about progress, quality of care, and side effects, which are important foundations for clinical and patient decision-making, as well as for regulatory oversight regarding the best disease management strategies available.

Registries function as longitudinal observational studies of the patient population and their findings reflect real-life situations arising from the use of therapies such as RA biologic therapies.

Randomized controlled trials (RCTs) also provide valuable information on safety and efficacy.[53, 54] However, their data are typically not generalizable to the broader population of patients or all clinical settings, making the findings more limited with respect to routine clinical practice and health policy.[8, 53, 55] This limitation is due to several inherent factors. Foremost is that RCTs generate results shaped by the trial parameters, which include a highly select patient cohort followed according to a strict protocol, over a predetermined period of time.[8] The interval is usually short-term, measured in months rather than in years, which is not necessarily relevant to RA patients who will be treated over their remaining lifetime.

In contrast, registries can capture data on a heterogeneous patient population treated in routine clinical practice over an extended period, beginning as early as referral and continuing through treatment and long-term monitoring.[56]

In effect, registries can function as longitudinal observational studies of the patient population, without exclusion. Important data can be collected in an RA registry on a large patient population and across all stages of the disease in the context of routine clinical practice. As such,

findings reflect real-life situations arising from the use of therapies such as DMARDs and biologics for RA patients.[8, 56] Findings reflect the disease population and all clinical settings, providing a means to measure and monitor the quality of care, patient adherence to therapy, patient outcomes, and health system performance. Researchers can also access data to identify rates of adverse events as well as long-term benefits to inform best practice, a capability that has important clinical, policy, and regulatory implications.[8, 56]

With comprehensive data collected across the continuum of care, we can inform clinical practice regarding the optimal sequence, beginning with DMARDs and progressing to combination therapies with and without biologic therapy when needed.

While registries offer advantages over RCTs in terms of the value and utility of the data they capture, it is crucial to recognize that they do not replace this type of research trial. In fact, registries complement RCTs by facilitating the identification of eligible patients who meet trial criteria, accelerating the trial recruitment process.

Given the benefits of registries, it is not surprising that biologic registries are growing in number worldwide. National and regional biologic registries have been established in over 30 countries on six continents.[54]

Six registries are in place in Canada, including one in Alberta, to collect data on patients receiving RA therapy. Three of these registries collect data only on patients receiving biologic therapy, but their interest is focused narrowly on just one or two biologic agents. The exclusive focus of these registries on biologics provides little or no comparative data on the safety, effectiveness, and cost-effectiveness of alternative RA therapies. The remaining three registries collect a varying range of biologic and non-biologic patient data.

Alberta's ABioPharm registry collects data on all biologic agents available to its population base, but data collection does not begin until the start of biologic therapy.[57] This leaves out important data related to the pre-biologic therapy period, including the onset of symptoms and the initial referral contact, as well as the first line of treatment with non-biologic therapies. ABioPharm also collects data on a single DMARD, leflunomide, but this data is from a small control group in the Edmonton clinic.[57]

ABioPharm has been operating for 10 years. It was established by investigators at the University of Alberta and the University of Calgary, with support from the Alberta Ministry of Health and the pharmaceutical industry to:

1) monitor the effectiveness of biologic therapies in individual patients and in patient groups;
2) monitor the short- and long-term safety of biologic therapies; and
3) provide valid economic data on the costs and benefits of biologic therapies.

ABioPharm has had the benefit of an advantageous collaborative arrangement between the clinical investigators in the subspecialty of Rheumatology at the University of Alberta and the University of Calgary, which provide clinical care to RA patients. ABioPharm continues to build a data repository using a standardized scientific approach to collecting information on efficacy, safety, and healthcare costs. The database is a growing body of evidence that has and will continue to provide greater insight into the risks and benefits of RA biologic therapies. The growing cohort of patients in the registry makes it possible to analyze rare events that may

otherwise not be identified in single-centre studies.[54] In addition to identifying these rare events, ABioPharm allows for longitudinal patient follow-up, which is needed to monitor the long-term efficacy and safety of current and future biologic therapies. As new treatment options emerge, in particular new innovator biologic agents and SEBs, ABioPharm will offer the necessary framework for performing comparative analyses of the safety, effectiveness, and cost of individual agents or combination treatments.

ABioPharm is a model of pharmacosurveillance involving a partnership between academic and community rheumatologists, government, and industry to assess long-term effectiveness, safety, and cost-effectiveness.[57] Data from ABioPharm have been used to evaluate outcomes and healthcare use and associated costs for RA patients treated with biologic therapies. For example, publications based on data from ABioPharm have compared the safety and effectiveness of different therapeutic regimens and gender differences in biologic therapy response.[58-60] It was demonstrated that predictors of remission for RA patients treated with anti-TNF therapy depend on the duration and definition of remission.[61] Using radiographic data from patients enrolled in ABioPharm, researchers determined that the simple erosion narrowing score captures disease progression reliably.[62] In addition to estimating healthcare utilization and associated costs for RA patients treated with and without biologic therapies, ABioPharm data provide evidence of economic benefit to the healthcare system when RA patients achieve persistent good disease control.[63, 64] The magnitude of cost savings depends on the definition of RA remission.[65]

The Future of an Expanded Rheumatoid Arthritis Registry in Alberta

ABioPharm has been a valuable resource within the field of biologic therapy. In the future, a comprehensive registry should include all therapies, both biologic and non-biologic, to capture outcomes across the continuum of care. Non-biologic therapy remains the first line of treatment for all RA patients, and the only method of treatment required for the majority of Albertans with RA. Without data on these patients and without longitudinal data collected at all points along the continuum of care, clinicians and policy-makers are missing important comparative information about the safety, effectiveness, and cost-effectiveness of the full range of RA treatment options available to Albertans.

Safety is among the most compelling reasons for expanding and improving data collection on RA patients in Alberta. Drugs that alter human immune responses warrant a high level of public vigilance. The long-term effects of biologic agents, which have only been available to Albertans for 16 years, remain unknown, and the subsequent entry biologics will be new to the Alberta market. A broad set of reliable longitudinal data across the continuum of care would make it possible to maintain a high level of vigilance against adverse effects of therapy. Further, a registry of all RA patients would make it possible to quickly identify and contact anyone affected by a drug recall.

The long-term effects of biologic agents remain unknown at a time when more of these drugs are expected to enter the Alberta market as SEBs.

Patients are important partners in the process of drug vigilance. A high degree of RA patient participation, in terms of both percentage of the diseased population and type of therapy, including biologic and non-biologic, is needed to ensure RA registry data are representative of the population. A broad patient population will produce valuable comparative data for identifying treatment response patterns that guide clinicians in developing best care practices, which are essential to generate high value for Alberta's health care dollars.

In developing a registry that, in effect, functions as a longitudinal observational study of the RA patient population without exclusion, Albertans will create a "learning system" not only for improving clinical care, but also for increasing the pace of improvement. Learning systems in healthcare delivery have been shown to improve quality of care and save money.[12]

Alberta has an opportunity to develop further its clinical expertise and RA research capabilities at a time when greater knowledge in this area is highly valuable to clinical practice and public policy. Healthcare costs per capita in Alberta are higher than in most other Canadian jurisdictions. Drugs are a significant contributor to these costs, and funds spent on biologics are among the top four drug expenditures in Alberta.[34]

Using the rigorous approach established with ABioPharm, an RA registry in Alberta would expand the collection of data across patients, across time, and beyond RA outcomes.

Using the rigorous approach to data collection established with ABioPharm, an RA registry in Alberta would expand the collection of data in important ways:

1. Across patients: all RA patients in Alberta, making it possible to compare the safety and clinical effectiveness of current and future biologic and non-biologic therapies.
2. Across time: data on patients from the point of referral and their entry into rheumatological care, and continuing through treatment, remission, and monitoring. Linkages to other data sources would capture information from the pre-diagnosis period.
3. Beyond RA outcomes: data on outcomes related to comorbidities. These data would be valuable, since people with RA typically have multiple serious comorbidities such as depression, cardiac disease, internal organ damage, and osteoarthritis.
4. Healthcare system performance: linkages to other data sources including administrative data from Alberta Health (physician claims, hospitalizations, procedures) would increase the power of the registry to include healthcare utilization and costs across the continuum of care. This information would enable healthcare planners to estimate cost-effectiveness and to assess the impact alternative models of care would have on healthcare service delivery and system performance.
5. Epidemiological data to further understanding of RA: capturing important epidemiological background information about RA patients, such as geographic location, occupation, and work setting longitudinally can help researchers understand the impact of RA in Alberta.

In summary, an RA registry capturing comprehensive data across patients, across time, and beyond RA outcomes in Alberta would be an invaluable tool for ensuring best practices, beginning with diagnosis and early disease management, are applied across the continuum of care. Applying best practices consistently is key to Alberta generating greater value for its

healthcare dollars. A comprehensive RA registry in Alberta would also help the province integrate ongoing surveillance, as new therapies are introduced to identify any potential safety issues.

An investment in capability and funding for a registry of this kind would vault Alberta to the forefront of capturing data and generating best practice evidence on RA management, helping solidify its position as a leading Canadian centre of excellence for patient care and research on arthritis prevention and treatment. As a future vision, such a registry in Alberta could also provide a solid foundation for the development of a national registry that would provide consistent and standardized metrics for reporting patient outcomes.

Importantly, Alberta has the attributes to generate maximal value from such investments. Its population, at four million, is right-sized: large enough to provide a good sample size for population studies, and small enough that collaboration and coordination is possible among research institutes, industry, advanced education, and government. Alberta's population demographics are similar to those in other parts of the country, making data and evidence from an RA registry valuable to decision-makers in other parts of the country. Alberta has a single public health authority structure, which facilitates implementation and operation of provincial initiatives such as registries. Alberta also has a first-class, modern research infrastructure and a growing body of world-renowned researchers who are doing leading-edge work, particularly in arthritis. A provincial RA registry would be a crucial asset to these researchers.

Finally, Alberta has a Strategic Clinical Network for bone and joint health care, the Bone and Joint Health Strategic Clinical Network. This network brings together all of the health care constituents—health professionals, patients, researchers, policy-makers, and economists. Working in teams, these individuals have the opportunity to profoundly change the way services are designed and delivered, and to expand and exploit research and development of technologies. The Bone and Joint Health Strategic Clinical Network has already set out to transform musculoskeletal care by strengthening the integration of primary care and specialty care. RA treatment is an area of much activity under this initiative, and a comprehensive RA registry in Alberta would be a valuable asset in this work.

References

1. Bombardier C, Hawker G, Mosher D. The impact of arthritis in Canada: Today and over 30 years. Arthritis Alliance of Canada, 2011.
2. Bombardier C, Hawker G, Mosher D. The impact of arthritis in Canada: Today and over 30 years. Province specific estimates – Alberta. Arthritis Alliance of Canada, 2011.
3. Bykerk VP, Akhavan P, Hazlewood GS, Schieir O, Dooley A, Haraoui B, et al. Canadian Rheumatology Association recommendations for pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs. The Journal of Rheumatology. 2012;39(8):1559-82.
4. Vermeer M, Kuper HH, Hoekstra M, Haagsma CJ, Posthumus MD, Brus HLM, et al. Implementation of a treat-to-target strategy in very early rheumatoid arthritis: Results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. Arthritis & Rheumatism. 2011;63(10):2865-72.
5. Schipper LG, Vermeer M, Kuper HH, Hoekstra MO, Haagsma CJ, Broeder AAD, et al. A tight control treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: A study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry. Annals of the Rheumatic Diseases. 2012;71(6):845-50.
6. Garrison LP, Neumann PJ, Erickson P, Marshall D, Mullins CD. Using real-world data for coverage and payment decisions: The ISPOR real-world data task force report. Value in Health. 2007;10(5):326-35.
7. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: Increasing the value of clinical research for decision making in clinical and health policy. JAMA. 2003;290(12):1624-32.
8. Agency for Healthcare Research and Quality. Registries for evaluating patient outcomes: A user's guide. Rockville, MD: Agency for Healthcare Research and Quality, 2007.
9. Centers for Medicare and Medicaid Services. Guidance for the public, industry, and CMS staff. National coverage determinations with data collection as a condition of coverage: Coverage with evidence development. 2006.
10. Agency for Healthcare Research and Quality. Comparative effectiveness: US Department of Health & Human Services; 2014 [Accessed: 20 November 2014]. Available from: http://effectivehealthcare.ahrq.gov/glossary-of-terms/?pageaction=showterm&termid=118.
11. Kobelt G, Kasteng F. Access to innovative treatments in rheumatoid arthritis in Europe. Sweden: 2009.
12. Dahabreh IJ, Kent DM. Can the learning health care system be educated with observational data? JAMA. 2014;312(2):129-30.
13. Choy E. Understanding the dynamics: Pathways involved in the pathogenesis of rheumatoid arthritis. Rheumatology. 2012;51(suppl 5):v3-v11.
14. Lee DM, Weinblatt ME. Rheumatoid arthritis. The Lancet. 2001;358(9285):903-11.
15. Canadian Institutes of Health Research. It's all relative: Early detection of rheumatoid arthritis in First Nations. Canadian Institutes of Health Research; 2013 [Updated: 05 December 2013; Accessed: 04 July 2014]. Available from: http://www.cihr-irsc.gc.ca/e/47127.html#3.
16. Lacaille D, Hogg RS. The effect of arthritis on working life expectancy. The Journal of Rheumatology. 2001;28(10):2315-9.

17. Burton W, Morrison A, Maclean R, Ruderman E. Systematic review of studies of productivity loss due to rheumatoid arthritis. Occupational Medicine. 2006;56(1):18-27.
18. Hermus G, Stonebridge C, Dinh T, Didic S, Theriault L. Reducing the health care and society costs of disease: The role of pharmaceuticals. Ottawa, ON: The Conference Board of Canada, 2013.
19. Li X, Gignac MAM, Anis AH. The indirect costs of arthritis resulting from unemployment, reduced performance, and occupational changes while at work. Medical Care. 2006;44(4):304-10 10.1097/01.mlr.0000204257.25875.04.
20. Cuellar ML, Espinoza LR. Methotrexate use in psoriasis and psoriatic arthritis. Rheumatic Diseases Clinics of North America. 1997;23(4):797-809.
21. Ahluwalia V, Frank C, Mosher D, Zummer M. A pan-Canadian approach to inflammatory arthritis models of care. Arthritis Alliance of Canada, 2014.
22. Lacaille D, Anis AH, Guh DP, Esdaile JM. Gaps in care for rheumatoid arthritis: A population study. Arthritis Care & Research. 2005;53(2):241-8.
23. Chan K, Felson DT, Yood RA, Walker AM. The lag time between onset of symptoms and diagnosis of rheumatoid arthritis. Arthritis & Rheumatism. 1994;37(6):814-20.
24. Hernandez-Garcia C, Vargas E, Abasolo L, Lajas C, Bellajdell B, Morado IC, et al. Lag time between onset of symptoms and access to rheumatology care and DMARD therapy in a cohort of patients with rheumatoid arthritis. Journal of Rheumatology. 2000;27(10):2323-8.
25. Choy EHS, Scott DL, Kingsley GH, Williams P, Wojtulewski J, Papasavvas G, et al. Treating rheumatoid arthritis early with disease modifying drugs reduces joint damage: A randomised double blind trial of sulphasalazine vs diclofenac sodium. Clinical and Experimental Rheumatology. 2002;20(3):351-8.
26. Cush JJ. Early rheumatoid arthritis—Is there a window of opportunity? Journal of Rheumatology Supplement. 2007;80:1-7.
27. Lard LR, Visser H, Speyer I, vander Horst-Bruinsma IE, Zwinderman AH, Breedveld FC, et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: Comparison of two cohorts who received different treatment strategies. The American Journal of Medicine. 2001;111(6):446-51.
28. Korpela M, Laasonen L, Hannonen P, Kautiainen H, Leirisalo-Repo M, Hakala M, et al. Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with disease-modifying antirheumatic drugs: Five-year experience from the FIN-RACo study. Arthritis & Rheumatism. 2004;50(7):2072-81.
29. van der Linden MPM, le Cessie S, Raza K, van der Woude D, Knevel R, Huizinga TWJ, et al. Long-term impact of delay in assessment of patients with early arthritis. Arthritis & Rheumatism. 2010;62(12):3537-46.
30. Huscher D, Mittendorf T, von Hinüber U, Kötter I, Hoese G, Pfäfflin A, et al. Evolution of cost structures in rheumatoid arthritis over the past decade. Annals of the Rheumatic Diseases. 2014.
31. Canadian Agency for Drugs and Technologies in Health. Clinical and economic overview: Biological response modifier agents for adults with rheumatoid arthritis. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health, 2010.
32. Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Public Law 108-173 (2003).

33. Patient-Centered Outcomes Research Institute. Patient-Centered Outcomes Research Institute: About us 2014 [Accessed: 21 November 2014]. Available from: http://www.pcori.org/about-us.
34. Alberta Health. Alberta Health Care Insurance Plan Statistical Supplement 2012-2013. Edmonton, AB: Alberta Health, 2014.
35. Joint Health. Report card on provincial formulary: Reimbursement listings for biologic response modifiers: Joint Health; 2014 [Updated: 01 August 2014; Accessed: 11 September 2014]. Available from: http://www.jointhealth.org/programs-jhreportcard.cfm.
36. Canada's Public Policy Forum. Subsequent entry biologics in Canada. The case for multi-sector collaboration. Ottawa, ON: Canada's Public Policy Forum, 2014.
37. Fleurence R, Spackman E. Cost-effectiveness of biologic agents for treatment of autoimmune disorders: Structured review of the literature. The Journal of Rheumatology. 2006;33(11):2124-31.
38. Athanasakis K, Petrakis I, Kyriopoulos J. Investigating the value of abatacept in the treatment of rheumatoid arthritis: A systematic review of cost-effectiveness studies. ISRN Rheumatology. 2013;2013:15.
39. Schoels M, Wong J, Scott DL, Zink A, Richards P, Landewé R, et al. Economic aspects of treatment options in rheumatoid arthritis: A systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Annals of the Rheumatic Diseases. 2010;69(6):995-1003.
40. Sullivan SD, Alfonso-Cristancho R, Carlson J, Mallya U, Ringold S. Economic consequences of sequencing biologics in rheumatoid arthritis: A systematic review. Journal of Medical Economics. 2013;16(3):391-6.
41. Iannazzo S, De Francesco M, Gomez-Ulloa D, Benucci M. A review of cost-effectiveness evaluations as part of national health technology assessments of biologic DMARDs in the treatment of rheumatoid arthritis. Expert Review of Pharmacoeconomics & Outcomes Research. 2013;13(4):455-68.
42. Scott DL. Biologics-based therapy for the treatment of rheumatoid arthritis. Clin Pharmacol Ther. 2012;91(1):30-43.
43. van der Velde G, Pham B, Machado M, Ieraci L, Witteman W, Bombardier C, et al. Cost-effectiveness of biologic response modifiers compared to disease-modifying antirheumatic drugs for rheumatoid arthritis: A systematic review. Arthritis Care & Research. 2011;63(1):65-78.
44. Health Canada. Access to insurance coverage for prescription medicines. Health Canada; 2004 [Updated: 01 October 2004; Accessed: 01 July 2014]. Available from: http://www.hc-sc.gc.ca/hcs-sss/pharma/acces/index-eng.php.
45. Alberta Health. Drug coverage and services: Alberta Health; [Accessed: 04 July 2014]. Available from: http://www.health.alberta.ca/services/drug-coverage-services.html
46. Shoppers Drug Mart Inc. Drug coverage.ca: A guide to reimbursement: Shoppers Drug Mart Inc.; 2012 [Accessed: 11 December 2013]. Available from: http://www.drugcoverage.ca/en-ca/.
47. Schmajuk G, Trivedi AN, Solomon DH, Yelin E, Trupin L, Chakravarty EF, et al. Receipt of disease-modifying antirheumatic drugs among patients with rheumatoid arthritis in medicare managed care plans. JAMA. 2011;305(5):480-6.

48. Health Canada. First Nations and Inuit health: Non-insured health benefits for First Nations and Inuit: Health Canada; 2014 [Accessed: 23 September 2014]. Available from: http://www.hc-sc.gc.ca/fniah-spnia/nihb-ssna/index-eng.php.
49. Health Canada. Guidance for sponsors: Information and submission requirements for subsequent entry biologics (SEBs). Ottawa, ON: Health Canada, 2010.
50. Health Canada. Drugs and health products: INFLECTRA. Ottawa, ON: Health Canada; 2014 [Updated: 02 July 2014; Accessed: 16 July 2014]. Available from: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2014_inflectra_159493-eng.php.
51. Health Canada. Drugs and health products: REMSIMA. Ottawa, ON: Health Canada; 2014 [Updated: 01 April 2014; Accessed: 16 July 2014]. Available from: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2014_remsima_160195-eng.php.
52. Canadian Agency for Drugs and Technologies in Health. Subsequent entry biologics—Emerging trends in regulatory and health technology assessment frameworks. Environmental Scan. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health, 2014.
53. de la Vega M, da Silveira de Carvalho H, Ventura Ríos L, Goycochea Robles M, Casado G. The importance of rheumatology biologic registries in Latin America. Rheumatology International. 2013;33(4):827-35.
54. Curtis JR, Jain A, Askling J, Bridges Jr SL, Carmona L, Dixon W, et al. A comparison of patient characteristics and outcomes in selected European and U.S. rheumatoid arthritis registries. Seminars in Arthritis and Rheumatism. 2010;40(1):2-14.e1.
55. Hajjaj-Hassouni N, Al-Badi M, Al-Heresh A, Al-Emadi S, El Bawendi A, El Garf A, et al. The practical value of biologics registries in Africa and Middle East: Challenges and opportunities. Clinical Rheumatology. 2012;31(3):407-16.
56. van Vollenhoven RR, Askling J. Rheumatoid arthritis registries in Sweden. Clinical and Experimental Rheumatology. 2005;23(Suppl. 39):S195-S200.
57. Barr SG, Martin L, Chung C, Maksymowych WP. Mandatory pharmacosurveillance—A Canadian model for access to therapy and research. Clinical and Experimental Rheumatology. 2004;22(Suppl. 35):S39-S43.
58. Barnabe C, Barr S, Martin L. Infliximab therapy efficacy and persistence at a Canadian academic centre despite a change in access procedure. Clinical Rheumatology. 2012;31(2):211-7.
59. Hazlewood GS, Barnabe C, Barr SG, Martin L. Abatacept use after failure of multiple biologic agents in patients with severe rheumatoid arthritis. JCR: Journal of Clinical Rheumatology. 2012;18(8):416-8 10.1097/RHU.0b013e3182784833.
60. Lee J, Mason R, Martin L, Barnabe C. Biologic therapy response and drug survival for females compared to males with rheumatoid arthritis: A cohort study. Rheumatology International. 2014:1-5.
61. Barnabe C, Homik J, Barr SG, Martin L, Maksymowych WP. The effect of different remission definitions on identification of predictors of both point and sustained remission in rheumatoid arthritis treated with anti-TNF therapy. The Journal of Rheumatology. 2014;41(8):1607-13.
62. Barnabe C, Hazlewood G, Barr S, Martin L. Comparison of radiographic scoring methods in a cohort of RA patients treated with anti-TNF therapy. Rheumatology. 2012;51(5):878-81.
63. Barnabe C, Thanh NX, Ohinmaa A, Homik J, Barr SG, Martin L, et al. Healthcare service utilisation costs are reduced when rheumatoid arthritis patients achieve sustained remission. Annals of the Rheumatic Diseases. 2013;72(10):1664-8.

64. Ohinmaa AE, Thanh NX, Barnabe C, Martin L, Russell AS, Barr SG, et al. Canadian estimates of health care utilization costs for rheumatoid arthritis patients with and without therapy with biologic agents. Arthritis Care & Research. 2014;66(9):1319-27.
65. Barnabe C, Thanh NX, Ohinmaa A, Homik J, Barr SG, Martin L, et al. Effect of remission definition on healthcare cost savings estimates for patients with rheumatoid arthritis treated with biologic therapies. The Journal of Rheumatology. 2014;41(8):1600-6.

Institute of Health Economics
1200 – 10405 Jasper Avenue
Edmonton AB Canada T5J 3N4
Tel. 780.448.4881 Fax. 780.448.0018
info@ihe.ca

www.ihe.ca

ISBN 978-1-926929-41-5 (print)
ISBN 978-1-929929-42-2 (online)