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The executive committee further extends their gratitude to all those who worked hard to make this issue of the McGill Journal of Medicine a reality.

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LETTER TO THE EDITOR

Participatory approach in Medicine: A road to take or to avoid?

Khayyat Kholgi

In theory, participatory approach is defined as a systemic investigation of a research problem with the collaboration of those affected by the issue under study for purposes of education, and taking action to induce effective social changes (Macaulay 2007). As the center of Participatory Research At McGill (PRAM) has stated, one of the important goals of participatory research is to answer important health related questions that will benefit the partners throughout the research process while developing valid knowledge that is applicable to other settings (Salsberg et al, 2008). The Canadian Institutes of Health Research has also identified participatory research as an integrated knowledge translation plan in which people who should be acting on the results obtained are full partners of the study (Parry et al, 2009). Even though these are clear definitions, what does participatory research means in practice? Participatory research from the point of view of many scientists is a time consuming method used to justify the usage of "lay" science in research projects. On the other hand, those researchers who conduct participatory research view it as a tool to transmit the knowledge gained throughout their studies to the community that is affected by those results in a very short amount of time. The question that remains to be answered is which one of these two points of view is accurate and valid?

Imagine you are a hiker and you want to climb a mountain to have a view on the city; you are being provided with two options. One of the options is to climb a very high mountain that is filled with many obstacles along the path, but once you reach the summit you would be able to see the most spectacular view of the city. On the other hand, there is an easier mountain to climb with fewer obstacles in the path. However, the summit only lets you see one small part of the town. Since it would take a shorter time to climb this mountain you will be able to climb many of these type of mountains in the same amount of time needed to climb the high altitude one. Which one would you choose?

As researchers in this busy and fast growing world of science and technology, we tend to choose the easier mountain to climb because it will let us get to the summit in a shorter period of time. In other words, we will be able to get the results faster, and publish as many articles as we can. We do not need to know the people that we are studying, we just have to collect data on them anonymously and make some associations between variables. But along the way, running up to the summit we might miss many opportunities to enjoy the path, and at the end we will get to see only fragmented pictures of the city. Choosing the other mountain to climb can give us a broader perspective of the city sight. It will give us the opportunity to work alongside other people to overcome the obstacles in the path. Nevertheless, the challenge to enter an unknown community, to build relationships with members of the community that are total strangers to researchers, and to gain their trust are barriers not everyone is willing to face. It is not easy to reach consensus on any discussions when 20 people from very different backgrounds comment on every single stage of a project. It is almost impossible to please everyone around a table. It requires effort and energy to maintain rigor research in a mixed environment where scientific facts are as important as non-scientific ones. But yet the best things in life do not come without a struggle.

As academic researchers we have developed expertise in designing and conducting

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rigorous science, but we have limited knowledge on the problems different communities are having. These communities can range from a small clinic to a large hospital center or to any geographical community. Regardless of the type of community, community members do not need to read the literature and take scientific courses to understand their problems. They know them by heart, as they live them every single day. Thus, as much as the community needs us researchers to use our statistical, and scientific expertise, we need the community to make us understand the depth and the complexity of their problems. From a practical point of view participatory research is a research approach that allows people who are willing to take actions to make a change in their communities to work alongside academic researchers to achieve their goals.

If we get the opportunity to work with people who are affected by the results of the study, we may see a far more complete picture. The perspectives of these people will be taken into account throughout all phases of the research project. The results of the study do not need to get archived for a long time before being transferred into practice. The results, whether positive or negative, will provide valuable evidence that influence the community immediately. It is only then that we can clearly see the impact of the study on the people and the community. We know that we have reached the summit once we feel we made a difference through time and perseverance, and then we can enjoy the magnificent view of the city. It is now up to us researchers to decide which road to take. But remember that the spectacular view at the end of the road is worth the time and effort that is needed to climb the mountain.

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LETTER TO THE EDITOR

Taxing Unhealthy Food: Is it an Effective Health Promotion Policy?

Hiba Farhat

Pursuing my Master's degree in the department of family medicine, I have the opportunity to work with research experts to study factors affecting health behavior change in the Quebec population. More specifically, my focus is on socio-economic status and the quality of care patients receive as possible predictors of health behavior change over time. Looking through the vast literature on health behaviors and primary prevention, it was unfortunate to see that most behavioral and health promotion studies have not been translated into practice. Additionally, most evidence-based health promotion interventions that have been developed through years of research show little to no effect on long-term outcomes. These findings made me contemplate the extent to which my research results will be disseminated and put into use. This notion pushed me to think of possible ways in which one can build an environment that is supportive of health behavior change. I came to the conclusion that prior to examining the effects of healthcare delivery on health behaviors, it is important to implement healthcare policy changes that encourage patients to adopt and maintain their healthy behaviors.

One of the most effective policies that resulted in a major health behavior change in the past was the taxation of tobacco products. Making tobacco products unaffordable to most people, resulted in a change in the purchasing behavior of Canadians. Additionally, advertisements that promote smoking were banned, which also resulted in a further decrease in the proportion of people that smoke. Building on this notion, the premise underlying this letter is that taxing unhealthy foods can result in better health behaviors in the population. Although there are multiple ways in which government policies can promote healthier diets, applying taxes on foods deemed unhealthy has received global attention. In doing so, the government can potentially change the purchasing behavior of the population, which would lead to healthier diets. This has been shown effective especially among children. In a study done by Beydoun et al., they were able to show that slightly increasing the price of fast food resulted in a decrease of total energy intake with an increase in fruits and vegetable intake.1 However, before implementing such policies, all the possible negative implications should be explored and possibly minimized.

One of the main concerns about introducing food taxation is adding financial constraints onto individuals with low income. According to studies done by the Canadian Food Information Council, cost can highly influence the food purchases of those with a household income of less than $35,000. Hence, to avoid such inequalities, subsidizing healthy alternatives, in addition to the taxation of unhealthy foods is necessary. Studies have shown that decreasing the price of healthy foods paired with minimal promotion in high schools resulted in an approximate 400% increase in sales.2 As a matter of fact, implementing such changes can result in greater health equalities between different socio-economic groups. Unhealthy foods have been shown to be considerably cheaper than healthy alternatives thus low-income individuals are more likely to purchase the former. Hence, lowering this discrepancy in food cost can change the purchasing behavior of the general population, and specifically those with low-income.

This taxation policy seems feasible since revenue generated through taxing unhealthy foods can be utilized to subsidize healthy alternatives. However, some issues and challenges have to be overcome prior to implementation. Firstly, there is a plethora of studies available on food and diet in the

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literature, but there is a debate on what constitutes health and unhealthy foods. Thus, a consensus for the definition of healthy food should be established. Secondly, it is difficult to determine how large the food tax should be to have a significant effect on the population. Hence, further research is necessary to ensure the effectiveness of such a policy.

All in all, taxing unhealthy foods and subsidizing healthy alternatives can provide an encouraging environment for people to adopt healthier lifestyles. Additionally, this health promotion policy can help maintain the effects of other healthcare interventions that will be introduced in the future.

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LETTER TO THE EDITOR

Challenges and Facilitators to Providing Health Care Services to Pregnant Women who use Drugs: The perspective of health care professionals

Kelly Boyd

INTRODUCTION

Although the delivery of prenatal health care services continues to improve in Canada, pregnant women within vulnerable populations often do not receive adequate prenatal care from health care professionals. Women who use both illegal and prescription drugs during pregnancy are considered to be one of these vulnerable populations. Previous research has repeatedly focused on the challenges experienced by the women themselves when seeking prenatal care however; there is a lack of information from the perspectives of health care professionals. Frameworks that encourage positive and trusting relationships must be developed to improve communication among health care professionals and pregnant drug users 1. While there is a general agreement that negative attitudes towards this population of women are prevalent among health care professionals, few suggestions have been made as to how to improve attitudes of health care professionals 2,3. Exploring the perspectives of health care professionals will help to further determine the challenges and facilitators to providing health care services to this population of women and what can be done to overcome the identified challenges. This will also improve the delivery of health care services, provide evidence that will help guide future programs and policies, and will assist in improving the communication gap between health care professionals from different disciplines. The purpose of this study was to explore the perspectives of health care professionals in regards to providing health care services to pregnant women who use illegal and prescription drugs and to gain a further insight into their experiences in working with this population of women. The study explored the following research questions:

1. What do health care professionals perceive as the challenges to providing health care services to pregnant women who use drugs?
2. What facilitates the delivery of health care services to this specified population of vulnerable women?
3. What do health care professionals suggest should be done to overcome the identified challenges?

METHODS

To further explore the perspectives of health care professionals and the diversity of their experiences, a qualitative research approach incorporating a grounded theory design was used. Five health care professionals (two nurses, one clinical nurse specialists, and two obstetricians) were recruited using email and poster distribution from the Perinatal Centre and Birth Unit within the largest maternal and child health care center in the Maritimes, the IWK Health Centre in Halifax, Nova Scotia. Eligible participants included health care professionals who have had previous experience working with women who used illicit and/or prescription drugs during their pregnancy. Data were collected using in depth, semi-structured,

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Table 1. Challenges to Providing Health Care Services

Core Category	Challenges to Providing Health Care Services			
Themes	Building Relationships	Continuity of Care	Time	Differences in Health Care
Sub-Themes	•Gaining Trust •Trust in Health Care Systems •Trust in Health Care Professionals	•Compliance with appointments •Spectrum of Women (i.e. incarcerated women & prostitutes)	•Women need the most amount of time •Willing to give the least amount of time •Point at which prenatal care is sought	•Ethical Issues •Different Concerns

face-to-face interviews. The interviews took place within the IWK during the months of March and April 2010, each lasting between 20 and 40 minutes. Interviews were audio recorded and transcribed verbatim by a transcriptionist. To compare views, experiences, and actions, the constant comparative method of the grounded theory approach was used to analyze the data 4,5. Interview transcripts were analyzed using open coding (comparison within a single interview), axial coding (comparisons between interviews), and selective coding (refines the themes into an explanatory scheme) 5,6. Ethical approval for this research study was obtained from the IWK Research Ethics Board under the expedited review category. Consent was obtained using a written consent form prepared according to specific IWK protocol.

RESULTS

Findings revealed challenges included building relationships with the women, the continuity of care, the amount of extra time that the women require, and the differences in care. Table 1 includes the sub-themes that emerged within the identified challenges.

Facilitators to providing care to this population of women included the opportunity to attend multidisciplinary educational workshops, experience as a health care professional, the clinical nurse specialist who works within the IWK, and the positive support systems available in the women's lives. Among these identified themes, numerous sub themes also emerged. Table 2 provides an overview of the facilitators that were discussed.

To overcome the identified challenges, participants indicated more educational workshops would be beneficial, working on a one-on-one basis with the women to better address individual concerns and tailor the delivery of care, and enhancing collaboration with community organizations.

DISCUSSION

The overall findings from this research study indicate that there are several challenges associated with the delivery of health care to pregnant women who use illicit and prescription drugs. In terms of relationships and time, the results of this study were relatively similar to the findings in the relevant literature 1. Health care professionals stress that relationships are critical and in order to build relationships, there is need for trust. There is also an agreement surrounding the challenge of time. Pregnant women who use drugs are willing to give health care professionals the least amount of time however; they need the most amount of time. This creates a problem because the women often do not get all the health services that they need in the short amount of time that they are willing to donate. While both participants in this study and existing literature mentioned differences in care, previous studies indicated that specialized care was needed and often could not be obtained therefore, challenges to providing care developed 1,7. Although differences in providing care were mentioned by the participants in this particular study, the need for specialized care was not a concern.

In terms of facilitators, the participants in this study indicated that attending educational workshops that focus on pregnancy and substance use are especially beneficial however, this was not mentioned in any existing literature. A surprising facilitator found within this study was the clinical nurse specialist who works within the IWK. There was nothing like this mentioned in the reviewed literature that I know of.

The findings from this study provide evidence that can assist in the formation of new programs or policies surrounding pregnancy and drug use in order to improve the delivery of care.

Table 2. Facilitators to Providing Health Care Services

Core Category	Facilitators to Providing Health Care Services			
Themes	Educational Workshops	Professional Experience	Clinical Nurse Specialist	Positive Support Systems
Sub-Themes	•Multidisciplinary aproach	•More Awareness •Improved Recognition Strategies •More Services	•Coordinates the Care Process •Collaborates	•Family

Limitations of this study include small sample size, health care professionals from within one hospital, and the limited diversity of the healthcare professionals who participated. Future research in this area should incorporate several levels of health care professionals (i.e. recent graduates all the way to very experienced professionals in the field) and be conducted over a longer period of time. An interesting concept that emerged from the data was the importance of collaboration with health care professionals from outside the immediate hospital environment. An interdisciplinary approach is important for future studies in order to develop the most effective care practices.

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LETTER TO THE EDITOR

Once a Caesarean, Why a Caesarean?

Frances Handley-Derry

Almost everything that I have written in the first year of my training in a Masters Program has begun with "the rate of Caesarean section is rising in Canada", and yet again I start with the same re-iteration. As this will eventually be the topic of my thesis, it is reasonable that it has become something I think about often. Currently, Caesarean sections (C-sections) represent approximately 26.3% of the births in Canada (1). There is concern among health care professionals over this rate due to the risks associated with C-section including: complication with the anaesthesia, residual pain at the incision site affecting mother-child bonding, and potential complications in future pregnancies (2). So, if we know the risks, and experts think that there should be fewer performed, why are C-section rates still rising?

The main media coverage of high C-section rates narrows in on the so-called "too posh to push" phenomenon, (or should that be "too Posh to push"?) where celebrities such as Victoria Beckham, Madonna and Jessica Simpson book C-sections to avoid labour. Apart from other areas sporting large, wealthy communities, such as Chelsea in London, and Los Angeles, is this really representative of national trends? Since starting my master's I have some first-hand experience talking to women who have C-sections and none that I have encountered so far fit into this box. Driving this trend is the experience of the average woman; therefore what we need to think about is how we have changed so that C-sections are now a more common practice.

There are of course physical trends seen in Canada that fit with a higher C-section rate. Women are giving birth on average at a later age, potentially leading to more complications requiring a C-section. Having an increased percentage of the female population being overweight, or obese, and the medical conditions associated with this, such as diabetes, may make physicians (or the women themselves) less likely to want to go through labour if the end results are the same as doing a C-section in the first place. However, these reasons can only account for a small part of the explanation.

Slowly and surely we have moved childbirth away from the 'natural' realm, the baby being delivered at home with the help of women in the community, to the 'medical realm', with the delivery in the hospital. Of course, this immediate access to medical technology has dramatically reduced the number of women and babies that die during childbirth by being able to provide interventions, such as C-sections. The other side of the 'medicalization' of birth is that women have become detached from the process. Many women do not know what to expect. They may experience fear about the labour, and a sense that they will not be able to have a successful vaginal delivery, particularly in the case of women who have previously had a Caesarean due to failure to progress in labour.

I would now like to focus on women who have repeat C-sections, which represents a significant part of the increasing rate. It used to be that once a woman had a C-section, she would be delivered this way for all subsequent pregnancies. Now, obstetrical recommendations are in favour of vaginal birth after caesarean (VBAC), but this does not seem to be translating into fewer caesarean births. In our culture, we have become very risk intolerant. Delivering vaginally after a caesarean is associated with the risk of uterine rupture; a very rare complication, but one that can be potentially fatal for the baby. When I talk to women about risks of VBAC, this is something that most women remember discussing.

One thing I find particularly interesting is that reasons for having a C-section are almost always framed in the negative for having a vaginal birth- something like "I have diabetes, so I can't

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delivery vaginally". What I think we need to be doing is increasing women's confidence in themselves, and in the natural process of childbirth if we want to see any change in the C-section rate. But the healthcare system has to change as well to support this. If we want to understand national trends, we should stop talking about the posh minority, and focus instead on examining how our everyday assumptions have changed to make the C-section rate what it is today.

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LETTER TO THE EDITOR

Excellence in Cardiovascular Research: The Louis and Artur Lucian Award

Simon Garceau, Alexandre Boutet, Jacques Genest

Figure 1. McGill's Louis and Arthur Lucian Award for Research for Circulatory Diseases first presented in October 1978 to Drs Nicolae and Maya Simionescu of Bucharest and Yale Universities for their work in cellular biology and atherosclerotic disease.
From left to right: Alan B. Gold, BA,PhD, chairman of the board of governors of McGill University,Montreal, Quebec, Canada; Dr Nicolae Simionesc; Dr Maya Simionescu; RFP Cronin, MD, a McGill professor in cardiology; Yves Clermont, PhD, chairman of the Department of Anatomy and Histology at McGill University Source: Circulation, Journal of the American Heart Association, 2008.

The Louis and Artur Lucian Award ranks amongst some of the most respected awards presented by an academic institution in the field of cardiovascular disease. Moreover, it represents the largest award bestowed by a Canadian university for research in cardiovascular medicine. Since 1978, the award has honored current work which is deemed to be of outstanding significance in the advancement of the treatment, diagnosis, prevention and understanding of circulatory diseases. Furthermore, the award has a rich history and also aims to promote a partnership between McGill University and Canadian academia with international figures and institutions.

The Lucian award was established in 1965 through a bequest to McGill University by Olga Leibovici, a New-Yorker born in Vaslui, Romania. After meeting with Dr. Ronald V. Christie, at the time dean at the Faculty of Medicine at McGill University, it was decided that a donation of 2 million dollars would be attributed to McGill University for the funding of the Louis and Artur Lucian Award for Research in Circulatory Diseases, named after Mrs. Leibovici's two brothers. A copy of the will from January 21st, 1965 is provided below.

Since it was first presented to Drs. Nicolae and Maya Simionescu in 1978 for their outstanding work on cellular biology and artherosclerotic disease, the prize has aided numerous globally acclaimed scientists. In fact, a recent recipient, Dr. Robert Lefkowitz, is this year's Nobel laureate in chemistry. His work on G-protein coupled receptors, receptors responsible for sensing and interacting with the body's environment, and the targets of half the medications used today, is unparalleled(1).

Currently, the chair of the Lucian selection committee is Dr. Jacques Genest, a researcher in cardiovascular medicine at McGill University's Royal Victoria Hospital. Each year, a panel composed of previous recipients, McGill graduates

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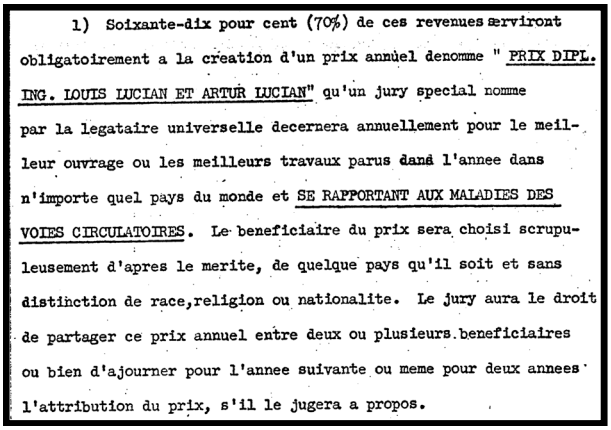

1) Soixante-dix pour cent (70%) de ces revenues serviront obligatoirement a la creation d'un prix annuel denomme " PRIX DIPL. ING. LOUIS LUCIAN ET ARTUR LUCIAN" qu'un jury special nomme par la legataire universelle decernera annuellement pour le meilleur ouvrage ou les meilleurs travaux parus dans l'annee dans n'importe quel pays du monde et SE RAPPORTANT AUX MALADIES DES VOIES CIRCULATOIRES. Le beneficiaire du prix sera choisi scrupuleusement d'apres le merite, de quelque pays qu'il soit et sans distinction de race,religion ou nationalite. Le jury aura le droit de partager ce prix annuel entre deux ou plusieurs beneficiaires ou bien d'ajourner pour l'annee suivante ou meme pour deux annees l'attribution du prix, s'il le jugera a propos.

Figure 2. Excerpt from the Will of the late Olga Leibovici to McGill University for the Creation of the Lucian Award, Courtesy McGill University Faculty of Medicine, Montreal, Quebec, Canada January 21st, 1965 " … Seventy percent of the income fund will obligatorily be used to create an award named "Louis and Artur Lucian (certified Engineers)" awarded annually by a jury nominated by the University for the best work published in the past year anywhere in the world RELATED TO DISEASES OF THE CARDIOVASCULAR SYSTEM. The Awardees will be scrupulously selected, according to merit from any country, without regard to race, religion or nationality. The Jury has the right to share this award between two or more recipients or to defer giving the Award the next year or even two if judged appropriate."

and faculty meet and independently evaluate the 20-30 applicants postulating for any given year. The jury evaluates candidates on present research productivity rather than life-time achievement. "Currently, the award totals 60 000$ with hopes to increase this amount to 100 000$ over the next five to ten years," says Dr. Genest. Thus, philanthropic donations to McGill University are of great importance in reaching this goal. A key element in raising funds and the university's reputation lies in "building relationships," as pointed out by Marc Weinstein, Vice-principal for development and alumni relations (3). The Lucian award, therefore, wishes to promote international collaborative efforts with McGill University and other Canadian researchers. Each recipient is therefore required to spend a minimum of 1-2 weeks at McGill University to give a formal lecture, interact with the faculty, and possibly undertake collaborative research in the field of circulatory disease with McGill University faculty members.

The current deadline to apply for this year's Lucian Award is March 22nd, 2013. More information on applying for this award can be found at the following website:
http://www.mcgill.ca/lucianaward/

CASE REPORT

An Unusual Case of Resistant Hepatic Hydrothorax Treated with Octreotide Infusion

Mehrdad Ghahremani-Ghajar, Mostafa Tabassomi, Scott Harada, Jose Joseph Vempilly

ABSTRACT: Hepatic hydrothorax is an uncommon clinical problem observed in patients with end stage liver disease and portal hypertension. The pathogenesis of pleural effusion in this condition is thought to involve the movement of ascitic fluid across diaphragmatic defects into pleural cavity facilitated by a negative pleural pressure. Therefore, tube thoracostomy is not considered to be a definitive treatment option in the management of hepatic hydrothorax. We present a case of massive pleural effusion secondary to hepatic hydrothorax not responding to conventional treatment successfully treated with intravenous infusion of octreotide.

Key words: TIPS: Transjugular Intrahepatic Portosystemic Shunt, tPA: Tissue Plasminogen Activator

INTRODUCTION

Hepatic hydrothorax is characterized as pleural effusion occurring in patients with end stage liver disease and portal hypertension in the absence of primary cardiac or pulmonary disease. It is an uncommon manifestation and is estimated to occur in 5-12% of cirrhotics.1 Hepatic hydrothorax usually accumulates in the right pleural space and can occur without concurrent ascites.1 The mechanism for pleural fluid formation in hepatic hydrothorax is proposed to involve the passive movement of ascitic fluid from peritoneal cavity to pleural space across the diaphragmatic defects facilitated by a negative intrathoracic pressure.2 Treatment options for hepatic hydrothorax that is refractory to diuresis and salt restriction are limited to serial thoracentesis, pleurodesis, thoracoscopic repair of diaphragmatic defect and transjugular intrahepatic portosystemic shunt (TIPS) placement. However, limited numbers of case reports have documented resolution of hepatic hydrothorax with octreotide (Sandostatin; Novartis Pharma Stein AG; Stein, Switzerland) infusion.3 We report a unique case of an abrupt onset hepatic hydrothorax in a patient with tuberculous pleurisy following a thoracoscopic fibrinolysis of pleural adhesions and its complete resolution with octreotide infusion.

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CASE

A 47-year-old man with alcoholic liver disease was admitted for syncopal attack, due to severe postural drop in blood pressure from gastrointestinal blood loss. Three days following admission, patient was transferred to medical ICU for respiratory failure secondary to delirium from alcohol withdrawal and a massive left pleural effusion [Fig 1]. A chest tube was placed to drain the left effusion in ICU. Pleural fluid analysis revealed a lymphocyte predominant exudate. Pleural fluid Gram stain and microbiology studies were unremarkable. A Quantiferon-TB test was found to be positive. Four-drug anti-tuberculous regimen was initiated due to high clinical suspicion for tuberculous pleurisy. However, a definite diagnosis of tuberculous pleurisy was necessary to continue

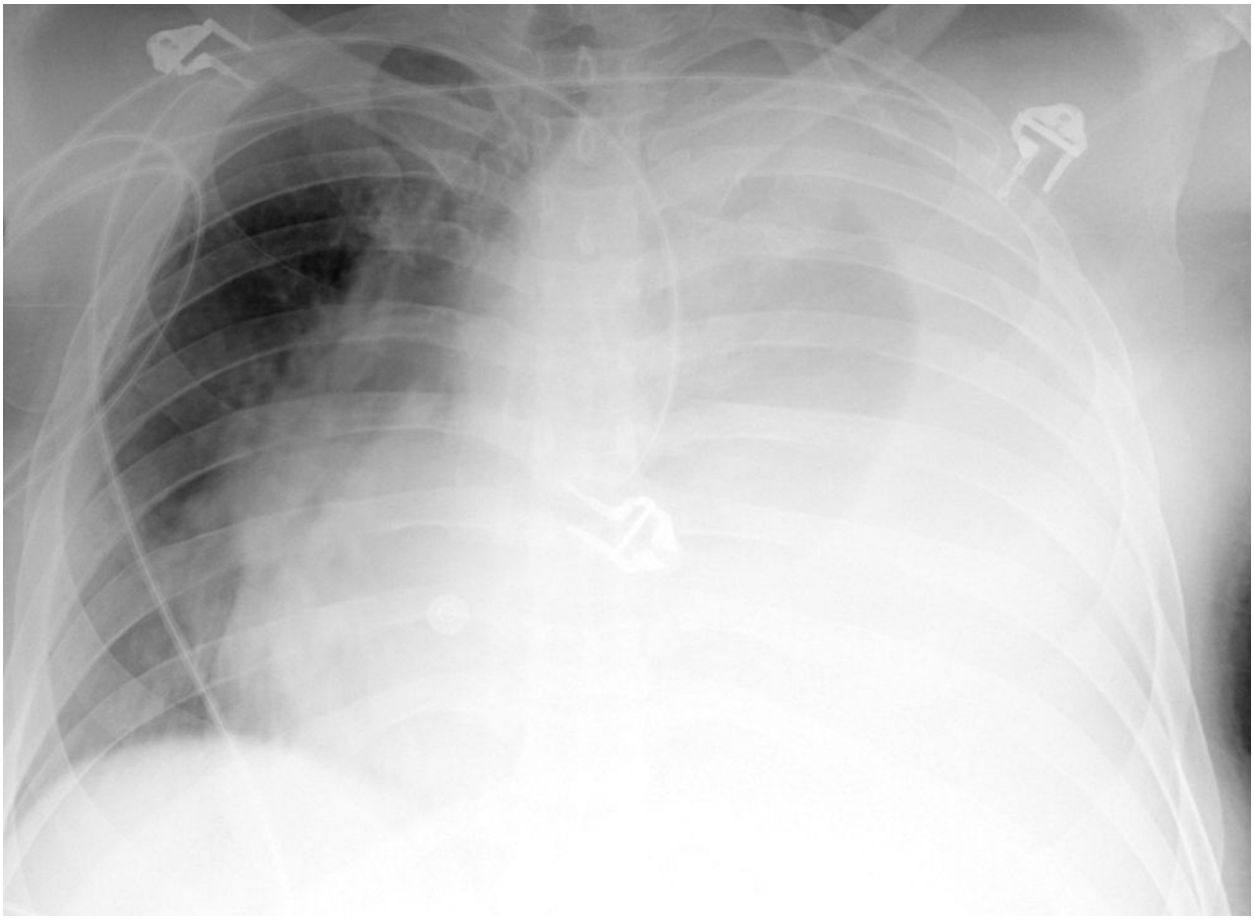

Figure 1: Chest x-ray on admission showing massive left pleural effusion.

the four drugs therapy in a patient with chronic liver disease. Therefore, a diagnostic pleuroscopy was done on left side which confirmed the diagnosis.

After obtaining a pleural biopsy, 100 ml of tissue plasminogen activator (tPA) was instilled into the pleural cavity to breakdown basal pleural adhesions. Post-extubation, the 24 hour pleural fluid drainage was minimal with good expansion of the lung. However, a day after thoracoscopy, there was an abrupt increase in pleural fluid output; totaling 2150 ml/day [Fig 2]. A repeat pleural fluid analysis showed a lymphocyte predominant transudative pleural effusion. A clinical diagnosis of hepatic hydrothorax was made based on history of cirrhosis and absence of heart failure or nephrotic syndrome. Therefore, diuresis with a loop diuretic was initiated with no reduction in daily pleural fluid drainage. Due to minimal response, a trial of octreotide infusion was initiated at 50ug/kg/hour. Thereafter, pleural fluid drainage reduced from 2000 ml/day to 600 ml within a day. As the initial response was satisfactory, the octreotide infusion was continued for another 48 hours with complete resolution of plural fluid drainage by third day. Subsequently the chest tube was removed and patient discharged with anti-tuberculous therapy. A follow-up chest x-ray at three months showed no recurrence of pleural effusion [Fig 3].

DISCUSSION

This was a case of lymphocyte rich exudative pleural effusion due to tuberculous pleurisy that resolved with chest tube drainage and anti-tuberculous therapy. Nevertheless, an increase in the size of pleural effusion while on anti-tuberculous therapy was considered a possible immune exacerbation of tuberculous pleurisy observed in some patients.4 However, an abrupt onset increase in fluid drainage as well as a change of pleural fluid chemistry from an exudate into a lymphocyte predominant transudate, made this possibility less likely. Furthermore, there was no evidence to support a diagnosis of heart failure associated pleural effusion. An iatrogenic diaphragmatic defect post thoracoscopic tPA seemed likely. Lack of response to conventional therapy prompted

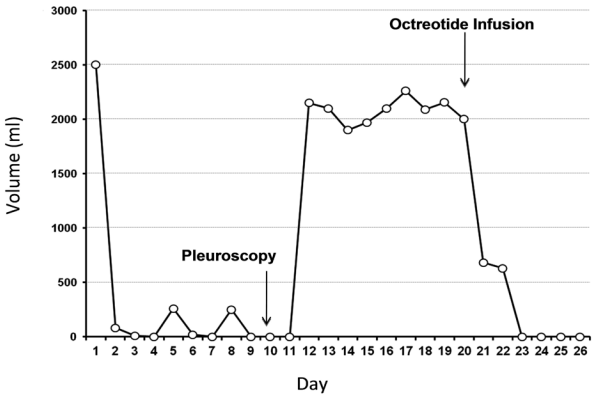

Figure 2: Pleural fluid drainage was negligible following initial chest tube placement. Post tPA administration for adhesion lysis, there was an abrupt increase in chest tube drainage, which did not respond to diuretic therapy. Following octreotide administration there was an abrupt drop in chest tube drainage.

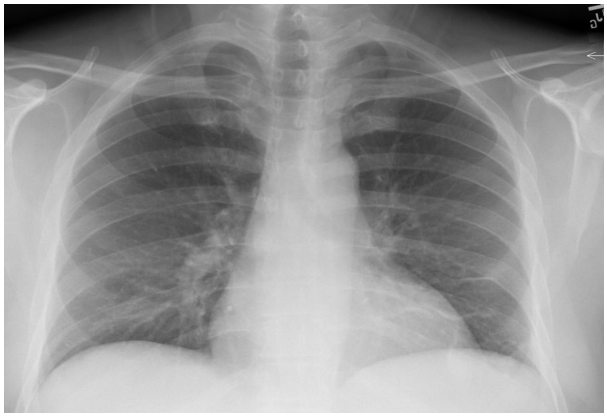

Figure 3: Chest x-ray follow-up in three months.

a trial of octreoide infusion, based on a limited number of previous case reports indicating efficacy of octreotide. An abrupt decrease in pleural fluid drainage with complete resolution within 72 hours following octreotide infusion indicated a therapeutic response. In this context, TIPS procedure has been shown to decrease the portal vein pressure and thereby reduce ascites and pleural effusion.5 Therefore; it is possible that octreotide therapy by reducing the portal pressure may have provided the same benefit as TIPS leading to the resolution of ascites and hepatic hydrothorax in this patient. As the clinical evidence for octreotide in the treatment of hepatic hydrothorax mounts, a multicenter controlled trial of octreotide is warranted.

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CROSSROADS ARTICLE

The Difference Between Disease and Illness

Katherine Lach

The terms illness and disease are both commonly used to describe deviations from what is considered "normal" in the context of health and medicine. Although these two terms may seem to point to a single, confounded meaning, the distinction between them has long been a source of debate. Indeed, medical historians, anthropologists, sociologists and physicians have not reached a consensus on how these concepts differ or overlap. Nevertheless, it is imperative that physicians have an understanding of how the distinctions are implicated in clinical practice and patient care. This essay explores the history of these concepts as separate entities, the key differences, and how this knowledge is important for physicians' practice.

In modern medicine, "disease" is often seen as an "objective" entity that afflicts all patients equally. In particular, diseases are the entities that have been given names – such as tuberculosis, malaria or diabetes – and are discoverable via some biological, chemical or other markers. This term thus conveniently delineates a "thing" that afflicts the patient from the outside and may be targeted for destruction by medicine. For example, the objective, "disease" aspect of cancer is characterized in all patients by uncontrollable, thus pathological, cell division. By contrast, "illness" refers not to an object, but to a patient's experience of having a disease. This experience of the "illness" is subjective and encompasses all of those aspects of being ill that are unique to individuals: their narratives of their own symptom history, their support network, their attitudes towards being sick, and the duration of the illness, to name just a few components.

The dichotomy between the objective and subjective, and the concept of illness as distinct from that of disease, has its own interesting history. Prior to the "scientific," modern medicine that is the widely accepted disease model of today, illness was seen as a deviation from health caused, not by outside "things" that we now think of as diseases, but by a "violation of natural laws." Violations encompassed a wide range of extrinsic factors that determined health, including the environment, food and drink, lifestyle and mental state – all of which could be seen as the direct cause of what we now know to be infectious disease.4 These "imbalances" were explained in terms of the four humors, which fundamentally held that there was "no such thing as specific diseases."4 This served as the explanatory model of medicine until the 18th century.4 It was only then that the Western medical tradition began to adopt the "anatomico-clinical method," based upon reasoning from symptoms before death to lesions found upon autopsy.1 This approach, along with the acceptance of the germ theory of disease, led to the commonly held idea that diseases are "discrete entities – real things."

The idea that diseases assail us from without and thus afflict all patients the same way has not been without usefulness. Indeed, there are biological facts about many diseases, now elucidated, that allow medicine to tackle them with unprecedented success. However, diseases do not act in a vacuum, but act upon individual and unique patients who will experience them differently. Facets of life outside of illness will come to bear upon how it is interpreted and integrated by the patient, including access to health care, economic status and education; this is a facet of sickness that physicians need to pay particular attention to.

Physician and anthropologist Cecil G. Helman has pointed out that lay concepts of disease may affect patients' interpretations of illness.2 He further outlines a "folk model of illness" that centers upon patients' questions about illness – the "why me's and why now's" – that shape patient behavior.2 The patients' answers to these questions can

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affect how and when they seek medical treatment. For example, patients are more likely to be accepted as truly "ill" by their communities and given care if they are perceived as "blameless," with symptoms that are extrinsically-inflicted, such as from an infection, rather than from lifestyle factors such as smoking or excessive drinking.2

Diseases may or may not produce symptoms; when they do, pain is universally among the most debilitating. Pain is inherently difficult to quantify or treat objectively because, like illness, it relies upon patient narratives to be assessed. One study has shown that patient attitudes towards cancer, or how "catastrophic" it was for them, were directly related to the level of pain that they experienced; similarly, their level of social support influenced their perceptions of pain. Related research made use of the McGill Pain Questionnaire to investigate links between patients' emotional disclosure during doctors' visits and their reported levels of pain. Researchers found that patients who were highly emotional in their narratives had "significantly less pain" and reported higher overall well-being.7 This demonstrates the crucial role of the physician in allowing patients to speak of their own experiences with illness, not merely to allow the "disease" to speak for itself. Our perceptions of our own illness, and of the care that we receive, determine how we experience pain, and to what degree.

Illness brings with it innumerable possibilities of experience; patients may feel any range of emotions, including fear and anxiety, self-pity, and a sense of disconnectedness from their "healthy" peers or communities. Assessing patient emotions is crucial in determining treatment, particularly when considering the patient's role in their own care. For example, managing diabetes mellitus requires lifelong compliance in order to maintain blood glucose homeostasis. This may be particularly difficult, given the role of food and eating as a cultural and social practice – indeed, it has been found that "compliance is often poor in teenage patients who are adversely influenced by peers." In treating this disease, as in all others, physicians need to be aware of how a patient's social setting and peer group influence not just their attitude towards "having a disease," but also, towards compliance with treatment models.

Modern medicine has found myriad ways to diagnose diseases and in many cases, even eliminate their causes. However, how a patient experiences illness cannot be measured in a lab or diagnosed via a physical exam. For this reason, physicians need to pay particular attention to patient narratives of their experiences in order to understand a patient's unique, individual "illness" and thus fully treat their "disease."

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“OPINION
IS GOOD.
BUT EVIDENCE
IS BETTER.”*

BRILINTA (ticagrelor), co-administered with acetylsalicylic acid (ASA), is indicated for the secondary prevention of atherothrombotic events in patients with Acute Coronary Syndromes (ACS) (unstable angina [UA], non–ST elevation myocardial infarction [NSTEMI] or ST elevation myocardial infarction [STEMI]) who are to be managed medically, and those who are to be managed with percutaneous coronary intervention (PCI) (with or without stent) and/or coronary artery bypass graft (CABG).

Based on a relationship observed in PLATO between maintenance ASA dose and relative efficacy of BRILINTA compared to clopidogrel, BRILINTA is recommended to be co-administered with low maintenance dose ASA (75-150 mg daily).

BRILINTA is contraindicated in patients who: are hypersensitive to this medication or to any ingredient in the formulation, have active pathological bleeding such as peptic ulcer or intracranial hemorrhage, have a history of intracranial hemorrhage, have moderate to severe hepatic impairment or are also taking strong CYP3A4 inhibitors.

BRILINTA should be used with caution in patients with a propensity to bleed (e.g., due to recent trauma, recent surgery, active or recent gastrointestinal bleeding, or moderate hepatic impairment) and in patients requiring oral anticoagulants (e.g., warfarin) and/or fibrinolytics agents (within 24 hours of BRILINTA dosing). Caution should also be used in patients with concomitant administration of medicinal products that may increase the risk of bleeding (e.g., non-steroidal anti-inflammatory drugs [NSAIDs]). Co-administration of BRILINTA and high maintenance dose ASA (>150 mg daily) is not recommended.

In the PLATO study, bleeding events associated with BRILINTA vs. clopidogrel included total major (11.6% vs. 11.2%) and combined total major + minor (16.1% vs. 14.6%). When minor bleeding was included, combined PLATO-defined major and minor bleeding events were significantly higher on BRILINTA than on clopidogrel (p=0.0084). There were few fatal bleeding events in the study, 20 (0.2%) for BRILINTA and 23 (0.3%) for clopidogrel. The most common adverse events associated with BRILINTA vs. clopidogrel were dyspnea (12.0% vs. 6.5%), headache (6.5% vs. 5.8%) and nosebleed (6.0% vs. 3.4%).

See the Product Monograph for full contraindications, warnings, precautions, dosing and administration.

Reference: 1. BRILINTA® Product Monograph. AstraZeneca Canada Inc. May 26, 2011.

*Fictitious quote. May not be representative of all healthcare professionals.

BRILINTA®
ticagrelor tablets

AstraZeneca

Member R&D PAAB
BR032E 08/12

See prescribing summary on page

BRILINTA®
ticagrelor tablets

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Platelet Aggregation Inhibitor

INDICATIONS AND CLINICAL USE: BRILINTA (ticagrelor), co-administered with acetylsalicylic acid (ASA), is indicated for the secondary prevention of atherothrombotic events in patients with Acute Coronary Syndromes (ACS) (unstable angina [UA], non–ST Elevation Myocardial Infarction [NSTEMI] or ST Elevation Myocardial Infarction [STEMI]) who are to be managed medically and those who are to be managed with percutaneous coronary intervention (PCI) (with or without stent) and/or coronary artery bypass graft (CABG).

Based on a relationship observed in PLATO between maintenance ASA dose and relative efficacy of BRILINTA compared to clopidogrel, BRILINTA is recommended to be co-administered with low maintenance dose ASA (75-150 mg daily).

Pediatrics (<18 years of age): The safety and efficacy of BRILINTA in pediatric patients below the age of 18 have not been established. Therefore, BRILINTA is not recommended in this population.

CONTRAINDICATIONS: BRILINTA (ticagrelor) is contraindicated in:

- Patients who are hypersensitive to this medication or to any ingredient in the formulation
- Patients who have active pathological bleeding such as peptic ulcer or intracranial hemorrhage
- Patients with a history of intracranial hemorrhage
- Patients with moderate to severe hepatic impairment
- Patients who are also taking strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir and atazanavir), as it may lead to a substantial increase in exposure to ticagrelor

SPECIAL POPULATIONS:

Pregnant Women: The safety of BRILINTA during pregnancy has not been established, as no clinical study has been conducted in pregnant women and limited clinical data on exposure to BRILINTA during pregnancy are available. Women of childbearing potential should use appropriate contraceptive measures to avoid pregnancy.

Nursing Women: It is not known whether this drug is excreted in human milk, as no clinical study has been conducted in lactating women. Studies in rats have shown that ticagrelor and its active metabolites are excreted in milk. Therefore, the use of BRILINTA during breastfeeding is not recommended.

Geriatrics (≥65 years of age): In PLATO, 43.1% of patients were ≥65 years of age and 15% were ≥75 years of age. The relative risk of bleeding was similar in both treatment and age groups. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Pediatrics (<18 years of age): The safety and efficacy of BRILINTA in pediatric patients below the age of 18 have not been established. Therefore, BRILINTA is not recommended in this population.

Hepatic Impairment: Use of BRILINTA is contraindicated in patients with moderate or severe hepatic impairment.

Renal Impairment: No dose adjustment is necessary for patients with renal impairment. No clinical study has been conducted in patients on renal dialysis. Ticagrelor is not thought to be dialyzable. Appropriate caution should be used in patients requiring renal replacement therapy. Creatinine levels may increase during treatment with BRILINTA. The mechanism has not been identified. Renal function should be monitored in the course of patient management.

Uric Acid Increase: In PLATO, patients on BRILINTA had a higher risk of hyperuricemia than those receiving clopidogrel. Caution should be exercised when administering BRILINTA to patients with history of hyperuricemia or gouty arthritis. As a precautionary measure, the use of BRILINTA in patients with uric acid nephropathy is discouraged.

Safety Information

WARNINGS AND PRECAUTIONS:

General

Bleeding Risk: As with other antiplatelet agents, the use of BRILINTA (ticagrelor) in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of thrombotic events.

If clinically indicated, BRILINTA should be used with caution in the following patient groups:

- Patients with a propensity to bleed (e.g., due to recent trauma, recent surgery, active or recent gastrointestinal bleeding, or moderate hepatic impairment). The use of BRILINTA is contraindicated in patients with active pathological bleeding, in those with history of intracranial hemorrhage, and moderate to severe hepatic impairment.
- Patients requiring oral anticoagulants (e.g., warfarin) and/or fibrinolytics agents (within 24 hours of BRILINTA dosing). Such agents confer an independent bleeding risk as they function in a distinct and complementary mechanism of hemostasis compared to BRILINTA. The combination of BRILINTA with either of these classes of drugs has not been studied.
  - **Warfarin Therapy:** Due to an increased propensity to bleed, caution is advised in patients taking warfarin during BRILINTA therapy. A specific drug-drug interaction study with warfarin has not been performed.
- Patients with concomitant administration of medicinal products that may increase the risk of bleeding, e.g., non-steroidal anti-inflammatory drugs (NSAIDs).

No data exist with BRILINTA regarding a hemostatic benefit of platelet transfusions; circulating BRILINTA may inhibit transfused platelets. Since co-administration of BRILINTA with desmopressin did not decrease template bleeding time, desmopressin is unlikely to be effective in managing clinical bleeding events.

Antifibrinolytic therapy (aminocaproic acid or tranexamic acid) and/or recombinant factor VIIa may augment hemostasis. BRILINTA may be resumed after the cause of bleeding has been identified and controlled.

Maintenance Dose Acetylsalicylic acid (ASA): Based on a relationship observed in PLATO between maintenance ASA dose and relative efficacy of BRILINTA compared to clopidogrel, co-administration of BRILINTA and high maintenance dose ASA (>150 mg daily) is not recommended.

Cytochrome P450 3A4 Strong Inhibitors: Co-administration of BRILINTA with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir and atazanavir) is contraindicated as co-administration may lead to a substantial increase in exposure to ticagrelor.

Peri-Operative Considerations

Surgery: If a patient requires surgery, clinicians should consider each patient's clinical profile as well as the benefits and risks of continued antiplatelet therapy when determining when discontinuation of BRILINTA treatment should occur.

To minimize the risk of bleeding, if a patient is to undergo elective surgery and antiplatelet effect is not desired, BRILINTA should be discontinued 5 days prior to surgery.

Respiratory

Dyspnea: In PLATO, approximately 13.8% of patients randomized to BRILINTA, versus 7.8% for clopidogrel, reported dyspnea, including dyspnea at rest, exertional dyspnea, paroxysmal nocturnal dyspnea and nocturnal dyspnea. The dyspnea is usually mild to moderate in intensity and often resolves during continued BRILINTA treatment. The mechanism has not yet been elucidated. If a patient reports new, prolonged or worsened dyspnea this should be investigated fully and if not tolerated, treatment with BRILINTA should be stopped.

ADVERSE REACTION SERIOUSNESS AND INCIDENCE:

Adverse Drug Reaction Overview: The commonly reported adverse events in patients treated with BRILINTA (ticagrelor) were dyspnea, headache and epistaxis and these events occurred at higher rates than in the clopidogrel treatment group (see Table 1).

Table 1: Summary of Adverse Events (Regardless of Causality) Reported for ≥1% of Patients in Either Group (PLATO)

Adverse Event (System Organ Class)	BRILINTA (%) N=9235	Clopidogrel (%) N=9186
Blood and Lymphatic System Disorders		
Anemia	1.9	1.7
Cardiac Disorders		
Atrial fibrillation	4.2	4.6
Bradycardia[a]	2.9	2.9
Cardiac failure	2.3	2.6
Ventricular tachycardia	2.0	2.1
Palpitations	1.2	1.1
Angina pectoris	1.2	1.1
Sinus bradycardia	1.1	0.8
Ventricular extrasystoles	1.1	1.1
Ventricular fibrillation	0.8	1.0
Ear and Labyrinth Disorders		
Vertigo[b]	1.5	1.3
Gastrointestinal Disorders		
Nausea[b]	4.3	3.8
Diarrhea[b]	3.7	3.3
Vomiting[b]	2.5	2.3
Constipation[b]	2.2	2.6
Dyspepsia[b]	2.0	1.8
Abdominal pain upper	1.9	2.0
Abdominal pain[b]	1.5	1.2
General Disorders and Administration Site Conditions		
Non-cardiac chest pain	3.7	3.3
Fatigue	3.2	3.2
Chest pain	3.1	3.5
Pyrexia	2.9	2.8
Edema peripheral	2.3	2.5
Asthenia	2.0	2.1
Hemorrhages or bleeding		
Epistaxis[b]	6.0	3.4
Contusion	3.9	2.0
Hematoma	2.2	1.3
Post-procedural hemorrhage[b]	2.1	2.0
Vessel puncture site hematoma	1.7	1.1
Ecchymosis	1.5	0.6
Infections and Infestations		
Urinary tract infection	2.0	1.8
Hematuria	1.9	1.6
Nasopharyngitis	1.8	1.6
Pneumonia	1.4	1.9
Bronchitis	1.3	1.4
Metabolism and Nutrition Disorders		
Diabetes mellitus	1.2	1.1
Dyslipidemia	1.0	1.0
Hypercholesterolemia	1.0	0.9
Hypokalemia	1.6	1.5
Musculoskeletal and Connective Tissue Disorders		
Back pain	3.6	3.3
Pain in extremity	2.1	2.3
Musculoskeletal chest pain	1.5	1.4
Musculoskeletal pain	1.5	1.5
Arthralgia	1.5	1.4
Myalgia	1.4	1.6
Nervous System Disorders		
Headache[b]	6.5	5.8
Dizziness[b]	4.5	3.9
Syncope	1.1	0.8
Psychiatric Disorders		
Anxiety	2.2	1.9
Insomnia	1.7	2.0
Depression	1.1	1.1
Renal and Urinary Disorders		
Renal failure	1.0	0.7
Respiratory Disorders		
Dyspnea[a,b]	12.0	6.5
Cough	4.9	4.6
Dyspnea exertional	1.9	1.4
Skin and Subcutaneous Tissue Disorders		
Rash[b]	1.8	1.7
Pruritus[b]	1.0	1.0
Vascular Disorders		
Hypertension	3.8	4.0
Hypotension	3.2	3.3

a Several MedDRA PT combined.
b These events have also been reported as Adverse Drug Reactions (possibly or probably related to BRILINTA).

DRUG INTERACTIONS: Cytochrome P450 (CYP) 3A4/5 are the major enzymes responsible for the metabolism of BRILINTA (ticagrelor) and the formation of the active metabolite. Clinical pharmacology and *in vitro* data show that there is a complex interaction between ticagrelor and CYP3A4/5. Indeed, depending on the substrate, ticagrelor and its active metabolite are shown to weakly inhibit or weakly activate CYP3A4/5 (see DETAILED PHARMACOLOGY). Therefore, co-administration of BRILINTA and CYP3A4/5 substrates with narrow therapeutic indices is not recommended. CYP enzymes 1A2, 2C19 and 2E1 do not contribute meaningfully *in vitro* to ticagrelor metabolism. BRILINTA is also a p-glycoprotein (P-gp) substrate and a weak inhibitor of P-gp.

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
Fax toll-free to 1-866-678-6789, or
Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9

Postage-paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada website at www.healthcanada.gc.ca/medeffect.

Administration

Recommended Dose and Dosage Adjustment

BRILINTA therapy should be initiated with a single 180 mg oral loading dose (two 90 mg tablets) and then continued at 90 mg twice daily. Patients taking BRILINTA should also take acetylsalicylic acid (ASA) daily, unless specifically contraindicated. Following an initial loading dose of ASA, BRILINTA should be used with a daily maintenance dose of ASA of 75-150 mg.

BRILINTA can be taken orally with or without food. In a study of healthy subjects, ingestion of a high-fat meal had no effect on ticagrelor C_{max} or the AUC of the active metabolite, but resulted in a 21% increase in ticagrelor AUC and 22% decrease in the active metabolite C_{max}. These changes are considered of minimal clinical significance. BRILINTA was administered without regard to food in PLATO.

Grapefruit juice interaction: A drug-drug interaction study with grapefruit juice has not been performed. Based on the pharmacokinetic data for ticagrelor, grapefruit juice is expected to increase ticagrelor exposure to a clinically insignificant extent. Therefore, BRILINTA can be taken with grapefruit juice.

Missed Dose

Lapses in therapy should be avoided. A patient who misses a dose of BRILINTA should take one 90 mg tablet (their next dose) at its scheduled time.

SUPPLEMENTAL PRODUCT INFORMATION

WARNINGS AND PRECAUTIONS:

Discontinuations: Patients who require discontinuation of BRILINTA are at increased risk for cardiac events. Premature discontinuation of treatment should be avoided. If BRILINTA must be temporarily stopped due to an adverse event, it should be re-initiated as soon as possible when the benefits outweigh the risks of the adverse event or when the adverse event has come to resolution.

Cardiovascular

Patients at Risk for Bradycardic Events: Due to observations of mostly asymptomatic ventricular pauses in an earlier clinical study, the Phase III study (PLATO) excluded patients with an increased risk of bradycardic events (e.g., patients who have sick sinus syndrome, 2nd or 3rd degree AV block or bradycardic-related syncope and not protected with a pacemaker). Therefore, due to the limited clinical experience, BRILINTA should be used with caution in these patients.

In addition, caution should be exercised when administering BRILINTA concomitantly with drugs known to induce bradycardia. However, no evidence of clinically significant adverse interactions was observed in the PLATO trial during concomitant administration with one or more drugs known to induce bradycardia: in PLATO, 96% of patients took beta-blockers, 33% took diltiazem or verapamil (calcium channel blockers) and 4% took digoxin.

Neurologic

Effects on Ability to Drive and Use Machines: No studies on the effects of BRILINTA on the ability to drive and use machines have been performed. BRILINTA has no or negligible influence on the ability to drive and use machines. During treatment for Acute Coronary Syndromes, dizziness and confusion have been reported. Therefore, patients who experience these symptoms should be cautious while driving or using machines.

Peri-Operative Considerations

In PLATO patients undergoing CABG, BRILINTA had a similar rate of major bleeds compared to clopidogrel at all days after stopping therapy except Day 1 where BRILINTA had a higher rate of major bleeding.

Because of the reversible binding of BRILINTA, restoration of platelet aggregation occurs faster with BRILINTA compared to clopidogrel.

In the OFFSET study, mean Inhibition of Platelet Aggregation (IPA) for ticagrelor at 72 hours post-dose was comparable to mean IPA for clopidogrel at 120 hours post-dose. The more rapid offset of effect may predict a reduced risk of bleeding complications, e.g., in settings where antiplatelet therapy must be temporarily discontinued due to surgery or trauma.

Adverse Drug Reaction Overview

In PLATO, a total of 6762 patients with Acute Coronary Syndromes (UA, NSTEMI and STEMI) were exposed to BRILINTA (180 mg loading dose followed by a 90 mg twice daily maintenance dose) for at least 6 months and up to 12 months for 3138 of them.

Serious adverse events were reported in a similar frequency between BRILINTA (20.2%) and clopidogrel (20.3%) treated patients. The most frequent serious adverse events observed were cardiac failure (1.1% vs. 1.0%), non-cardiac chest pain (0.9% vs. 0.9%) and dyspnea (0.7% vs. 0.4%).

The rate of study drug discontinuation because of adverse events was 7.4% for BRILINTA and 5.4% for clopidogrel. Dyspnea was the most common adverse event leading to study drug discontinuation for BRILINTA (0.9% for BRILINTA and 0.1% for clopidogrel).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Bleeding Events: The primary safety endpoint in the PLATO study was the composite endpoint of 'Total Major' bleeding, which consisted of the components of 'Major Fatal/Life-threatening' and 'Major Other'. Table 2 shows the 12-month rates of patients experiencing bleeding events in the PLATO study (PLATO-defined).

Table 2: Analysis of Overall Bleeding Events – PLATO-defined

	BRILINTA (%) N=9235	Clopidogrel (%) N=9186	*p*-value*
Primary Safety Endpoint			
Total Major	11.6	11.2	0.4336
Secondary Safety Endpoints			
Major Fatal/Life-threatening	5.8	5.8	0.6988
Combined Total Major + Minor	16.1	14.6	0.0084
Non-procedural Major	3.1	2.3	0.0058
Non-procedural Major + Minor	5.9	4.3	<0.0001
Non-CABG Total Major	4.5	3.8	0.0264
Non-CABG Major Fatal/Life-threatening	2.1	1.9	0.2516

*Nominal *p*-value not corrected for multiple testing.
Major Fatal/Life-threatening: Clinically apparent with >50 g/L decrease in hemoglobin or ≥4 red cell units transfused; or fatal; or intracranial; or intrapericardial with cardiac tamponade; or with hypovolemic shock or severe hypotension requiring pressors or surgery.
Major Other: Clinically apparent with 30-50 g/L decrease in hemoglobin or 2-3 red cell units transfused; or significantly disabling.
Minor: Requires medical intervention to stop or treat bleeding.

There were few fatal bleeding events in the study, 20 (0.2%) for BRILINTA and 23 (0.3%) for clopidogrel. When minor bleeding was included, combined PLATO-defined Major and Minor bleeding events were significantly higher on BRILINTA than on clopidogrel.

Location of 'Total Major + Minor' Bleeding (BRILINTA vs. clopidogrel): Intracranial 0.3% vs. 0.2%, pericardial 0.1% vs. 0.1%, retroperitoneal 0.03% vs. 0.03%, intraocular 0.02% vs. 0.04% and intra-articular 0.02% vs. 0.01%. Other common locations were in rank order of event frequency: gastrointestinal 1.8% vs. 1.5%, epistaxis 1.3% vs. 0.7%, urinary 0.5% vs. 0.4%, subcutaneous/dermal 0.5% vs. 0.4% and hemoptysis 0.1% vs. 0.08%.

Non-procedural Fatal Bleeding: There was no difference with BRILINTA compared to clopidogrel for overall non-procedural fatal bleeding. There were numerically more 'Major Fatal/Life-threatening' intracranial non-procedural bleeding events with BRILINTA (n=27 events, 0.3%) than with clopidogrel (n=14 events, 0.2%). Of the intracranial non-procedural bleeding events, 11 bleeding events with BRILINTA and 1 with clopidogrel were fatal. 'Major Fatal/Life-threatening' gastrointestinal bleeding was the same with BRILINTA and clopidogrel, with numerically more fatal events for clopidogrel (5) than for BRILINTA (none).

Bleeding in Subgroups Patient Population: Baseline characteristics including age, gender, weight, race, geographic region, medical history, concurrent conditions and concomitant therapy were assessed to explore any increase in risk of bleeding with BRILINTA. No particular risk group was identified for any subset of bleeding.

Table 3 shows the overall rates of TIMI-defined bleeding events.

Table 3: Analysis of Overall Bleeding Events – TIMI-defined

	BRILINTA (%) N=9235	Clopidogrel (%) N=9186	*p*-value
Major	7.9	7.7	0.5669
Major + Minor	11.4	10.9	0.3272
Non-CABG Major	2.8	2.2	0.0246
Non-CABG Major + Minor	4.5	3.6	0.0093

TIMI Major: Clinically apparent with >50 g/L decrease in hemoglobin or intracranial hemorrhage.
TIMI Minor: Clinically apparent with 30 to ≤50 g/L decrease in hemoglobin.

Additional clinical Adverse Drug Reactions that were reported as possibly or probably related to BRILINTA are listed below by body system:

Common (≥1% to <10%)
- *Skin and subcutaneous tissue disorders:* subcutaneous or dermal bleeding
- *Gastrointestinal disorders:* gastrointestinal hemorrhages
- *Renal and urinary disorders:* urinary tract bleeding

Uncommon (≥0.1% to <1%)
- *Nervous system disorders:* intracranial hemorrhage (may be fatal or life threatening), confusion, paraesthesia
- *Gastrointestinal disorders:* gastritis, retroperitoneal hemorrhage
- *Eye disorders:* eye hemorrhage (intraocular, conjunctival, retinal)
- *Respiratory, thoracic and mediastinal disorders:* hemoptysis

Rare (≥0.01% to <0.1%)
- *Musculoskeletal connective tissue and bone:* hemarthrosis

DRUG INTERACTIONS:

Drug-Drug Interactions

Effects of Other Drugs on BRILINTA

Ketoconazole (Strong CYP3A4 Inhibitors): Co-administration of ketoconazole with ticagrelor increased the ticagrelor C_{max} and AUC equal to 2.4-fold and 7.3-fold, respectively. The C_{max} and AUC of ticagrelor's active metabolite were reduced by 89% and 56%, respectively. Other strong inhibitors of CYP3A4 (clarithromycin, nefazodone, ritonavir and atazanavir) would be expected to have similar effects and are contraindicated with BRILINTA.

Diltiazem (Moderate CYP3A4 Inhibitors): Co-administration of diltiazem with ticagrelor increased the ticagrelor C_{max} by 69% and AUC by 174% and decreased its active metabolite C_{max} by 38% and AUC was unchanged. There was no effect of ticagrelor on diltiazem plasma levels. Other moderate CYP3A4 inhibitors (e.g., amprenavir, aprepitant, erythromycin, fluconazole and verapamil) would be expected to have similar effects. These exposure changes are not considered clinically significant, and therefore can as well be co-administered with BRILINTA.

Rifampin and Other CYP3A4 Inducers: Co-administration of rifampin with ticagrelor decreased the ticagrelor C_{max} and AUC by 73% and 86%, respectively. The C_{max} of its active metabolite was unchanged and the AUC was decreased by 46%. Other CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine and phenobarbital) would be expected to decrease the exposure to ticagrelor as well and may result in reduced efficacy of BRILINTA.

Others: Clinical pharmacology interaction studies showed that co-administration of ticagrelor with heparin, enoxaparin and acetylsalicylic acid (ASA) did not have any effect on ticagrelor or its active metabolite plasma levels. Co-administration of ticagrelor and heparin had no effect on heparin based on activated partial thromboplastin time (aPTT) and activated coagulation time (ACT) assays. Co-administration of ticagrelor and enoxaparin had no effect on enoxaparin based on factor Xa assay.

Effects of BRILINTA on Other Drugs

Simvastatin: Co-administration of ticagrelor with simvastatin increased the simvastatin C_{max} by 81% and AUC by 56% and increased simvastatin acid C_{max} by 64% and AUC by 52% with some individual increases equal to 2- to 3-fold. Consideration of the clinical significance should be given to the magnitude and range of changes on the exposure to patients requiring greater than 40 mg of simvastatin. There was no effect of simvastatin on ticagrelor plasma levels. BRILINTA may have similar effect on lovastatin, but is not expected to have a clinically meaningful effect on other statins.

Atorvastatin: Co-administration of atorvastatin and ticagrelor increased the atorvastatin acid C_{max} by 23% and AUC by 36%. Similar increases in AUC and C_{max} were observed for all atorvastatin acid metabolites. These increases are not considered clinically significant.

Tolbutamide: Co-administration of ticagrelor with tolbutamide resulted in no change in the plasma levels of either drug, which demonstrates ticagrelor is not a CYP2C9 inhibitor and unlikely to alter the metabolism of other drugs metabolized via CYP2C9.

Warfarin: A drug-drug interaction study with warfarin has not been performed. As with other oral antiplatelet therapy, there is a potential for increased risk of bleeding, therefore, warfarin and BRILINTA should be co-administered with caution.

Oral Contraceptives: Co-administration of ticagrelor and levonorgestrel and ethinyl estradiol increased the ethinyl estradiol exposure approximately 20% but did not alter the PK of levonorgestrel. No clinically relevant effect on oral contraceptive efficacy is expected when levonorgestrel and ethinyl estradiol are co-administered with BRILINTA.

Digoxin (P-gp Substrate): Concomitant administration of ticagrelor increased the digoxin C_{max} by 75% and AUC by 28%. Therefore, appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp dependent drugs like digoxin concomitantly with BRILINTA.

Other Concomitant Therapy: In clinical studies, BRILINTA was commonly administered with ASA, heparin, low molecular weight heparin, intravenous GpIIb/IIIa inhibitors, proton pump inhibitors, statins, beta-blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers as needed for concomitant conditions. These studies did not produce any evidence of clinically significant adverse interactions.

DOSAGE AND ADMINISTRATION:

General

The PLATO trial data suggest the efficacy of BRILINTA (ticagrelor) relative to clopidogrel is associated with ASA dose during maintenance therapy. Patients receiving a low maintenance dose of ASA benefit more than those receiving a high maintenance dose of ASA. Because the data from patients receiving high maintenance dose ASA (>300 mg daily) do not provide conclusive evidence of the efficacy of BRILINTA compared to clopidogrel, high maintenance dose ASA (>150 mg daily) is not recommended for maintenance dual antiplatelet therapy with BRILINTA. There is no conclusive evidence regarding the underlying biological mechanism. Based on analysis of the available clinical data, it is recommended that BRILINTA be used with a daily low maintenance dose of ASA (75-150 mg).

Furthermore, no safety and efficacy data is available on the use of BRILINTA beyond one year treatment duration.

Recommended Dose and Dosage Adjustment

Switching from clopidogrel to BRILINTA: Patients can be switched from clopidogrel to BRILINTA without interruption of antiplatelet effect. This results in an absolute inhibition of platelet aggregation (IPA) increase of 26.4%. Conversely, switching from BRILINTA to clopidogrel results in an absolute IPA decrease of 24.5%. Clinicians who desire to switch patients from clopidogrel to BRILINTA should administer the first 90 mg dose of BRILINTA 24 hours following the last dose of clopidogrel.

Dosing Considerations in Special Populations

Geriatrics (≥65 years of age): No dosage adjustment is required in elderly (≥65 years) patients.

Patients with Renal Insufficiency: No dosage adjustment is required in patients with renal impairment. No clinical study has been conducted in patients on renal dialysis. Ticagrelor is not thought to be dialyzable. Appropriate caution should be used in patients requiring renal replacement therapy.

Patients with Hepatic Insufficiency: No dosage adjustment is required in patients with mild hepatic impairment. BRILINTA has not been studied in patients with moderate or severe hepatic impairment.

OVERDOSAGE:

For management of suspected drug overdose, contact your regional Poison Control Centre.

Treatment

There is currently no known antidote to reverse the effects of BRILINTA (ticagrelor), and ticagrelor is not expected to be dialyzable. Treatment of overdose should follow local standard medical practice. The expected effect of excessive BRILINTA dosing is prolonged duration of bleeding risk associated with platelet inhibition. If bleeding occurs, appropriate supportive measures should be taken.

ACTION AND CLINICAL PHARMACOLOGY:

Pharmacodynamics

Inhibition of platelet aggregation (IPA) mediated by ticagrelor increases with increasing plasma concentrations of ticagrelor and its active metabolite (AR-C124910XX), until almost complete inhibition is attained. The inhibition of platelet aggregation gradually decreases with declining plasma ticagrelor and active metabolite concentrations, as the IPA mediated by ticagrelor is reversible. Since ticagrelor reversibly binds to the $P2Y_{12}$ receptor, the recovery of platelet function is expected to be dependent on the plasma concentrations of ticagrelor and the active metabolite and not on the replacement of irreversibly inhibited platelets as with thienopyridine antiplatelet agents.

The IPA of ticagrelor is generally independent of factors such as race, hepatic or renal disease or co-administered ASA, heparin and enoxaparin.

Pharmacokinetics

Ticagrelor demonstrates linear pharmacokinetics. Exposure to ticagrelor and its active metabolite are approximately dose proportional.

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The Prescribing Summary provides the most current information at the time of printing. For access to the most up-to-date information, view the full Product Monograph (prepared for health professionals) by visiting www.astrazeneca.ca or by contacting AstraZeneca Canada Inc.

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CROSSROADS ARTICLE

Questioning What the Doctor Ordered: The Shortcomings of Defensive Medicine

Janelle Wen Hui Teng

The Hippocratic Oath speaks of good doctors being “respected by all men in all times”. Unfortunately, the days of Hippocrates are long over, and so too are the golden days when a doctor’s professional judgment was well-respected and deemed to be unquestionable. Malpractice litigation is ubiquitous in modern day medical practice. In America alone, there are more than 17 malpractice claims per year for every 100 full-time practicing physicians ( ). This trend is also emerging in Asian countries, such as in Singapore where there was a 90% increase in malpractice claims in 2010 as compared to 2006 ( ). The increasing risk of malpractice liability and fear of devastating economic and professional ramifications have led more doctors to practice defensive medicine as a pre-emptive measure. Defensive medicine, broadly defined as medical practices undertaken primarily due to concern about malpractice liability, may be manifested as assurance behaviors which have marginal added value, such as the ordering of additional tests or overprescribing of unnecessary medicines; or as avoidance behaviors, whereby a doctor avoids high-risk patients and procedures ( ).

A staggering 83% to 93% of doctors surveyed have admitted to practicing defensively (3-). The pervasiveness of this phenomenon has impacted different stakeholders in various ways. Ostensibly, from the patients’ viewpoint, defensive medicine acts positively as a deterrent against poor-quality care, and helps to reduce tolerance for medical ambiguity. However, a more detailed analysis reveals many negative repercussions of defensive medicine on healthcare quality. Firstly, patients experience reduced access to care. For instance, while practicing defensively, some family physicians in Florida, Mississippi, Texas and Pennsylvania have stopped offering obstetrics services ( ). Secondly, while defensive practices result in precious resources being wasted on some patients, other patients who genuinely require care, such as the critically ill, are deprived of urgent attention as they contend with long lines, fully-occupied machines and overworked healthcare workers ( ). Thirdly, defensive medicine may delay the adoption of new medical innovations in patient treatment. A study found that 53% of physicians were not keen to implement new technologies due to conscious concern over potential liability ( ). Lastly, even the apparent benefits of defensive medicine can become detrimental. For example, doctors tend to be overly cautious when interpreting mammograms as failure to diagnose breast cancer is a common malpractice allegation. This leads to more false-positive results, which not only increase healthcare costs by 33%, but also cause unnecessary stress to both patient and doctor (1).

Defensive practices also subject patients to additional risks and can worsen their clinical outcomes. Studies have shown that there is a substantial risk of cancer development due to radiation overexposure from defensive CT scan ( ). Additionally, the overuse of antibiotics stemming from defensive medicine could result in the emergence of a multi-drug resistant superbug which could threaten mankind’s survival ( ).

From an economic perspective, defensive medicine inflates healthcare costs on many micro and macro levels. Doctors ordering panels of additional or clinically-unwarranted tests ultimately translate into a greater financial burden for patients ( ). In one case, a patient with a stomach ache was sent immediately for a US$6,500 CT scan ( ).

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She was subsequently found to be suffering from a harmless ovarian cyst, which could have been easily detected if a US$1,400 ultrasound had been ordered initially based on her symptoms. Approximately 25% of annual healthcare costs in America is wasted on unnecessary defensive procedures (7). The estimated annual cost of defensive Cesarean Sections ranges from US$8.7 million to over US$5 billion; and the annual cost of defensive radiologic procedures for young emergency room patients is approximately US$45 million (7,). Collectively, annual estimated defensive medicine costs in America range from US$50 billion to US$850 billion (7, -).

Ultimately, defensive medicine does not augur well for the future of the medical community. It places a huge strain on the doctor-patient relationship. 71% of doctors surveyed felt that practicing defensive medicine caused them to view their patients in a negative light (7). Whilst practicing defensively, doctors also divert much of their focus to filling up paperwork to document their actions, which detracts from their time spent with patients (6). Defensive medicine shifts the practice of medicine from being patient-centered to being test-centered, causing doctors to rely on tests to rule out ailments, rather than focusing on the patient's concerns. This long-term reliance on tests for diagnosis may reduce the astuteness of some doctors, and 57% claim that defensive medicine hampers their professional decision-making ability (7). Another dire concern is that defensive medicine may deter individuals from entering the medical profession, thereby exacerbating the shortage of doctors in certain countries (7).

Despite being a common practice, defensive medicine should not be passively accepted as an inevitable component of the healthcare industry. Some countries have implemented traditional tort reforms, such as reducing the statute of limitations, as a means to protect doctors from litigation (13). Society should also focus on eliminating defensive medical practices through the establishment of an explicit legal standard of basic medical care using clear practice guidelines. Such a standard could be built upon the tenets of the Bolitho and Bolam Tests, where a doctor's actions are in accordance with a responsible body of medical opinion and can withstand logical analysis and scrutiny.

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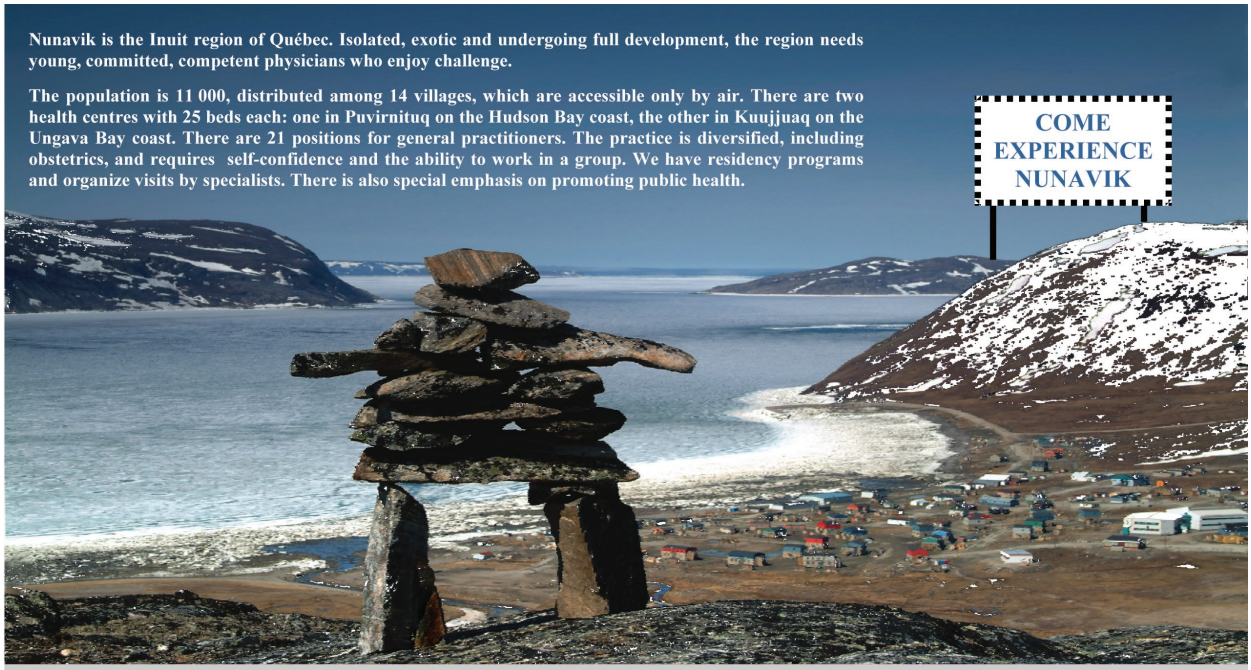

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ORIGINAL ARTICLES

Mortality trends in a Cohort of Canadian Psoriatic Arthritis Patients

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ABSTRACT

Methods: We reviewed retrospectively the charts of psoriatic arthritis patients who died from 1995-2010.We included 13 deceased patients with a psoriatic arthritis diagnosis and compared them with 140 patients living with psoriatic arthritis that attend the same clinic. The population was derived from a single academic rheumatologist's practice in St. John's, Newfoundland, Canada. Patients are seen at six-month intervals with a history and physical exam performed at each visit. Laboratory data was collected at each visit. Diagnosis of psoriatic arthritis is based on the CASPAR Classification and Diagnostic Criteria for Psoriatic Arthritis.

Results: The mean age of the 13 deceased patients was 62.9 years. Of these, 38.5% were female and 85.7% had an erythrocyte sedimentation rate greater than 15 mm/hour vs. 36.4% of patients living with psoriatic arthritis. Of deceased patients, 16% had dystrophic nail changes of vs. 59.6% of living patients. Health Assessment Questionnaire was found to show a significantly greater loss in function in deceased patients. (1.39 vs. 0.70, p= 0.002). Almost half of the deceased patients had used Prednisone (46.2%) as opposed to 11.2% of living patients.

Conclusions: We realize that this study employs a small sample size. Increased ESR and Health Assessment Questionnaire score were found to be associated with mortality in psoriatic arthritis patients. Dystrophic nail changes were found to be protective for psoriatic arthritis patients.

Key Words: Psoriasis, Psoriatic Arthritis, Mortality, Arthritis Epidemiology

INTRODUCTION

Psoriatic arthritis (PsA) is often classified as a seronegative inflammatory spondylarthropathy and affects about 10% of individual affected with psoriasis. PsA occurs at a median of 10 years after the onset of psoriases but 15-20% of PsA patients will develop joint lesions before skin lesions due to psoriases appear (1).

Psoriatic arthritis was once thought to be a milder form of rheumatoid arthritis however many studies have subsequently established that PsA is often aggressive and is associated with various comorbidities and often takes a chronic, progressive course(2).The population of Newfoundland and Labrador, Canada lends itself to the study of PsA because of unique genetic characteristic in this population. Geographic isolation, relative genetic homogeneity and the founder effect lend this population with unique genetic distribution that proves useful in investigation diseases such as PsA compare to admixed Caucasian populations in the world. A significant association between the presence of PsA and a gene named CARD15 has been discovered in a 2003 study by Rahman et al. (OR=2.97, p= 0.0005) (3). There is a paucity of literature that investigates which factors affect mortality in psoriatic arthritis patients

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Table 1. Demographics and family history in deceased PSA vs early and established psa

	Deceased PsA Patients (n=13)	Early & Established PsA Patients (n=140)
Mean Age	55.5 Years	49.7 Years
Sex	61.5% Male 38.5% Female	47.2% Male 52.8% Female
Family History of Psoriasis	25%	27.8%
Family History of Arthritis	38%	55.3%
Family History of Psoriatic Arthritis	7.7%	18.6%

in a Newfoundland and Labrador rheumatology practice.

Incidence of psoriatic arthritis has been estimated to be six per 100,000 adults aged 16 and over in Finland by Kaipiainen-Seppanen and Aho (4) with a mean age of diagnosis of 46.8 years of age. Shbeeb et al (5) conducted a study in Minnesota, USA and considered inflammatory

METHODS

We identified patients in a rheumatology practice in St. John's, Newfoundland & Labrador, Canada with a definite diagnosis of PsA that have died in the period from January 1st 1999 to December 31st 2009. Similarly to Gladman and colleagues, (11,13), the patients that compose both the deceased PsA patients and living patients in this study are treated in a single outpatient clinic.

Patients are seen at six-month intervals with a history and physical exam performed at each period. Further, laboratory data was collected at each visit. Diagnosis of psoriatic arthritis based on the CASPAR Classification and Diagnostic Criteria for Psoriatic Arthritis (14).

Similarly to a study by Khraishi and Murphy, (15) patient death will be ascertained by the following means: review of charts in the arthritis clinic, review of hospital records and death certificates. Further, local newspaper obituary section and contact with family members as well as family physicians will be employed to document patient death.

Basic demographic variables as well as clinical variables relevant to psoriatic arthritis such as nail involvement (pitting or onycholysis), family history of psoriasis, PsA or other arthropathy and presence and severity of psoriasis will be compared in the deceased psoriatic arthritis patients with patients living with psoriatic arthritis in that attended the same clinic. Health Assessment Questionnaire (HAQ) score gives a measure of how debilitating arthritis is in terms of reduced capacity to perform daily activities and will also be assessed. This tool has been validated in use with psoriatic arthritis patients. (16) HAQ is a patient self-assessment scale that ranges from a low of zero to a high of three for high self-perceived disability. In this study, we will investigate the Standard Disability Index portion of the HAQ.

Clinical signs related to psoriatic arthritis that will be evaluated include distal interphalyngeal joint (DIP) involvement, axial skeleton involvement, dystrophic nail changes (nail involvement), asymmetry of joint involvement, oligoarthritis, psoriasis and erythrocyte sedimentation rate. Asymmetry of joint involvement was defined as a difference of more than one in the number of affected joints between contralateral hands and feet. Oligoarthritis was defined as four or fewer joints displaying swelling or tenderness.

Medications that will be investigated include concomitant use of diabetes mellitus and hypertension medication as well as medication for depression or anxiety. The following disease-specific medicationswere investigated: methotrexate, sulfasalizine, prednisone, hydroxychloriquine, calcipotriol, (Dovonex), etanercept (Enbrel), infliximab (Remicade), and adalimumab (Humira). Disease-modifying anti-rheumatic drugs (DMARDS) included defined utilization of one or more of the following medications: methotrexate, sulfasalozine, hydroxychloroquin and plaquenil. The use of biologics includes the use of one or more of the following medications: etanercept, infliximab, and adalimumab.

STATISTICAL METHODS

Proportions for categorical variables will be reported as well as means and standard deviations doe continuous variables analyzed and compared between deceased patients that were diagnosed with PsA and patients living with PsA. Further, an Independent samples T-test will be employed to test

Table 1. Demographics and family history in deceased PSA vs early and established psa

Clinical Sign	Deceased PsA Patients (n=8)	Early & Established PsA Patients (n=140)
DIP Involvement	25%	39.8%
Axial Involvement	13%	19.8%
Axial and Peripheral Involvement	13%	21.2%
Nail Involvement*	38%	59.6%
Asymmetry of Joints	57%	50.4
Oligoarthritis	43%	42.1%
Erythrocyte Sedimentation Rate > 15*	63%	36.4%

Asterisk (*) represents a statistically significant difference at p= 0.05.
Erythrocyte sedimentation rate over 15 was significantly more prevalent in decreased PsA patients (63%) than in early and established

for statistically significant differences in continuous variables between deceased patients with PsA and patients living with PsA.

The Chi-square statistic was used to detect associations between mortality and medication use, presence of comorbidities as well as clinical features of PsA. Fisher's exact test was employed in the case of low numbers. For all analyses, the minimum level of statistical significance, is 0.05, determined a priori. All statistical analyses were performed using SPSS version 15.0 for Windows (SPSS Inc.).

RESULTS

There were statistically significant differences between prevalence of hematological comorbidities between deceased patients and patients living with PsA. (38% vs. 8.3%, p= 0.033). Of these, the most common hematological comorbidity in both groups was anemia. In a review by Gabriel and Michaud, anemia was found to be a comorbid condition commonly found with Rheumatoid arthritis as well. Musculoskeletal comorbidies were very common in both deceased patients and patients living with PsA (50% and 57.6%).

Psoriasis is part of the criteria for diagnosing psoriatic arthritis (83% of deceased patients and 95.1% of patients living with PsA).

Not surprisingly, there was a greater proportion of deceased psoriatic arthritis patients with malignancy than those with early and established diseased. Specifically, Bowel cancer (13% vs 0.7%), breast cancer (0% vs 1.4%), lymphoma (25% vs 0.7%), other cancers (13% vs 5.6%) and total proportion of patients with a malignancy (38% vs 7.6%). Of those, only the total number of malignancies was statistically significant at a= 0.05.

When comparing medications between patients with early and established disease, the only medications that were shown to be statistically significantly higher in use in early and established patients was Prednisone. (p = 0.011). Other mediations investigated including methotrexzte, Enbrel, Remicade, Sulfasalazine, Hydroxychloroin, Humira, were not found to be used in a different amount between the early & established and mortality.

Neither a family history of psoriasis (p = 0.864), psoriatic arthritis (p= 0.180) or other type of arthritis (p= 0.464). In terms of clinical features characteristic for psoriatic arthritis, there was a statistically significant increase in the proportion of deceased patient with an ESR greater than 15 mm/hour in deceased patients and a statistically significant decreases proportion of nail involvement in deceased patients.

Other clinical signs of psoriatic arthritis were not found to have a statistically significant prevalence in the two groups investigated including axial involvement (p= 0.611), distal interphalangeal joint involvement (p= 0.482), asymmetrical joint distribution (p = 0.699), oligoarthritis (p= 0.441).

DISCUSSION

Though cardiovascular comorbidities have been specifically implicated in rheumatoid arthritis patients and indeed a major source of their increased mortality, prevalence of cardiovascular comorbidities is not significantly elevated in either group of PsA patients in this study.

When we compared the following continuous variables ages, age at diagnosis of PsA and diagnosis of psoriasis, most recent Health Assessment Questionnaire score (HAQ) , systolic

Table 3. Comorbidities in deceased versus early and established Psoriatic Arthritis

Comorbidity	Deceased PsA Patients (n=13)	Early & Established PsA Patients (n=140)
Hypertension	38%	32.6%
Psoriasis	83%	95.1%
Coronary Heart Disease	13%	4.2%
Musculoskeletal History	50%	57.6%
Gastrointestinal History	38%	45.8%
Angina	0%	0%
TIA	0%	0.7%
Respiratory System History	13%	20.8%
Obesity	38%	47.2%
Thyroid Disease	13%	4.2%
Peripheral Vascular Disease	0%	11.8%
Hepatobiliary System History	25%	16.0%
Peptic Ulcer	13%	4.9%
Hematological-Lymphatic History*	38%	8.3%
Cardiovascular System History No cardiovascular comorbidities	87%	91.5%
Cardiovascular System History One cardiovascular comorbidities	0%	6.4%
Cardiovascular System History Two or more cardiovascular comorbidities	13%	2.1%

Asterisk (*) represents a statistically significant difference at p= 0.05.

blood pressure, erythrocyte sedimentation rate (ESR) and total number of tender joints between deceased PsA patients to those defined with early or established PsA, we found HAQ score and ESR to have statistically significant associations with mortality. The deceased patients with PsA had a significantly higher HAQ score than patients still living with PsA: 1.47 vs. 0.70 (p = 0.014). The eight equally-weighted areas of the HAQ are difficulty in everyday activities, arising, dressing & grooming, eating, grip, performing activities related to hygiene, reach and walking.

Since ESR is a non-specific marker for inflammation, ESR may be related to severity of this seronegative inflammatory condition. The mean ESR of 84.6mm/hour for deceased PsA patients vs. 20.6mm/jour for patients living with PsA is significant. (p = 0.021) This is similar to a study by Gladman et al, (11) which found that ESR > 15mm/hour had value in predicting mortality of PsA patients. When ESR was categorized as such in this study, there was a significant association between mortality and ESR status in PsA patients. (p = 0.013)

Beside erythrocyte sedimentation rate, presence of nail lesions (pitting or onchylysis) seems to be the only other statistically significant clinical variable. Similarly to Gladman et al (2), we discovered that a higher proportion of patients living with PsA that deceased patients that were diagnosed with PsA had nail involvement (59.6% vs. 38%, p= 0.013), this acts as a protective factor against mortality in PsA patients. This may be because the presence of nail involvement may cause patients to seek treatment earlier in the course of their disease.

There was no statistically significant difference in the proportions of prescribed non-PsA (concomitant) medication between deceased patients and those living with PsA. Methotrexate is the most commonly-prescribed DMARD in both groups and was prescribed to 38% of deceased PsA patients and 28% of patients with established PsA (Table 4). Prednisone was found to be

Table 4. Quantitative data in deceased PSA patients vs early & established PSA

Quantitative Variable	Deceased PsA Patients (n=13)	Early & Established PsA Patients (n=140)
Age as of December 31, 2009 or Age at Death	55.50 Years	49.67 Years
Age of Diagnosis Psoriasis	31.75 Years	35.70 Years
Age of Diagnosis Psoriatic Arthritis	47.00 Years	44.78 Years
Systolic Blood Pressure	134.14 mmHg	126.58 mmHg
Erythrocyte Sedimentation Rate *	84.60 mm/hour	20.62 mm/hour
Total Tender Joints	5.00	7.42
Health Assessment Questionnaire*	1.4725	.6968

Asterisk (*) represents a statistically significant difference at p= 0.05.

statistically associated with morality in PsA patients (p= 0.011) as 50% of deceased patients had been prescribed Prednisone while only 11.2% of patients living with PsA enrolled at the same rheumatology clinic were using Prednisone. Further, use of any DMARDS was found be to significantly associated with mortality in PsA patients (p = 0.007). When we removed patients that had been treated with prednisone from our analysis, we found that results were not significant p= 0.121.

For each of the individual malignancies of breast cancer, bowel cancer and lymphoma, there was no statistically significant difference between the prevalence of these comorbidities in the two groups. However, when the proportion (Table 4) of patients with any type of malignancy was compared between patients with early and established PsA and deceased patients with PsA, we found that a significantly greater proportion of deceased patients suffer from at least one malignancy (38% vs. 7.6%, p= 0.027) We found no statistically significant relationship between rheumatoid factor and positive history of cardiovascular events in PsA patients.

CONCLUSION

The presence of at least one malignancy was found to be related to increased likelihood of mortality in PsA patients though a relationship between particular cancers and mortality could not be ascertained. Moreover, use of DMARDS was also found to b statistically associated with mortality in PsA patients. Specifically, the use of Prednisone as found to be associated with mortality in PsA patients. Further, increased ESR and the absence of dystrophic nail changes are associated with mortality in PsA patients.

LIMITATIONS

We understand that it may be difficult to apply conclusions for these results to all who suffer from psoriatic arthritis since the information is relevant to individuals that have been treated at a clinic; milder cases of psoriatic arthritis may be missed.

Further, the relatively small sample size of deceased psoriatic arthritis patients makes it difficult to properly interpret results from this group.

Since all patients from this study are seen in an outpatient clinic, we the results may show greater overall morbidity and mortality that in PsA in the general population that may be so mild as to go undetected or not require medical attention.

As a cross-sectional study, this study does not support inferences in causality. That is, though we can say that specific comorbidities and medications are associated with mortality in PsA patients, we cannot ascertain whether or not these characteristics cause an increased risk of death from PsA or whether these patients were sicker on the whole and therefore needed numerous disease-specific drugs.

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