Considering Sex and Gender in Therapeutics throughout the Product Life Cycle: A Narrative Review and Case Study of Gilteritinib

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ABSTRACT

Background: Biological sex–related factors influence pharmacokinetic, pharmacodynamic, and disease processes that may affect the predictability of drug dosing and adverse effects, which may in turn have clinical consequences for patients' lives. Nonetheless, sex-related factors are not always taken into account in clinical trial design or clinical decision-making, for multiple reasons, including a paucity of studies that clearly and objectively study and measure sex-disaggregated and sex-related outcomes, as well as gaps in regulatory and policy structures for integrating these considerations.

Objectives: To complete a narrative review and use a case study to understand available evidence, inform future research, and provide policy considerations that incorporate information on sex- and gender-related factors into clinician-facing resources.

Methods: A comprehensive review of available literature was conducted using a sex- and gender-based analysis plus (SGBA Plus) approach to identify sex- and/or gender-disaggregated information for gilteritinib, a chemotherapeutic agent. Systematic searches were performed in MEDLINE (Ovid), Embase (Ovid), CENTRAL (Wiley), International Pharmaceutical Abstracts (Ovid), Scopus, and ClinicalTrials.gov, from inception to March 18, 2021. The information was then summarized and compared with the Canadian product monograph for this drug.

Results: Of 311 records screened, 3 provided SGBA Plus information as a component of outcomes, rather than just as categories or demographic characteristics. Of these, 2 were case studies, and 1 was a clinical trial. No studies from the ClinicalTrials.gov database that were in progress at the time of this review provided details about sex-disaggregated outcomes. The Canadian product monograph did not include sex-disaggregated outcome data.

Conclusions: The available evidence from clinical trials, other published literature, and guidance documents does not provide details about sex-disaggregated outcomes for gilteritinib. This paucity of available evidence may create a challenge for clinicians who are making decisions about the efficacy and safety of prescribed therapies in sex-specific populations that have not been well studied.

Keywords: sex-related factors, oncology, knowledge translation, sex- and gender-based analysis Plus (SGBA Plus, SGBA+), drug management

RÉSUMÉ

Contexte : Les facteurs liés au sexe biologique influencent les processus pharmacocinétiques, pharmacodynamiques et pathologiques, qui peuvent avoir une incidence sur la prévisibilité du dosage des médicaments et des effets indésirables. Ceci peut à son tour avoir des conséquences cliniques sur la vie des patients. Néanmoins, les facteurs liés au sexe ne sont pas toujours pris en compte dans la conception des essais cliniques ou la prise de décision clinique, et cela pour de nombreuses raisons – notamment le manque d'études qui examinent et mesurent clairement et objectivement les résultats ventilés par sexe et liés au sexe ainsi que les lacunes dans les réglementations et structures politiques pour intégrer ces considérations.

Objectifs : Mener un examen narratif et utiliser une étude de cas pour comprendre les preuves disponibles, éclairer les recherches futures et fournir des considérations politiques qui intègrent des informations sur les facteurs liés au sexe et au genre dans les ressources destinées aux cliniciens.

Méthodes : Une revue complète de la littérature disponible a été réalisée à l'aide d'une analyse comparative fondée sur le sexe et le genre Plus (ACSG Plus) pour identifier les informations ventilées par sexe et/ou par genre pour le giltéritinib, un agent chimiothérapeutique. Des recherches systématiques ont été effectuées dans MEDLINE (Ovid), Embase (Ovid), CENTRAL (Wiley), International Pharmaceutical Abstracts (Ovid), Scopus et ClinicalTrials.gov, depuis la création de chaque base de données jusqu'au 18 mars 2021. Ces informations ont ensuite été résumées et comparées avec la monographie canadienne de produit pharmaceutique pour ce médicament.

Résultats : Sur les 311 documents examinés, 3 ont fourni des informations ACSG Plus en tant que composante des résultats, plutôt que simplement en tant que catégories ou caractéristiques démographiques. Parmi ceux-ci, 2 étaient des études de cas et 1 était un essai clinique. Aucune étude de la base de données ClinicalTrials.gov en cours au moment de cette revue n'a fourni de détails sur les résultats ventilés par sexe. La monographie de produit canadienne ne comprenait pas de données sur les résultats ventilées par sexe.

Conclusions : Les preuves disponibles issues d'essais cliniques, d'autres publications et de documents d'orientation ne fournissent pas de détails sur les résultats ventilés par sexe pour le giltéritinib. Ce manque d'éléments probants disponibles peut constituer un défi pour les cliniciens qui prennent des décisions sur l'efficacité et l'innocuité des thérapies prescrites chez des populations sexospécifiques qui n'ont pas été bien étudiées.

Mots-clés : facteurs liés au sexe, oncologie, application des connaissances, analyse comparative fondée sur le sexe et le genre Plus (ACSG Plus, ACSG+), gestion des médicaments

INTRODUCTION

There is evidence that biological sex-related factors influence pharmacokinetics, pharmacodynamics, disease processes, and response to therapeutic agents.[1] More specifically, pharmacokinetic and pharmacodynamic evidence shows sex-related biological variations in gastrointestinal motility, gastric pH, and enzymatic activity, which can affect the absorption and bioavailability of oral medications.[1] Examples of therapeutic variability by sex include reduced absorption of metoprolol and verapamil due to prolonged gastrointestinal transit time for females relative to males and reduced renal clearance of some antimicrobials, such as fluoroquinolones and cephalosporins, in females relative to males.[1]

Furthermore, a relationship between sex and drug metabolism exists for most of the major cytochrome P450 (CYP450) enzymes. Cytochrome P450 isozymes, such as CYP1A2, CYP2C9, CYP2C19, and CYP2D6, appear to be more active in males, whereas CYP3A4 is more active in females.[2] This difference is important to consider, given that CYP3A4 is the major CYP450 isozyme in the gastrointestinal tract and liver[2] and that it is responsible for the metabolism of more than half of all medicines, including oncology medications such as gilteritinib.[3] These processes are highly relevant to investigating molecular features that may act as drivers in various types of cancer.[4]

A component of understanding the effect of sex and gender on therapeutics is assessing the effect of a medication's efficacy and safety on clinical outcomes and the effect of biological sex on disease distribution. In the case of leukemia, for which gilteritinib is predominantly studied, the biological sex of an individual confers a risk for development of disease with an excess risk of acute myeloid leukemia (AML) in males who are very young or elderly and a U-shaped distribution of sex-related differences in the epidemiologic presentation.[5] Studies have shown that sex-specific mutations, such as the *fms*-like tyrosine kinase 3 internal tandem duplication (*FLT3*-ITD), and other important marker mutations may be overexpressed in females.[6,7] *FLT3* is the target for agents such as gilteritinib. A recent study examined 4 patient cohorts, focusing on sex and *FLT3* mutation status in the sex differences related to clinical parameters.[6] Multiple allelic mutations and variations may be associated with drug sensitivity and survival, with sex-associated molecular differences being prevalent in the AML population with *FLT3*-ITD mutations.[7] Based on this evidence, it is likely that sex-specific considerations could potentially affect prognostication, prediction, and therapeutic strategies in AML.[7]

Despite this knowledge, sex-related factors are not often taken into account in clinical trial design or clinical decision-making, in part because of the paucity of studies that clearly and objectively measure a range of sex-related outcomes. Furthermore, the lack of available evidence regarding the effect of sex- and/or gender-related factors on therapeutics limits clinicians' ability to determine whether differences in pharmacokinetic properties lead to significant effects on clinical factors such as drug efficacy and safety. A lack of evidence pertaining to sex- or gender-related factors in a tertiary reference, such as a product monograph, can prevent a clinician from accurately applying evidence to all patients. The clinician may often have to depend on the experts who synthesize the evidence into a usable tertiary reference to assist in constructing sex- and/or gender-related interpretations. Key questions that clinicians might ask of tertiary references that could affect their interpretation of the reference include the following:

- Was sex-related outcome information collected in the conduct of preclinical and clinical trials or in other literature that informs the tertiary reference being used for clinical decision-making?
- Has such information on sex-related outcomes been reviewed in the knowledge synthesis process, and if so, has it been determined nonsignificant to the clinical decision-making process?

In the current review, we applied these questions to the pharmacist's role in caring for patients with cancer. The pharmacist is often involved with reviewing medication regimens, educating patients and caregivers about therapies, titrating dosages, monitoring, mitigating drug interactions and drug–disease interactions, and providing information and education to members of the health care team about medications used in cancer care.[8] To make the best clinical decisions, pharmacists reviewing oncology medication regimens require information about various target populations, such as males and females with reproductive potential; pregnant, lactating, pediatric, or geriatric populations; racialized/ethnic groups; gender-diverse individuals; or other underresearched populations. However, if sex-related information was not considered, other than descriptive statistics based on demographic characteristics in trials,[9] then the full understanding and effect of sex-related factors on different aspects of therapeutics, such as adverse effects or therapeutic efficacy, may be limited. It is important to note a paucity in the primary literature itself that may lead to a different interpretation of the strength of the evidence informing the knowledge synthesis in a product monograph.

To gather further evidence about the inclusion of sex and gender in therapeutic interpretation, we conducted a comprehensive review of available literature using a sex- and gender-based analysis plus (SGBA Plus) approach to identify evidence related to sex and gender in the life cycle of a prescription drug, which includes premarketing, clinical trial, review and approvals, and postmarketing pharmacovigilance phases. In our review, sex- and/or gender-disaggregated information incorporates sex as a biological variable and gender as a sociocultural variable.[10]

The SGBA Plus approach involves assessing data, policies, and/or programs for differential effects on diverse groups of females, males, men, women, and gender-diverse people. Gilteritinib was selected to understand how SGBA Plus has been integrated into the assessment of a recently approved drug in Canada. This review summarizes published literature and clinical trials related to gilteritinib that discuss sex-, gender-, or equity-related factors; it also provides details on various sex-related outcomes defined a priori. We compared this with public information from Health Canada, including the available contents of the drug product monograph in the Drug Product Database. Drawing upon our findings, we make recommendations for future research and policy considerations that incorporate SGBA Plus into clinician-facing resources, such as product monographs.

METHODS

Search Strategy

A search of the literature was completed to identify potentially relevant studies. An experienced health sciences librarian (M.-L.L.) designed the search, using a combination of subject terms and keywords, which was then translated for each database. Systematic searches were performed in MEDLINE (Ovid), Embase (Ovid), CENTRAL (Wiley), International Pharmaceutical Abstracts (Ovid), Scopus, and ClinicalTrials.gov, from inception to March 18, 2021. The MEDLINE search can be found in Appendix 1 (available from https://www.cjhp-online.ca/index.php/cjhp/issue/view/215), and all strategies are available upon request to the corresponding author. Identified studies were deduplicated in EndNote (version X9). Studies were indexed in COVIDENCE for review by a single individual (M.M.). A secondary search of the ClinicalTrials.gov database was performed on July 15, 2021, to ensure that all clinical trials still in progress and those that had begun since March 2021 were considered for inclusion. Screening of this literature was performed by the same reviewer.

Inclusion Criteria

Literature on clinical trials review, submission review, monitoring, intervention, and pharmacovigilance studies was included. All study designs (case–control, case report, case series, cohort studies, cross-sectional studies, correlational studies, interrupted time series, mixed methods, qualitative, randomized trials, and systematic reviews or meta-analyses, where the primary focus is on an aspect of the life-cycle management of drugs) were considered, as were in-progress studies indexed in the ClinicalTrials.gov database that included sex-disaggregated outcomes defined a priori. Pharmacokinetic and pharmacodynamic trials with SGBA Plus commentary, as well as phase 1, 2, or 3 and postmarketing trials that included SGBA Plus commentary, were also included.

Exclusion Criteria

The following materials were excluded: literature focused primarily on cost, budget, or cost analysis; abstracts that did not specifically mention gilteritinib; book chapters; in vitro trials; conference abstracts, presentations, and posters; editorials, commentaries, perspective articles, and opinion pieces; literature focused primarily on the theory behind mechanisms of action; studies that did not include sex, gender, or SGBA Plus commentary; clinical trial protocols that did not describe a focus on sex-disaggregated outcomes (outcomes related to males, females, women, men, sex, gender, pregnancy, lactation analysis of sex-related factors, or information related to gender); and studies unavailable in the English language.

RESULTS

After removal of duplicates, there were 311 unique studies, for which titles and abstracts were screened against the exclusion criteria. Of these, 187 were excluded for various reasons (see Figure 1). The remaining 124 studies underwent full-text review, which resulted in exclusion of an additional 121 articles (see Figure 1).

Therefore, of all articles screened, only 3 included information related to sex as a component of outcomes, rather than just as categories or demographic characteristics, and none included information regarding gender. Figure 1 incorporates the PRISMA diagram for the case study search process. None of the studies from the ClinicalTrials.gov database that were enrolling participants at the time of the initial search provided details about sex-disaggregated outcomes, and the secondary search of this database, performed on July 15, 2021, yielded only 3 additional trials, none of which met the inclusion criteria.

SGBA Plus Literature Review of Gilteritinib

Of the 3 included studies, one was a case report of acute macular neuroretinopathy associated with gilteritinib in a 28-year-old female, with improvement in the scotoma and optical coherence tomography 3 months after gilteritinib was switched to azacitidine and midostaurin.[11] Another case report described Sweet syndrome in a 55-year-old female who presented with neutrophilic dermatosis after 4 weeks of gilteritinib therapy for AML.[12] The patient was started on prednisone but experienced flare with tapering. The gilteritinib was eventually stopped because of nonresponse and the drug's potential contribution to the Sweet syndrome flare. The patient died shortly afterward, secondary to disease progression and complications of sepsis.[12] The third included study aimed to investigate the clinical benefit of gilteritinib in the treatment of relapsed or refractory *FLT3*-mutated AML in a randomized trial comparing gilteritinib with conventional salvage chemotherapy regimens, also known as the ADMIRAL trial.[13] In the ADMIRAL trial,

females accounted for 53% of participants in the gilteritinib arm and 56.5% in the salvage chemotherapy arm. An analysis of overall survival looked at sex-disaggregated outcomes related to the hazard ratio for death between gilteritinib and salvage chemotherapy, based on the number of events relative to the total number of patients enrolled in each arm. The findings showed that males in the gilteritinib arm experienced fewer events than males in the chemotherapy arm, but this result was not statistically significant. Similarly, females in the gilteritinib arm experienced fewer events than females in the chemotherapy arm, with this being a statistically significant outcome. Reported adverse events and response to therapy were not sex-disaggregated. We reviewed the supplementary material for any further outcome data that were sex-related but found none.

SGBA Plus of the Product Monograph

The overall project (from which the current article is derived) is described in a report entitled *Risk Reviewed: Integrating Sex and Gender into the Lifecycle Management of Prescription Drugs*.[14] The project reviewed the processes for approval, regulation, and monitoring of prescription drugs in Canada, with a view to understanding how sex- and gender-related factors are considered in their life-cycle

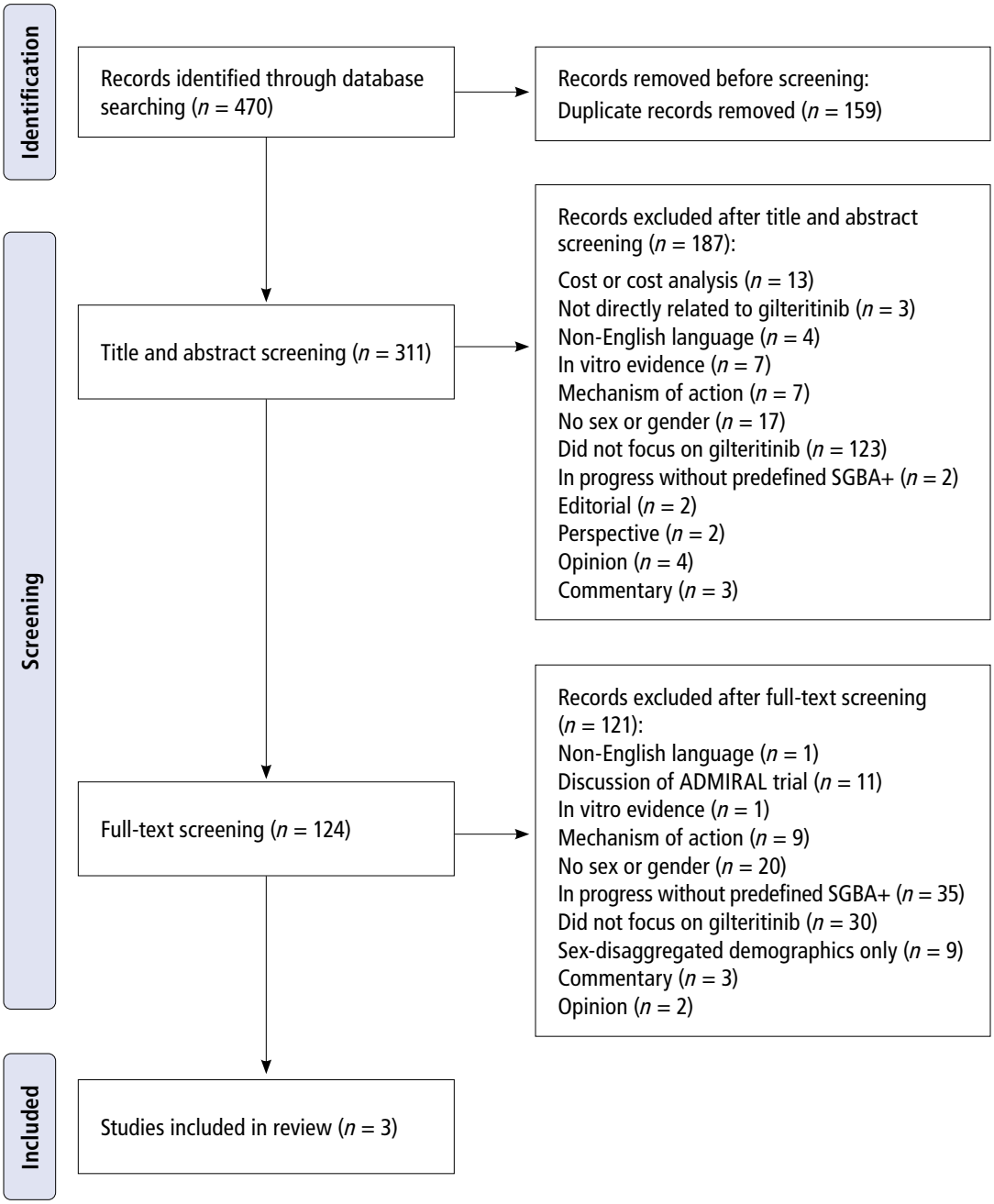

FIGURE 1. PRISMA diagram for case study. SGBA+ = sex- and gender-based analysis Plus approach.

management. A component of this project focused on a case study of gilteritinib, for which a review of the product monograph was conducted.

The product monograph is a resource that is commonly accessed by clinicians. A survey of Quebec community and hospital pharmacists in 1987 indicated that the *Compendium of Pharmaceuticals and Specialties* (*CPS*), which contains Canadian product monographs, was one of the resources most frequently found in community and hospital pharmacies.[15] A 2014 study intended to identify how clinicians obtain information about dry mouth in pharmaceutical products included the *CPS* in the referenced databases, and the authors of the study noted that at least 40% of medication monographs were included in this resource.[16] Finally, the Canadian Drug Product Database, which includes medications authorized for sale by Health Canada, is a comprehensive and freely accessible database of product monographs, which clinicians can use as a tertiary reference for drug information related to medications, such as gilteritinib. We assessed this popular resource for the present case study of gilteritinib, and areas where information was present, absent, or unclear are discussed below.

General Sex-Based Considerations

The product monograph for gilteritinib[17] includes data from the ADMIRAL study. Sex was mentioned as a demographic descriptor, with the monograph noting that 47.0 % of participants were male and 53.0% female in the gilteritinib arm versus 43.5% male and 56.5% female in the chemotherapy arm. However, sex-disaggregated outcomes and further SGBA Plus analyses were not provided. The sex-disaggregated outcomes from the ADMIRAL trial, noted above, were not discussed in the monograph.[17]

Evidence for Pregnancy and Lactation

The sections of the product monograph that discuss pregnancy and lactation note that there is no available evidence regarding human pregnancy or human milk, the drug-associated risk of adverse developmental outcome(s), or pharmacokinetics/pharmacodynamics. However, the monograph includes some data from animal studies, in which administration of gilteritinib to pregnant rats caused embryo and fetal deaths and suppressed fetal growth at exposures below the exposure that occurs in patients receiving the recommended dose based on the nonclinical toxicology section[17]; in addition, gilteritinib and/or its metabolite(s) were distributed to the tissues of infant rats through the dams' milk. On the basis of these animal data, the monograph concludes that because of the potential for fetal and offspring exposure to gilteritinib and serious adverse reactions, this agent is to be avoided in pregnancy and lactation. Although the product monograph provides important safety parameters recommending against use of the drug in pregnancy and lactation, supporting references for the chosen timeline for avoidance of pregnancy or breastfeeding after cessation of gilteritinib are not provided.

Patient Information

The section of the monograph dealing with patient medication information mentioned that use of effective birth control is needed while taking gilteritinib and for 6 months after stopping this medication; however, there was no mention of why 6 months is the chosen timeline. This section did suggest that male patients should use condoms during sex while under treatment and for 4 months after stopping gilteritinib. Again, although the information in the product monograph provided parameters for safety, there was no explanation for the timelines chosen.

DISCUSSION

A range of pharmacokinetic and pharmacodynamic sex-related factors support an argument for ensuring that manufacturers consider and include information regarding the efficacy, safety, and tolerability of medications and that regulators apply a comprehensive SGBA Plus approach during approval processes for prescription drugs. For example, according to the product monograph for gilteritinib, this agent can be administered with or without food; however, concomitant food intake delays absorption. Considering sex differences in absorption of medications, the difference in delayed absorption with food may be more significant in females; however, sex-disaggregated data are unavailable to support or refute this hypothesis. Furthermore, according to the pharmacokinetic profile of gilteritinib, this drug is primarily metabolized through the CYP3A4 isozyme.[17] Hence, sex-related considerations regarding drug interactions and metabolism should be taken into account in sex-disaggregated outcomes and in product information.

Despite Canadian guidance documents, such as *Considerations for Inclusion of Women in Clinical Trials and Analysis of Sex Differences*,[18] the availability of evidence from clinical trials to allow an analysis on sex-related factors is limited. Most clinical trial designs are limited to recording and reporting participant sex simply as a demographic characteristic. Indeed, some of the studies excluded from our review reported the sex of participants without further analyses regarding outcomes. If sex is not considered as a category of analysis, sex-disaggregated outcomes cannot be provided in the published literature. Similarly, none of the studies indexed in the ClinicalTrials.gov database had a prior plan for analyses that include sex disaggregation of the outcomes or any other sex-related factors, such as those involved in the pharmacokinetic/pharmacodynamic processes related to the cytochrome P450 pathway. Our review of the literature yielded only 3 studies providing sex-disaggregated outcomes: 2 case reports of adverse drug events in female patients and a large, randomized trial (the

ADMIRAL study). Although case reports do not provide amalgamated evidence on trends for efficacy and safety, each one adds to the available evidence for whether sex-related factors matter in postmarket use of a drug and can potentially inspire questions for assessment through post-marketing pharmacovigilance.

Although a policy of the National Institutes of Health (US) requires the inclusion of women and minorities as participants in clinical research[19] and provides information on how to report results and conduct subgroup analyses based on sex, only 1 clinical trial identified in our search met the inclusion criteria for this review. The other included studies were case reports of adverse reactions. Furthermore, stratification of most outcomes by sex was not presented in either the ADMIRAL study or its supplementary material, creating a void of information regarding the potential effect on clinical decision-making. Whether or not the outcomes were statistically significant, the information might have been clinically significant. This paucity makes it even more important for regulators to ask for such data in submission review processes.

For clinician-facing resources, such as product monographs,[17] information related to sex-disaggregated outcomes is typically not available, nor are references to the primary literature listed in the monographs, which prevents further review by pharmacists, physicians, other health care professionals, and research scientists. Although the recommendations set forth in the monograph for gilteritinib may be reasonable in terms of the risk associated with an oncology medication in females and males with reproductive potential, the primary references are not provided. In practice, recommendations about the use of medications in special populations, such as patients who are pregnant or breastfeeding, are usually based on expert opinion informed by available pharmacokinetic data and evidence extrapolated from animal models. Including such references in the product monograph could help clinicians in better understanding and providing clinical support regarding the evidence about fertility, pregnancy, and lactation to patients with reproductive potential who are being considered for therapy with gilteritinib.

Limitations

The literature was systematically reviewed by a single pharmacist reviewer. In addition, the literature about gilteritinib could be indexed under a different name (such as a preclinical drug reference name), and such information might not have been found in our search. The lack of referencing in the product monograph limited our ability to cross-reference information in the monograph with any further relevant studies. Lastly, grey literature (unpublished reports, conference abstracts, theses or dissertations, preprint servers, and other internet or print reports and resources)[20] was used for context, but was not examined in detail in this review because of our focus on acquiring evidence for sex- and gender-related outcome measures in the published literature that would be considered by regulatory bodies for purposes of evaluation and eligibility for marketing.

Recommendations

On the basis of our review of the literature and information available in the product monograph for gilteritinib,[17] we make the following recommendations to Health Canada for its consideration of SGBA Plus in the drug approval process for this drug and others:

- Require that product monographs include references for recommendations and supporting studies.
- Note the paucity of evidence related to sex-disaggregated data in the primary literature used to support the review and approval processes for the medication.
- State possible effects based on general pharmacokinetic and pharmacodynamic considerations, where available.
- Clarify whether sex-disaggregated outcomes are present or absent for a medication.
- Require that manufacturers submit information related to SGBA Plus to the regulator.
- Provide a section on the Health Canada website where SGBA Plus commentary for approved medications can be accessed, to improve review processes by scientists, clinicians, and interested consumers.

CONCLUSION

Although a growing body of knowledge illustrates the importance of understanding and incorporating sex-related pharmacokinetic and pharmacodynamic factors into clinical decision-making related to drug therapies, evidence from clinical trials, research literature, and guidance documents does not typically integrate this knowledge or provide details about sex-disaggregated outcomes. This situation results in a paucity of available data regarding sex-related outcomes in the primary literature. The emblematic case study summarized here illustrates this paucity for a specific medication and the subsequent lack of SGBA Plus analyses that can potentiate suboptimal prescribing or differences in drug efficacy and safety, where sex- or gender-based differences exist for certain medications. An SGBA Plus review of other medications would provide further evidence of the generalizability of our conclusions. Drug regulators could make changes to assist in the clinical interpretation of drug monographs, to facilitate more sex-sensitive and sex-specific care and treatment.

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