



Exploring Biologic Treatment Hesitancy Among Black and Indigenous Populations in Canada: a Review

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Received: 9 August 2021 / Revised: 9 March 2022 / Accepted: 9 March 2022
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Abstract

Biologics are becoming an increasingly important part of patient care across Canada. Recent studies from the USA show that Black patients are less likely than White patients to receive biologic treatment for several medical conditions. The relative lack of race-based data in Canada makes it difficult to replicate such studies in Canada. As a result, there is a paucity of literature that explores the association between biologic usage and race in Canada. Our review aims to explore the factors that might be driving racial treatment disparity in Canada that likely parallels the inequalities found in the USA. We provide a summary of the available literature on the factors that contribute to biologic treatment hesitancy among Black and Indigenous populations in Canada. We highlight several solutions that have been proposed in the literature to address biologic treatment hesitancy. Our review found that biologic treatment decision at the individual level can be very complex as patient's decisions are influenced by social inputs from family and trusted community members, biologic-related factors (negative injection experience, fear of needles, formulation, and unfamiliarity), cultural tenets (beliefs, values, perception of illness), and historical and systemic factors (past research injustices, socioeconomic status, patient–physician relationship, clinical trial representation). Some proposed solutions to address biologic treatment hesitancy among Black and Indigenous populations include increasing the number of Black and Indigenous researchers involved in and leading clinical trials, formally training physicians and healthcare workers to deliver culturally competent care, and eliminating financial barriers to accessing medications. Further research is needed to characterize and address race-based new treatment inequalities and hesitancy in Canada.

Keywords Racialized · Biologics · Hesitancy · Canada · Race-based health data · Clinical trials · African Canadians · Indigenous

Introduction

Recent advances in molecular immunology have led to the development of new monoclonal antibody-based drugs called biologics. Biologic medicines include therapeutic proteins, DNA vaccines, and fusion proteins. Due to the large size, poor oral absorbability, and stability in the gastrointestinal tract, biologics are administered by injection,

inhalation, or infusion [1]. These drugs have revolutionized how health professionals treat patients with autoimmune and inflammatory diseases [2]. Currently, more than 350 biologic medicines have been brought to market [3]. Sales of biologic medicines in Canada have tripled over the last decade, reaching a high of \$7.7B in 2018 [4].

Biologics offer the opportunity for targeted medical therapy and have a significant clinical impact on the management of a wide variety of diseases including inflammatory bowel disease, dyslipidemia, psoriasis, rheumatoid arthritis, osteoporosis, and asthma. Biologics have been shown to decrease the need for bowel resection in patients with inflammatory bowel disease [5] and significantly slow disease progression by reducing pain, swelling, and joint damage in patients with rheumatoid arthritis [6]. Despite the rapidly growing number of efficacious biologic therapeutics, studies from the USA show that Black patients are less likely than White patients to

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receive biologic treatment for several medical conditions [7]. A study of rheumatoid arthritis patients in California highlighted that African Americans were found to have 53% lower odds of receiving disease-modifying anti-rheumatic drugs (DMARDs) compared to White patients [8]. Another study found that Black patients with moderate-to-severe psoriasis were 70% less likely to receive biologics than White patients [9]. In addition, Black patients often present with worse disease severity [10]. As such, the difference in autoimmune and inflammatory disease prevalence between Whites and Blacks can only account for some of the disparity in biologic usage. The disproportionately lower use of biologics among Black individuals is posited to be due to the greater level of unfamiliarity with biologics, relative high cost of biologics, preference to avoid needles, and an apprehension of side effects among Black patients compared with Whites [7].

There are important differences between healthcare delivery in Canada and the USA. Compared to the US system, the Canadian system has universal access to healthcare without significant financial barriers [11]. This limits the generalization of the findings from the American studies on the disparity in biologics usage among Whites and Blacks to Canada. However, Canada's healthcare system does not include universal coverage for prescription drugs. Prescription drugs in Canada are funded by a fragmented network of public and private drug plans that vary across provinces and leave many Canadians with inadequate coverage [12]. Most public and private plans require patients to pay deductibles and co-pays on prescribed medications which become barriers for low-income patients. It is reasonable to assume the findings from the USA related to cost and access are applicable here in Canada.

The relative lack of race-based data in Canada makes it challenging to track and address race-based inequalities across health outcomes [13]. As a result of this poor infrastructure, there is a paucity of literature that explores the association between biologic usage and race in Canada.

Objective

Our review aims to summarize the multifactorial facets that contribute to biologic treatment hesitancy among racialized populations in Canada, with a focus on Black and Indigenous populations. We seek to describe any reported interventions and suggest recommendations to address new treatment hesitancy in a culturally sensitive context. This overview is summarized in Fig. 1.

Methods

A literature search was conducted in PubMed, Google Scholar, and ScienceDirect databases for articles written in English. Search terms included “biologics,” “biological

product,” “treatment disparity,” “hesitancy,” “racial differences,” “ethnic groups,” “patient preference,” and “new medication hesitancy.” To identify further sources, the bibliography sections of each retrieved article were also followed. Lastly, published books, government webpages, and other forms of gray literature were scanned to provide more contexts on this topic. There were no date restrictions. However, preference was given to articles published before the COVID-19 outbreak to exclude the plethora of commentaries on vaccine hesitancy that flooded the scientific literature during the pandemic.

While the lack of a systematic search strategy may be a limitation of this review, the laxity enabled us to synthesize the complex and multifaceted aspects of treatment hesitancy into a coherent summary.

Treatment Hesitancy: Definition and Overview

Treatment hesitancy, like vaccine hesitancy, can be defined as the delay in acceptance or refusal of a form of medical treatment despite it being indicated for one's condition [14]. Healthcare outcomes depend upon patients' adherence to recommended effective treatment regimens. Patient non-compliance to recommended treatments can be a pervasive threat to the health and wellbeing of the patient [15]. The determinants of treatment hesitancy have been stratified into three main categories: systemic, individual, and treatment-related factors.

Unraveling the Causes of Treatment Hesitancy

The Historical and Systemic Context

Mistrust of medical advances among racialized populations continues to persist. The mistrust reflects the historical injustices and current systemic deficiencies experienced by racialized and marginalized populations. The infamous Tuskegee experiment which intended to study the natural progression of untreated syphilis is widely cited as a major stimulus for the mistrust of medical advances among Black populations [16]. The researchers failed to obtain informed consent from the 600 African American participants and did not offer treatment to infected participants, even after treatment became widely available. The implications of the study are far-reaching and have had ripple effects in Canada. Recent discovery that similar studies occurred in Canada has further propagated the mistrust of the healthcare system

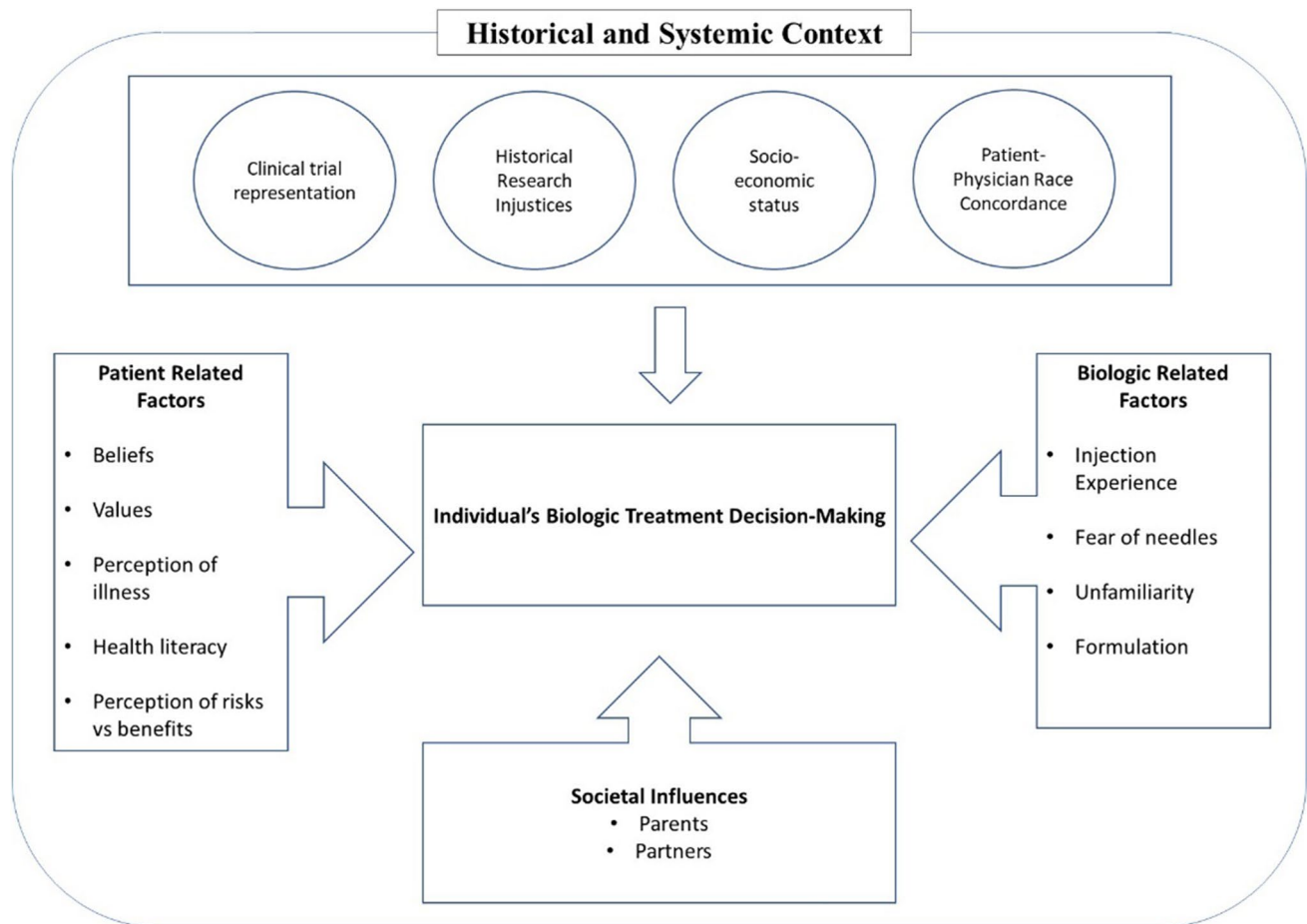


Fig. 1 A conceptual model of biologic treatment decision-making at the individual level. Conceptual model of treatment decision-making. Adapted from the Schema summary of discussions held during the Workshop on the cultural and religious roots of vaccine hesitancy:

Explanations and implications for the Canadian healthcare. Historical and systemic context: as an overarching theme, the historical and systemic context broadly influences new treatment hesitancy in racialized populations

among Black and Indigenous populations [17]. Mistrust in the healthcare system is a precipitating factor for the relatively low participation of Black and Indigenous populations in clinical trials. Black participants made up 7.7% of US and Canadian cancer clinical drug trials while making up 12.6% of the US population. Globally, Black participants made up 2.6% of cancer clinical drug trials [18]. Representation within clinical trials is important as it ensures inter-ethnic differences in drug response and metabolism are uncovered during the drug development phase as medications may have varying efficacy on patients based on their age, gender, and ethnicity [19]. It is well-established that Black patients with hypertension respond poorly to ACE inhibitors and β -adrenergic blockers compared to other classes of anti-hypertensives [20]. It therefore comes as no surprise that racialized populations are skeptical and hesitant about new treatments as they are not represented in clinical trials which validate the efficacy of such treatments [18].

The lack of Black and Indigenous representation is not limited to clinical trials; it creeps into academia and the research ecosystem. Black and Indigenous academics remain significantly underrepresented and underpaid in Canada [21]. The lack of diversity among principal investigators involved in clinical trials is a contributing factor to the low participation of Black and Indigenous populations in these trials. Diversity is also lacking in the broader Canadian health workforce. This stems from the lack of representation in our health workforce training programs. In 2012, only 4.4% of medical students in Canada identified as Aboriginal, a modest increase from the 1.6% reported in 2007. However, only 2.9% reported identifying as Black, compared to 4.2% of the population nationally [22]. Efforts to improve health workforce diversity are critical as race concordance has been positively associated with measures of patient satisfaction and health outcomes [23]. A study found that although patients of all races reported being more

satisfied with physicians who used a participatory approach, which is an approach that seeks patients' input before making treatment decisions, Blacks had less participatory visits than Whites. However, Black patients in race-concordant relationships with their physicians rated their visits as significantly more participatory than patients in race-discordant relationships [24]. This dissatisfaction could be an underlying factor for the disproportionately lower use of new modalities of treatments among Blacks as they may be hesitant to take treatment recommendations from race-discordant physicians [25].

Indigenous peoples in Canada experience the highest levels of poverty. One in 4 indigenous peoples are living in poverty. The overall poverty rate for racialized persons was 22%, doubling the rate of non-racialized persons [26]. In Canada, patients with a low income visit specialists at a lower rate than those with a high income despite the existence of a free universal health system [27]. A study controlling for disease severity found that patients seen in primary care settings were less likely to receive novel regimens than those seen by specialists [28]. A survey of primary care physicians in the USA found that only 9% of primary care physicians reported being confident in starting a patient on a DMARD [29]. Considering Indigenous and Black individuals are more likely to be of lower socioeconomic status and as such more likely to receive care in primary care settings, this may partially account for some of the disparity in biologic usage between Whites and Blacks. Physicians may also change their prescription strategy when seeing patients from lower socioeconomic status. They are likely to shift to a cheaper drug within a therapeutic class or shift to another drug that is covered by the patient's drug plan [27]. While programs exist across Canadian provinces to improve access to medications, most require a deductible and can be a barrier for low-income patients. A cross-sectional study of over 28,000 Canadians as part of the Canadian Community Health Survey found that out-of-pocket charges for medications are associated with foregoing prescription drugs and other necessary healthcare services [30]. Cost-related medication underuse or non-adherence is an important issue and disproportionately affects racial minorities and uninsured young Canadians (< 65 years) [31].

Societal Influences

The principle of respect for autonomy is associated with empowering patients to make their own decisions about which therapeutic interventions they will or will not receive [32]. A study on young people's decisions about biologic therapies found that while young people claim decisional autonomy, most exhibit a relational autonomy [33]. This implies their autonomy in making treatment decisions is enabled by others who influence the making and enactment

of these decisions. The literature suggests adults also exhibit relational autonomy, but different people are involved. While mothers play a meaningful role in young adults' decision-making, partners replace parents sometimes [33]. Social influences play a significant role as patient's source of information from people they perceive as reliable and trustworthy around them to make decisions [34]. Feedback from family and community members regarding the negative effects and efficacy of medications influences patients' decision to accept or refuse treatments. The surrounding community's perceptions of the negative effects of a specific type of medication, especially if there is a risk of becoming dependent, greatly influence patients' treatment preferences [35].

Patient-Related Factors

In addition to the societal input, there are patient-centered factors that influence a patient's ultimate treatment decision. The patient's sociocultural background, personal beliefs, and values influence their perception of illness and treatment decision-making [36]. Treatment decisions for Indigenous patients are influenced by cultural beliefs not yet evident within western medicine [37]. Indigenous culture emphasizes the harmonious relationships between the individual, the land, and the community as a component of health [38]. As such, Indigenous patients may hold a different view on disease etiology and symptomatology [39]. These beliefs inform the expectations that Indigenous patients may bring to health encounters [40]. Indigenous patients' whose traditional disease etiology aligns closely with western biomedical etiology are more likely to accept medications. A study in southern Alberta concluded that Indigenous patients preferred to use a combination of nonpharmacologic and pharmacologic treatments to manage their rheumatoid arthritis. Patients' preference for pharmacologic treatment was positively influenced by clinical factors such as understanding the drug's mechanisms of action, the clinical benefits, and trust in the healthcare provider [35]. Religion and spirituality influence some patients' beliefs about their health condition and treatment decisions. A study done in the USA found that African American individuals were more likely to report God played an influential role in their asthma and its control compared to White individuals [41]. Similarly, a study from Ghana found that some patients declined treatment or risked not taking their medications in anticipation of divine healing [42]. In a multicultural country like Canada, Black patients can present with varying beliefs, customs, and attitudes. A study examining African Canadians living in Nova Scotia affirmed the important role spirituality and religion plays in treatment decisions [43].

Health literacy indirectly affects patients when they are faced with complex information and treatment decisions. Patients do not reap the benefits of new treatments unless

they understand their diagnosis, why certain treatments are recommended, and how to correctly take the medication [44]. Health literacy limits miscommunications and misunderstanding between the healthcare provider and patient. According to the Canadian Council on Learning, about 60% of Canadians aged 16 years and above lack the capacity to obtain health information and make appropriate health decisions on their own [45]. Extrapolating from American findings, it is reasonable to assume that the percentage is higher for Indigenous and Black populations in Canada [46]. Studies have shown that many patients with asthma hold the belief that if they are asymptomatic, then they do not have asthma. These patients do not perceive their condition as a chronic disease and as such do not manage it daily with prescribed medication. This is contrary to the biomedical classification of asthma as a chronic condition requiring continuous management [47]. In a diverse cohort of patients with rheumatoid arthritis, stronger beliefs in the necessity of medication were associated with better adherence to DMARDs [48]. This highlights how low literacy contributes to treatment noncompliance and patients making uninformed decisions leading to subpar health outcomes.

Regardless of a patient's health literacy level, there are factors that most patients consider before beginning a new treatment. A Canadian study of multiple sclerosis patients indicated that the most important characteristics of treatment that patients consider are effectiveness and side effects [49]. Patients were also hesitant to try new treatment if they felt that their current medication was providing benefits. The study also found that convenience and route of administration were secondary considerations and as such patients only considered it if they expected the risks and benefits to be equal or superior to their existing treatment [49].

Biologic-Related Factors

Characteristics related to the formulation and administration of biologics may also contribute to treatment hesitancy. As the administration of biologic drugs is usually via subcutaneous self-injection, Black and Indigenous patients with trypanophobia, which is the fear of needles, may be hesitant to initiate biologic therapy. A study on patients with psoriasis found that there is a greater preference to avoid needles among Black patients compared with Whites [7]. Patients may also be hesitant to initiate or continue biologic therapy if they have limited dexterity due to arthritis or hand deformities that may reduce their ability to self-inject [50].

Negative injection experience is a significant contributing factor to biologic treatment hesitancy. Negative past experiences involving needles such as injection site reactions, pain, and swelling may make patients hesitant to initiate or continue biologic therapy. A study involving rheumatoid arthritis patients who had discontinued biologic therapy

reported that 40.8% of participants cited negative injection experience as a reason for discontinuation [51].

Unfamiliarity with biologics, particularly among Black patients, may contribute to biologic treatment hesitancy. A study from the USA suggests that there is a greater level of unfamiliarity with biologic therapy in Black individuals compared to Caucasian patients. The unfamiliarity may partly explain the racial disparity in biologic treatment for psoriasis that exist in the USA [7]. In Canada, a national survey on adult patients with moderate-to-severe psoriasis found nearly one-third of the patients who were non-biologic users were unfamiliar with it and did not have enough information to form an opinion about biologics [52].

A Way Forward: Recommendations for Key Stakeholders

Rebuilding Trust

Effectively addressing new treatment hesitancy requires new initiatives to rebuild trust among racialized populations. This section reviews and describes strategies that have been proposed to help build trust. Representation is critical when addressing the low participation of Black and Indigenous populations in clinical trials. Black members as part of the research team have been shown to contribute to successful recruitment strategies of Black patients [53]. It is reasonable to assume this finding applies to Indigenous and other racialized populations. Other strategies that have been proposed to increase participation from racialized populations include circulating research information directly to members of racialized populations and involving key community organizations and leaders, especially churches for Blacks and Chiefs for Indigenous populations. It is recommended that both community leaders and members feel empowered and have an interest in clinical trials.

To increase Black and Indigenous researchers in academic medicine, organizations need to adopt targeted recruitment and retention strategies for marginalized populations [54]. These include early exposure to health professions through career days, science summer camps, and funding opportunities (e.g., industry sponsored entrance scholarships). Attrition has often been cited as a barrier to graduating more Black healthcare workers, especially in the field of nursing. Mentoring has been proven to be an effective retention strategy. Mentorship can take many forms such as student, faculty, clinical, and industry mentoring [54].

Cultural sensitivity may bridge the satisfaction gap that exists in race-discordant patient–physician encounters. Most medical residents report receiving little instruction or evaluation on cultural sensitivity during their medical training. The importance of formally training physicians and

healthcare workers to deliver culturally safe care to diverse patient populations has been widely advocated [55]. Guidelines recommend medical curricula develop learning objectives that explore and examine mistrust, subconscious bias, stereotyping, and the magnitude of health disparities. They also call for trainees to develop skills to effectively communicate across cultures, languages, and literacy levels [56].

The relationship between low socioeconomic status and health is well-established [57]. Considering 22% of racialized persons and 1 in 4 indigenous peoples in Canada are living in poverty [26], eliminating financial inequality will improve health outcomes for Black and Indigenous populations. However, the solution is far from simple. In light of this multifaceted systemic problem, we focus on addressing how some of the current structures that exist to support patients from lower socioeconomic status in Canada can be improved. The Non-Insured Health Benefits (NIHB) exists to increase access to medically necessary services, including to registered First Nations and Inuit individuals. While this program is commendable, less than half of Indigenous people in Canada qualify for the program [58]. In addition, the program is poorly utilized as it is disliked by Indigenous leaders and communities [58]. The dislike stems from inadequate coverage, lack of timely access, and the burdensome administrative processes associated with the program. The NIHB program needs to be revamped in consultation with healthcare providers and Indigenous peoples [59].

Enhancing Patient-Centered Care

It is evident that some patients' treatment decisions are enabled by others who influence the making and enactment of these decisions. For these patients, involving family members and trusted support individuals when discussing and planning treatment plans may have a positive influence on initiating and adhering to new treatment [60]. Family members possess valuable information and may provide insights to factors that may be driving a patient's hesitancy for a new treatment. The healthcare team should be proactive in including family members in shared decision-making activities when appropriate [61].

As patients may hold a different view on disease etiology and symptomatology than the biomedical view a healthcare provider may hold, it is important that providers have the sensitivity to navigate these often-challenging encounters. The inability to recognize and incorporate perspectives of illness that deviate from those of biomedicine can derail any attempts at identifying problems and developing mutually beneficial plans for solving them. To resolve this dichotomy between disease and illness, healthcare providers must be prepared to accommodate to the principles of biomedicine as well as the experience of illness as narrated by the patient and their family. When alternative therapies are clearly

contraindicated and will put the patient at risk, respectful education and justification are recommended [62].

The efficacy of patient education is interconnected with health literacy. Acknowledging differences in health literacy among patients is critical to effectively supporting and empowering patients in self-managing health conditions — a hallmark of patient-centered care [63]. Patient empowerment among individuals with lower-than-average health literacy requires an intervention, usually an educational session. Effective methods of education may include individual and/or peer group instruction and distribution of educational materials with dedicated follow-up and personal feedback. The creation of supportive environments within local communities has been shown to enhance skill building to encourage healthy habits and increase willingness for self-management [63]. Differences among patients' literacy make it necessary to avoid the one size fits all approach when developing patient education materials. Complex scientific and technical information should be transformed into simple language, analogies that patients can relate to and understand. To advance the work on patient engagement and empowerment, there have been calls for research to shift from describing differences in health outcomes to discovering practical interventions that are suitable for patients at all levels of health literacy to reduce health inequalities [63].

Enhancing the Palatability of Biologics

Healthcare providers should offer patients, especially biologic-naïve individuals a range of biologic administration options to choose from when recommending biologic therapy. Informing the patient on the variety of devices for biologic administration gives individuals the opportunity to choose a device that addresses their unique challenges and can maximize a patient's injection experience. For example, because needles are not visible to patients with an autoinjector pen, this device may be preferred by a patient who experiences anxiety when a needle is sighted before an injection. Generally, subcutaneous administration of biologics has been shown to provide a better treatment experience for patients compared to intravenous infusions [64, 65]. Patient preference studies have found that patients generally find autoinjector pens easier to use than pre-filled syringes [64, 66]. However, a preference study found that some patients prefer using the syringe due to ease of control of the injection and less pain [64]. These varying reports within a patient group speak to the individuality of medication experience and the need for continuous dialogue between patients and their healthcare providers as means to voice these individual preferences. Evidence suggests that consideration of patient preference and satisfaction in this process of device selection can improve continuity of therapy [50, 64].

As highlighted by the national survey on adult patients with moderate-to-severe psoriasis, some patients are unfamiliar with biologic therapy [52]. The poor familiarity with this group of medical products may stem from less exposure to biologics as a treatment option or lack of understanding of biologics as pharmacological choices even after the products have been presented by a medical provider [7]. Therefore, we propose that prescribers engage in productive discussions with patients regarding medical interventions to improve exposure to and understanding of biologics as therapeutic interventions especially when indicated for Black and Indigenous patients. This may bridge the racial treatment disparity in Canada that likely parallels the inequalities found in the USA. Physicians should consider preparing patients for the biologic decision earlier in the disease process and exposing patients to the overall treatment landscape [67, 68].

Like all medications, biologics have been associated with adverse events. Findings from an American study conducted by Constantinescu et al. showed a statistically significantly different risk–benefit balance in therapy decision-making by Blacks relative to White patients where Black patients were collectively more risk-averse [69]. Based on these results, we propose effective risk communication between healthcare professionals and racialized patients in Canada. Providing patients with accurate information on the risks and benefits of using biologic therapy would allow patients to make informed therapy decisions and manage their expectations during and after therapy. It is hoped that greater understanding in this way would enhance treatment acceptance.

Limitations

Although efforts are being made by Canadian government agencies such as the Canadian Institute for Health Information to improve race-based health data collection and reporting in Canada, data and statistics on race-based health outcomes remains a challenge in Canada. Addressing and tracking racial health disparities rely on the collection and availability of Canadian race-based data. The relative lack of race-based health data limited the ability of this review article to effectively examine treatment hesitancy among racialized populations in a Canadian context. Where possible and appropriate, we relied on literature and findings from the USA. This limitation is unlikely to have a significant impact on the conclusions drawn from this review due to the similarities between the two countries.

As our review focused on biologics, it is worth highlighting that prescription of biologics for indications such as psoriasis and rheumatoid arthritis is dependent on disease severity among other clinical and patient-specific factors [70, 71]. Although the available literature from the USA shows that certain health conditions for which biologics are indicated are more prevalent in Caucasians compared to African

Americans, Black patients often present with worse disease severity [10]. A statistically significant greater severity of immunological mediated conditions between Caucasians in Canada compared to those of African descent would necessitate a greater need for biologic therapy, hence contributing to apparent differences in biologic usage between these ethnic groups. Further investigation is needed to explore the similarity, or lack thereof, of clinical manifestations of these conditions in individuals belonging to various ethnic groups.

Conclusion

To our knowledge, this is the first review exploring biologic treatment hesitancy among racialized populations in a Canadian context. Our review found that treatment decisions at the patient level are influenced by biologic-related factors (negative injection experience, fear of needles, formulation, and unfamiliarity), social inputs from family and trusted community members, cultural (beliefs, values, perception of illness), and historical/systemic (past research injustices, socioeconomic status, patient–physician relationship, clinical trial representation) factors. Some proposed solutions to address treatment hesitancy among Black and Indigenous populations include increasing the representation of Black and Indigenous researchers involved in and leading clinical trials, formally training physicians and healthcare workers to deliver culturally sensitive care, and eliminating financial barriers to accessing medications.

Funding This review article was funded by Amgen Canada Inc.

Availability of Data and Material Not applicable.

Code Availability Not applicable.

Declarations

Conflict of Interest Edgar Akuffo-Addo is a Graduate Intern at Amgen Canada Inc. Theodora Udounwa is a Graduate Intern at Amgen Canada Inc. Jocelyn Chan is a PharmD Resident at Amgen Canada Inc. Laura Cauchi is an employee of Amgen Canada Inc.

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