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Fingolimod and risk of skin cancer among individuals with multiple sclerosis: a population-based cohort study protocol

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ABSTRACT

Introduction Long-term population-based safety studies, applying advanced causal inference techniques, including an active comparator with new-user design, are needed to investigate skin cancer outcomes among individuals with multiple sclerosis (MS) treated with fingolimod. This study aims to describe a protocol for investigating the relationship between fingolimod use and the incidence of skin cancer among individuals with MS.

Methods and analysis We will use population-based administrative health data from two Canadian provinces (British Columbia and Alberta) to conduct an observational cohort 'trial emulation' study with an active comparator and new-user design. Individuals with MS aged ≥18 years will be identified using a validated algorithm. Incident users of fingolimod and active comparators (natalizumab, alemtuzumab, dimethyl fumarate, teriflunomide) will then be identified. The outcome of interest will be skin cancer (melanoma and non-melanoma skin cancers). Survival analysis will be used to estimate HRs and corresponding 95% CIs, adjusted for potential confounders.

Ethics and dissemination Ethics approval for this study was obtained from the University of British Columbia Clinical Research Ethics Board (H24-03199). No personal identifying information will be made available as part of this study. Findings will be disseminated through presentations and peer-reviewed publications.

Trial registration number NCT06705608.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A population-based cohort study on drug safety and skin cancer among patients with multiple sclerosis.
⇒ A trial emulation approach, including a new-user and an active comparator design.
⇒ Observational analogues of intention-to-treat and per-protocol analyses to estimate the effect of treatment strategy assignment and the effect of adhering to the treatment strategy.
⇒ Potential confounding variables may not be captured by administrative data.
⇒ Data on drug dispensations may not correspond to medication usage if adherence is low.

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disorder that affects the central nervous system (CNS), including the brain, spinal cord and optic nerves.[1 2] MS occurs when the immune system mistakenly attacks the myelin sheath that covers and protects nerve fibres, causing scarring and disruption of nerve signals.[3] Symptoms of MS can vary widely depending on the location and extent of nerve damage. Common signs and symptoms include fatigue, muscle weakness, spasticity, difficulty with coordination and balance, cognitive impairment, vision problems and bladder and bowel dysfunction. Typically, MS manifests as a relapsing-remitting disease (RRMS); however, as more severe neurological disabilities accumulate over time, the majority of patients transition to a secondary progressive disease course.[1] In a minority of patients, the disease is progressive from onset (primary progressive MS (PPMS)).[1] The exact cause of MS remains unknown, but it is thought to be caused by a combination of genetic and environmental factors, such as viral infections, smoking and low vitamin D levels.[4–6] MS is more common in females and is typically diagnosed between the ages of 20 and 40.[7]

There is currently no cure for MS, but there are several disease-modifying therapies (DMTs) available that can slow down the progression of the disease, reduce the frequency and severity of relapses, reduce the number of new lesions in the brain and spinal cord, and improve quality of life.[8–10] DMTs have different mechanisms of action and routes of administration (table 1), and can be classified according to their order in the therapeutic strategy (first-line, second-line and off-label use).[11] Following MS diagnosis,

Table 1 List of DMTs and respective characteristics

DMT agent	Group	Mechanism of action	Indications	Route of administration
Azathioprine	Suppressing	Purine antagonist that impairs the synthesis of DNA, RNA and proteins, and damages T-cell lymphocyte function.	▶ Renal homotransplantation ▶ Rheumatoid arthritis	Oral tablet
Cladribine	Suppressing	Nucleoside analogue disrupts DNA synthesis and chain termination. It specifically targets and damages lymphocytes and monocytes, exhibiting cytotoxic effects.	▶ MS ▶ Hairy cell leukaemia	Oral tablet (MS) Intravenous (hair cell leukaemia)
Cyclophosphamide	Suppressing	Alkylating agent that prevents DNA replication and transcription through DNA crosslinking.	▶ Cancer: lymphoblastic leukaemia, myeloid leukaemia, breast cancer, Hodgkin lymphoma, mycosis fungoides, multiple myeloma, neuroblastoma, non-Hodgkin lymphomas, ovarian adenocarcinoma, and retinoblastoma ▶ Nephrotic syndrome	Oral tablet Intravenous
Methotrexate	Suppressing	Inhibits dihydrofolate reductase and thymidylate synthase involved in DNA development and cell metabolism; reduces inflammation by suppressing the production of B and T cells.	▶ Acute lymphoblastic leukaemia ▶ Breast cancer ▶ Cutaneous T cell lymphoma ▶ Gestational trophoblastic neoplasia ▶ Head and neck squamous cell carcinoma ▶ Meningeal leukaemia ▶ Non-Hodgkin lymphomas ▶ Osteosarcoma ▶ Polyarticular juvenile idiopathic arthritis, psoriasis, rheumatoid arthritis	Oral tablet Oral solution Intravenous
Mitoxantrone	Suppressing	Affect cells in the CNS by intercalating into DNA; impairs DNA replication and DNA-dependent RNA synthesis; can bind to topoisomerase II, causing DNA repair to be inhibited.	▶ MS (US only) ▶ Acute myeloid leukaemia ▶ Prostate cancer	Intravenous
Teriflunomide	Suppressing	Inhibits the enzyme dihydroorotate dehydrogenase, involved in mitochondrial de novo pyrimidine synthesis; reduces number of circulating lymphocytes.	▶ MS	Oral tablet
Dimethyl fumarate	Modulating	Modulates levels of Nrf2 and glutathione in T cells; induces antioxidant effect by upregulating antioxidant response genes.	▶ MS	Oral capsule (delayed release)
Glatiramer acetate	Modulating	Amino acid polymer; shifts the immune response from a pro-inflammatory state to regulatory, non-inflammatory state; reduces inflammation in the CNS.	▶ MS	Subcutaneous injection
Interferon β	Modulating	Regulates the migration and retention of immune cells; decreases T cell activation and proliferation; decreases the migration of lymphocytes across the blood-brain barrier.	▶ MS	Subcutaneous injection
Fingolimod	Sequestering	Sphingosine 1 phosphate receptor modulator; reduces T lymphocytes in circulation.	▶ MS	Oral capsule
Natalizumab	Sequestering	Monoclonal antibody; selective adhesion molecule inhibitor, prevents adhesion of leukocytes to endothelial cells.	▶ MS ▶ Crohn's disease	Intravenous
Alemtuzumab	Depleting	Monoclonal antibody; binds on CD52 (cell surface antigen) present on T and B lymphocytes; antibody-dependent lysis of malignant cells.	▶ MS ▶ B-cell chronic lymphocytic leukaemia	Intravenous
Ocrelizumab	Depleting	Monoclonal antibody; targets CD20-expressing B cells; depletes CD20 positive B cells.	▶ MS	Intravenous

Continued

Table 1 Continued

DMT agent	Group	Mechanism of action	Indications	Route of administration
Rituximab (off-label)	Depleting	Monoclonal antibody; targets CD20-expressing B cells; promotes cell lysis.	▶ Chronic lymphocytic leukaemia ▶ Granulomatosis with polyangiitis ▶ Microscopic polyangiitis ▶ CD20-positive non-Hodgkin lymphomas ▶ Rheumatoid arthritis	Intravenous Subcutaneous injection
Minocycline (off-label)	Minocycline	Tetracycline antibiotic; binds to the bacterial 30S ribosomal subunit and interferes with protein synthesis.	▶ Acne vulgaris ▶ Infections of susceptible microorganisms, bacterial infections	Oral capsule Subgingival powder (extended release)

CNS, central nervous system; DMT, disease-modifying therapy; MS, multiple sclerosis.

most begin use of a DMT, with the exception of a subset of patients exhibiting a very mild clinical course.[12] There are different treatment strategies for DMTs: the escalation approach and the early high-efficacy therapy (HET) approach.[13] The escalation approach consists of starting with a first-line medication, intended as a moderate efficacy and highly safe drug, and switching to a second-line treatment (more effective but lower safety profiles) if the first-line treatment is ineffective or not tolerated (this is typically the scenario in patients with mildly or moderately active disease).[12] By contrast, the HET approach starts with a highly effective treatment, commonly used second-line in an escalation approach, which encompasses both continuous treatment with high-efficacy DMTs and induction therapy to achieve rapid remission.[13] This strategy is intended for cases of MS characterised by frequent (two or more episodes per year) and severe relapses, particularly those at increased risk of rapid accumulation of disability.[12] The choice of treatment strategy also includes considerations such as comorbidities, pregnancy planning, cost and insurance coverage, and the preferred route and frequency. While studies have shown no increased risk of all-cause cancer for patients with MS,[14–16] concerns have been raised regarding the role of DMTs in an elevated cancer risk due to their immunosuppressive effects, though the evidence is mixed, particularly with respect to fingolimod.[17 18]

Fingolimod belongs to a class of medications called sphingosine-1-phosphate (S1P) receptor modulators. The mechanism of action of fingolimod involves its interaction with S1P receptors on immune cells, particularly lymphocytes. Normally, lymphocytes move freely between the lymph nodes and the bloodstream. However, fingolimod binds to S1P receptors on lymphocytes, preventing them from leaving the lymph nodes. By sequestering lymphocytes in the lymph nodes, fingolimod limits their migration into the CNS, where they could cause inflammation and damage the myelin sheath that protects nerve fibres.[19] The reduction in circulating lymphocytes helps decrease the peripherally mediated immune response, thereby reducing the frequency and severity of MS flare-ups.

In 2010, fingolimod became the first oral drug approved by the US Food and Drug Administration (FDA) indicated as monotherapy for the treatment of RRMS.[20] It was later approved in 2018 for paediatric populations (10 years to <18 years of age).[21] It was approved as a second-line treatment in Canada and Europe and as first-line in the USA, Australia and other countries.[20 22] In adults, the recommended dose of fingolimod is 0.5 mg once per day. In paediatric patients, the recommended dose is dependent on body weight (≤40 kg: 0.25 mg, >40 kg: 0.5 mg once per day orally).[23 24] Fingolimod has a half-life of 6–9 days and will remain in the body for up to 2 months after stopping treatment.[24] A 10-year study using the German MS registry showed that the median disease duration at fingolimod initiation was approximately 8 years, with interferon β (30.7%) being the most common pre-fingolimod treatment and ocrelizumab (19.8%) being the most frequent subsequent treatment in patients who switched.[25] Fingolimod is associated with adverse effects, such as increased infection risk, lymphopenia, leucopenia, macular oedema and atrioventricular block,[24 26 27] which contributes to the second most frequent reason for treatment switching following disease activity (relapse).[25] However, owing to its high clinical efficacy, Canada's Drug and Health Technology Agency proposed a review in 2022 to investigate the clinical efficacy and safety of fingolimod as a first-line option in adults with highly active relapsing MS.[28]

Prior to its approval, the development of neoplasms was considered a potential risk in clinical studies for fingolimod. Annual dermatological full-skin examinations were integrated into the clinical phase III trials for fingolimod after phase II studies showed a higher-than-expected rate of skin malignancies (7 skin cancers in 0–36 months out of n=173 who maintained follow-up at 36 months): basal cell carcinoma (n=3); squamous cell carcinoma (n=2) and malignant melanoma (n=2); see box 1 for definitions.[29] In the phase III TRANSFORMS trial with patients treated with fingolimod for 1 year,

Box 1 Types of skin cancers

Basal cell carcinoma: the most common form of skin cancer, occurring in the basal layer of the skin.
Squamous cell carcinoma: a type of cancer occurring in the squamous cell layer of the skin.
Melanoma: the most lethal form of skin cancer, occurring in the melanocytes of the skin.

there were no melanomas in 420 patients on 1.25 mg daily fingolimod, 3 melanomas in 429 patients on 0.5 mg daily fingolimod and no melanomas in 431 patients on interferon β-1a.[30] Following the TRANSFORMS study, a 1-year randomised extension study was conducted which further observed four cases of localised skin cancer including one case of malignant melanoma (1.25 mg daily) in participants who continued to receive fingolimod.[31] In the phase III FREEDOMS trial, there was one case of melanoma in 429 patients on 1.25 mg daily fingolimod, no melanoma in 425 patients on 0.5 mg daily fingolimod and one melanoma in 418 patients in the placebo arm.[32] In the phase III INFORMS trial, which demonstrated a lack of efficacy of fingolimod treatment over a period of 3–5 years in PPMS, there were a total of 21 cases of skin cancer (squamous cell carcinoma (n=6); melanoma (n=1); basal cell carcinoma (n=14)) in the fingolimod-treated group (0.5 mg daily, n=336) and a total of 10 skin cancers (squamous cell carcinoma (n=1), melanoma (n=0), basal cell carcinoma (n=9)) in the placebo group (n=487).[33]

In the USA, the FDA drug label for fingolimod includes malignancies ('suspicious skin lesions should be evaluated').[34] Since its approval, several case reports have suggested an association between fingolimod use and melanoma.[35–39] Moreover, a nationwide study using the Swedish Cancer registry noted a 'borderline-significant' increased risk of invasive cancer with fingolimod compared with both the general population and to rituximab, but was not able to analyse specific cancers.[18] In addition, the study did not use an active comparator to address indication bias and did not include information on dose or duration of fingolimod use.[18] Further, a pharmacovigilance study detected a potential safety signal for fingolimod for basal cell carcinoma and also an increased signal of disproportionate reporting for melanoma and squamous cell carcinoma.[40]

From a mechanistic point of view, phosphorylated fingolimod activates S1P receptors, resulting in functional S1P antagonism with inhibition of lymphocyte egress from lymph nodes[41] associated with a decreased number of circulating lymphocytes. It has been suggested that such lymphocyte reduction might eliminate or neutralise melanoma-specific lymphocytes, thereby undermining cancer immune surveillance.[39] Additionally, immunohistochemical analyses suggest that fingolimod could act in the tumour microenvironment, influencing the secretion of VEGF-A by melanoma cells and favouring melanoma development indirectly.[42] By contrast, two *in vitro* studies have suggested a protective role of fingolimod in relation to melanoma.[43 44] Furthermore, S1P signalling might also be linked with other skin cancers as SphK1 is highly expressed in advanced squamous cell carcinomas of the head and neck and is associated with poor survival.[45] An alternative hypothesis is a pro-oncogenic effect of fingolimod via activation of the IL6/JAK/STAT3 pathway.[46] Apart from MS, an increased risk of skin cancer is also linked to the lifelong use of immunosuppressive treatments in organ transplant recipients, and the incidence of skin cancers increases with the duration of immunosuppressive therapy.[47]

Ideally, questions about drug exposures on outcomes would be answered using a randomised experimental design. However, randomised trials are unethical to perform in light of safety concerns and have limited follow-up periods which may not be suitable for capturing outcomes that can take time to develop, such as concerns related to elevated skin cancer risk. Epidemiologists have therefore proposed 'trial emulation' as a strategy for elucidating causal relationships from large observational databases.[48 49] A trial emulation strategy has not been previously used to examine the relationship between fingolimod and skin cancer outcomes. Evaluating the long-term safety profile of DMTs is crucial to assist healthcare professionals and individuals in making informed decisions about therapy options. To bridge this knowledge gap, here we present a protocol for assessing the risk of skin cancer in individuals initiating fingolimod, under optimal epidemiological conditions (new users with an active comparator design) in two population-based samples.

METHODS AND ANALYSIS

Study design and data source

This will be an incident-user, dual-cohort observational study using data from 1 January 2003 to 31 December 2020. The lower bound of this time period was selected based on the earliest approval dates for the main drugs of interest (fingolimod and active comparators). Two administrative health data sources will be used and analysed separately (since preanalysis pooling is not possible due to data sharing and privacy regulations), from the provinces of British Columbia (Population Data BC) and Alberta (Alberta Health) in Canada. Canada has a single-payer, publicly administered healthcare system, with full coverage of inpatient and outpatient services for all legal residents. These databases are extensive data repositories that hold individual-level, deidentified, longitudinal data covering the entire insured population of each respective province. These data sources have been extensively used to study risk factors for MS, MS comorbidities and MS progression.[50–55] The linked databases that will be used are shown in table 2. In general, this study will implement an active comparator design with a 'trial emulation' approach which is considered optimal epidemiological conditions to infer causal relations that would be

Table 2 Summary of administrative health data sets in British Columbia and Alberta

Administrative data	British Columbia data sets	Alberta data sets
Practitioner claims	Population Data BC: Medical Services Plan; Consolidation Files (data available from 1 January 1997 to 31 December 2023)	Practitioner claims (data available from 1994)
Hospital admissions, discharges, transfers	Population Data BC: Discharge Abstracts Database (data available from 1 January 1997 to 31 December 2023)	Inpatient (Discharge Abstract Database) (data available from 1993)
Emergency, day surgery and outpatient clinics	Population Data BC: National Ambulatory Care Reporting System (NACRS) (data available from 1 January 1997 to 31 December 2023)	Ambulatory Care (NACRS) (data available from 2011)
Prescriptions	Population Data BC: BC Ministry of Health PharmaNet (data available from 1 January 1997 to 31 December 2023)	Pharmaceutical Information Network Dispenses (data available from 2008)
Immigration, age, sex	Population Data BC: Citizenship and Immigration Canada; BC Vital Statistics Agency (all data available from 1 January 1997 to 31 December 2023)	Longitudinal Demographic Profile (data available from 1 January 1997 to 31 December 2023) Alberta Health Care Insurance Plan Cumulative Registry
Income	Population Data BC: The Statistics Canada Income Band file (data available from 1 January 1997 to 31 December 2023)	Longitudinal demographic profile
Clinical data	BC MS Clinical Database	Administrative data linkage with MS clinics in Calgary, AB

similar to a randomised trial if such a trial were possible (table 3).[48] Reporting of this protocol is in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (see online supplemental materials for SPIRIT checklist and online supplemental table S1).[56]

Study population

We will first identify an adult MS cohort with hospital/physician and prescription claims classified according to the International Classification of Diseases (ICD-9: 340; ICD-10: G35) and drug identification numbers, respectively (see online supplemental table S2), using a validated case definition.[50] This case definition requires an individual to have at least three healthcare encounters (any combination of inpatient encounter, outpatient encounter or DMT dispensation) for MS in a 1-year window and has a sensitivity of 86.6–96.0%, specificity of 66.7–99.0% and positive predictive value of 95.4–99.0%. Paediatric MS (<18 years old) cases will be excluded from the analysis since fingolimod was only approved for the paediatric population in Canada in 2018, which would not allow for sufficient follow-up or baseline assessment. To create an incident (new-user) cohort, we will only include MS cases with at least 3 years of baseline data prior to the first drug dispensation. MS cases with skin cancer in the 3-year baseline period will also be excluded based on inpatient and outpatient claims (see a list of skin cancer ICD codes in table 4). 3 years will be selected to allow for sufficient time to ensure only incident skin cancer will be captured during follow-up, while also balancing sample size considerations since a longer period would exclude more individuals.

Exposure and outcomes

We will identify patients with MS who initiated treatment with fingolimod or the active comparator (natalizumab or alemtuzumab), treated as a binary (yes/no exposure variable). To reduce potential confounding by indication, the choice of active comparators was selected based on drug indication (ie, same indication as fingolimod), approved treatment order (ie, first-/second-line treatment), route of administration and date of drug approval in Canada (for data availability). Natalizumab and alemtuzumab were selected to be active comparators based on being approved as second-line treatment for RRMS and are non-continuous therapies. Although they are administered intravenously, both drugs have follow-up durations that are comparable to or longer than fingolimod (natalizumab approved in Canada in 2006; alemtuzumab in 2013), which ensures a similar duration of exposure and allows for a comparable population being observed. Notably, natalizumab blocks lymphocyte trafficking but at a different location (blood-brain barrier) compared

Table 3 Emulation of a target trial

Protocol component	Target trial protocol	Emulated trial using observational data
Eligibility criteria	► Physician-diagnosed MS ► Patients ≥18 years of age ► No prior receipt of DMTs under study ► No history of skin cancer ► RRMS disease course	► MS defined with validated algorithm ► Patients ≥18 years of age ► No documented prior receipt of DMTs under study ► No skin cancer-related encounters in the last three years ► DMT indication-derived RRMS cohort
Treatment strategies	► Initiation of fingolimod at baseline and continuation over follow-up until the development of a contraindication (cardiac condition). Treatment is considered to be continuous if there is a gap of less than 90 days between successive dispensation. ► Initiation of natalizumab at baseline and continuation over follow-up until the development of a contraindication (PML). Treatment is considered to be continuous if there is a gap of less than 6 days between successive prescriptions. ► Initiation of alemtuzumab at baseline and continuation over follow-up until the development of a contraindication (HIV or cardiac condition). Discontinued treatment is considered if there is a gap longer than 18 months between the first and second course of treatment. ► Initiation of dimethyl fumarate at baseline and continuation over follow-up until the development of a contraindication (PML). Treatment is considered to be continuous if there is a gap of less than 90 days between successive dispensation. ► Initiation of teriflunomide at baseline and continuation over follow-up until the development of a contraindication (hepatic impairment). Treatment is considered to be continuous if there is a gap of less than 90 days between successive dispensation.	Same as for the target trial. Date of medication initiation is defined to be the first date of drug dispensation. Discontinuation dates will be calculated using the dose and quantity of pills in the dispensation record.
Treatment assignment	Eligible persons will be randomly assigned to one strategy at baseline and will be aware of which strategy they were assigned to (due to different route of administration).	Adjustment for confounding factors to ensure exchangeability of groups.
Outcomes	Skin cancer diagnosis.	Skin cancer-related encounter. Cancer diagnoses are ascertained via administrative health records using ICD-9/10 codes.
Follow-up	For each eligible individual, follow-up starts at treatment initiation and ends at the time of the skin cancer outcome of interest, death, loss of follow-up, end of trial, whichever happens first.	From the first date of drug dispensation until the outcome of interest, death, loss of follow-up (defined by a period of more than 24 months with no national health insurance reimbursement), administrative end of follow-up (31 December 2020), change to comparator drug, whichever occurs first.
Causal contrasts	Intention-to-treat effect. Per-protocol effect.	Observational analogues of the intention-to-treat effect and per-protocol effect.

Continued

Table 3 Continued

Protocol component	Target trial protocol	Emulated trial using observational data
Data analysis	Intention-to-treat, per-protocol analysis.	Pooled logistic regression to estimate HRs and standardised risk curves. Intention-to-treat analysis: IP weighting to adjust for baseline confounding. Per-protocol analysis: Censor individuals if and when they deviate from their assigned treatment strategy. IP weighting to adjust for pre- and post-baseline factors associated with adherence and loss to follow-up.

DMT, disease-modifying therapy; ICD, International Classification of Diseases; IP, inverse probability; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy; RRMS, relapsing-remitting multiple sclerosis.

with fingolimod, and, unlike fingolimod, does not cause lymphopenia.[57] Some first-line treatments (ie, glatiramer acetate, interferon β), off-label treatments (ie, rituximab), treatments with multiple indications (ie, ocrelizumab: approved for both RRMS and PPMS) and recently approved treatments (ie, cladribine: approved on December 2017) were not considered ideal candidates as active comparators. The characteristics of the potential comparators for fingolimod are listed in table 5. Additional exposure definitions will be applied in various sensitivity analyses (below). For the study outcomes, ICD codes will be used. The ICD-9/10 codes for skin cancer (melanoma and non-melanoma skin cancers) are provided in table 4.[58 59] Skin cancer will be treated as a composite outcome of basal cell carcinoma, squamous cell carcinoma and melanoma, as well as disaggregated by skin cancer subtype in a separate analysis.

Follow-up

Follow-up will begin from the index date (drug initiation). All participants will be followed until the first of the following events, whichever occurred first: outcome of interest (development of skin cancer); lost to follow-up, defined by a period of more than 24 months with no health insurance reimbursement; death; administrative end of follow-up (ie, study end) and initiation of a comparator drug.

Table 4 ICD-9/10 codes for skin cancer

	ICD-9	ICD-10
All skin cancer	172–173 232	C43-C44 D03.x
Melanoma	172.x	C43.x D03.x
Basal cell carcinoma	173.x1	C44.x1x
Squamous cell carcinoma	173.x2	C44.x2x
Other malignant neoplasms of skin	173.x0 173.x9 232.x	C44.x0x C44.x9x

x indicates all values.
ICD-9, International Classification of Diseases, 9th Revision; ICD-10, International Classification of Diseases, 10th Revision.

Confounders and covariates

Variables thought to be associated with skin cancer only and potential confounders of the relationship between fingolimod exposure and skin cancer will be considered for adjustment. Baseline covariates will be measured in the 3-year period prior to the index date (the most recent value will be selected for measures that vary over time) and will include age at MS diagnosis, age at drug initiation, sex, race, neighbourhood income quintile-based residence; sun exposure, the Charlson Comorbidity Index,[60 61] smoking status (using validated proxy for smoking that uses diagnosis codes for tobacco use and chronic obstructive pulmonary disease, as well as smoking cessation medications),[62] MS severity at index date (using a validated proxy including ICD codes for home care or long-term care use or rehabilitation admission)[63] and rheumatoid arthritis encounter prior to index date (ICD-10: M05, M06; ICD-9: 714.0).[64 65] To account for factors associated with adherence, time-varying inverse-probability weights will be estimated using baseline and time-varying variables. See online supplemental table S3 for details on covariates.

Statistical analysis

Descriptive statistics will be used to describe patient characteristics. Pooled logistic regression with inverse-probability weights for treatment will be used to estimate the HRs and corresponding 95% CIs over time, adjusted for potential time-fixed and time-varying confounding variables. Observational analogues of intention-to-treat and per-protocol analyses are planned to estimate the effect of treatment strategy assignment and the effect of adhering to the treatment strategies, respectively. For each province, the HRs will be separately estimated and combined with weighted pooling. The active comparators will be treated separately in analyses (ie, fingolimod vs natalizumab and fingolimod vs alemtuzumab). R Statistical software will be used for all analyses. The planned

Table 5 Choice of active comparator for fingolimod

Disease-modifying therapy	Indication	Approved treatment order	Route of administration	Approval year in Canada
Fingolimod	RRMS	2	Oral	2011
Natalizumab	RRMS	2	Intravenous	2006
Alemtuzumab	RRMS	2	Intravenous	2013
Dimethyl fumarate	RRMS	1	Oral	2013
Teriflunomide	RRMS	1	Oral	2013
Cladribine	RRMS	2	Oral	2017
Glatiramer acetate	RRMS	1	Subcutaneous injection	1997
Interferon β	RRMS	1	Subcutaneous injection	1995
Rituximab	Off-label for RRMS	N/A	Intravenous	N/A
Ocrelizumab	RRMS; PPMS	1	Intravenous	2017

Green represents consistency with fingolimod properties, red represents inconsistency.
PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

start date for construction of the analytical data set is late 2024, and the planned start date for the statistical analyses is mid-2025.

Sensitivity and secondary analyses

Several sensitivity and secondary analyses will be conducted. First, an analysis of a dose-response (sample size permitting) will be completed, with cumulative fingolimod exposure between first dispensation and censoring. This sensitivity analysis will be completed to strengthen the causal inference, but will not be part of the primary analysis due to potential limitations in sample size. Second, we will perform sensitivity analyses in which we include a delayed follow-up (to account for reverse causation) and a latency period for the skin cancer outcome. Third, in secondary analyses, fingolimod will be compared with first-line DMTs, DMF and teriflunomide. These were selected as active comparators due to their similar indications and approval dates (both approved in 2013) compared with fingolimod, which received approval in 2010 for monotherapy in the treatment of RRMS in Canada, thereby enhancing the comparability of the patient populations exposed to the treatments. Additionally, they have a similar route of administration and usage patterns as fingolimod as they are administered orally on a daily basis, which may help minimise potential confounding related to patient adherence. Despite the fact that DMF and teriflunomide are considered first-line treatments, they have often been used as second-line following initial treatment with interferon β.[66]

Patient and public involvement

The importance of patient and public involvement in every aspect of clinical research is becoming increasingly apparent. Study investigators (LL, AT, JO) have engaged individuals with lived experience with MS during annual virtual education events and in-person scientific meetings as part of the CANadian PROspective COhort Study for People Living with MS. As the study is executed, we will continue with this sort of engagement, including establishing a dedicated group of patient experts to obtain ongoing feedback, in particular regarding knowledge dissemination materials. This type of engagement is essential to increase the relevance and impact of people living with MS.

STUDY STRENGTHS AND LIMITATIONS

The primary strength of this study lies in the richness of the data used to analyse the relationship between fingolimod and skin cancer. This includes unbiased 'participation' in the population-based sample (ie, not a volunteer sample) and extensive long-term follow-up. While using administrative data collected for another purpose is efficient, there are trade-offs in terms of limitations. Confounding variables may not be captured. For example, sun exposure measured as vitamin D status or an outdoor occupation is not available, but is available if measured by postal code. Moreover, the algorithm used as a proxy for smoking status has a low sensitivity. Lastly, we will not be able to capture medications used outside of the databases, including medications (DMTs or others) provided as part of clinical trials or over-the-counter medications. Another potential limitation of administrative data is that medication *usage* is not captured (only dispensations are captured). However, fingolimod has been shown to have very high adherence rates.[67] As an oral medication, it has higher adherence (as measured by proportion of days covered and medication possession ratio) and fewer discontinuations compared with intramuscular and subcutaneous DMTs in both experienced and naïve DMT users.[68] Meanwhile, the choice of DMF and teriflunomide as daily oral active comparators also provide comparability and reduce the possibility of confounding by medication usage/adherence. Moreover, the risk of non-adherence for natalizumab is not significantly different compared

with fingolimod, as defined by proportion of days covered <80%.[69]

Another major strength of the study design is the use of 'trial emulation' to create optimal epidemiological conditions to investigate the relationship between fingolimod and skin cancer outcomes, and address major biases common in pharmacoepidemiology studies. This includes the new-user design, in which the index event is based on the first dispensing of fingolimod. The new-user design enforces appropriate temporal ordering of measurements of fingolimod and cancer and confounders, addressing reverse causation. In contrast, with the prevalent-user design, both current (prevalent) and new users of fingolimod would be included. Restricting to incident users of fingolimod is also advantageous because it enables comparisons at a comparable time in the natural history of MS. Similarly, mixing incident and prevalent users may lead to selection bias since the effect measure is weighted towards prevalent users who likely provide the majority of person-time.

Also consistent with trial emulation (ie, exchangeability of the exposed/unexposed groups), we will be able to address indication bias by using active comparators with highly similar indications (as opposed to users vs non-users as the exposure groups, or fingolimod use in MS vs fingolimod use in the general population as exposure groups), and also by adjusting for other indications for DMTs (rheumatoid arthritis). This new-user active comparator design resembles a head-to-head randomised controlled trial that answers both the question of 'which second-line treatment to initiate' through the second-line comparators, and 'whether to initiate a second-line treatment or not' through the first-line comparators.[70] The choice of active comparators (natalizumab, alemtuzumab, DMF, teriflunomide) had similar indication, approval dates and route of administration as fingolimod, which will ensure selection of a more homogeneous MS population (indicated for treating patients with RRMS during a similar time period). Additionally, DMTs are prescribed in sequence as a monotherapy, so there should not be an overlap in drug use in the comparator groups. Nevertheless, while guidelines recommend a sequential transitioning from first-line to second-line therapies for treatment switching, intra-class switch within both first- and second-line treatments has been observed.[25 66 71]

STUDY IMPACT

Administrative databases are well suited for investigating safety outcomes in the MS setting and allow for monitoring of rare events in clinically relevant patient populations. The assessment of the safety profile is important to support clinicians and patients in the choice of therapy. Using prospectively collected data, we will compare the risk of skin cancer in a large population of patients with MS treated with fingolimod, natalizumab, alemtuzumab, DMF and teriflunomide. This study could have implications for dermatological follow-up among individuals with MS and their care providers, and could have implications for drug labelling. In addition, assessing drugs based on skin cancer safety endpoints may help select the most appropriate drug for an individual patient out of the numerous available DMTs. Finally, information on the safety profile of DMTs can help guide policymakers in their decisions on reimbursement.

ETHICS AND DISSEMINATION

Ethics approval for this study was obtained from the University of British Columbia Clinical Research Ethics Board (H24-03199). No personal identifying information will be made available as part of this study. This observational study is registered on clinicaltrials.gov (registration number: NCT06705608). Findings, including important protocol modifications, will be disseminated through presentations and peer-reviewed publications.

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