Risk Of Malignancies In Newly Treated Patients with Disease-modifying Drugs For Multiple Sclerosis

Assessment
according to cohort and nested-case control approaches

Pauline Bosco-Lévy[1], Emmanuelle Boutmy[2], Angela Grelaud[1], Meritxell Sabidó[2], Pauline Diez[1], Clémentine Lacueille[1], Régis Lassalle[1], Caroline Foch[2], Cécile Droz-Perroteau

[1]*Bordeaux PharmacoEpi, INSERM CIC1401, Université de BORDEAUX, Bordeaux, France;*
[2] *The healthcare business of Merck KGaA, Darmstadt, Germany.*

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Disclosure

- Study sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945)
- Designed, conducted and analysed independently by the Bordeaux PharmacoEpi platform of Bordeaux University
- Registered in EMA EUPAS n°26535
- Conflict of interest
  - **AG, PBL, PD, CL, RL** and **CD-P** are employees of the Bordeaux PharmacoEpi, INSERM of Bordeaux University, an independent nonprofit research organization that works in collaboration with government agencies and pharmaceutical companies.
  - **PBL** declares to have received speaker fees from Biogen outside of the submitted work
  - **MS**, **CF**, and **EB** are employees of the healthcare business of Merck KGaA, Darmstadt Germany.

Context (1)

- Disease Modifying Therapies (DMT)
  - Main treatment for Multiple Sclerosis
    - Target inflammation settings to delay disability progression
  - Include
    - Immunomodulators (IM) *interferon beta-1a, interferon beta-1b, glatiramer acetate and pegylated interferon beta 1-a*
    - Immunosuppressants (IS)
      - Multiple sclerosis specific* *teriflunomide, fingolimod, dimethyl fumarate, alemtuzumab, or natalizumab*
      - Multiple sclerosis non-specific* *methotrexate, cyclophosphamide, mitoxantrone, mycophenolate mofetil, azathioprine, rituximab or tacrolimus*

* Specific or non-specific does not refer to MOA but to exclusively indicated for MS treatment (specific IS) or for MS and other indications (non-specific IS)

Context (2)

- Risk of malignancy with DMTs
  - No increased risk reported with IM in 20 years of use
  - Potential risk reported for several IS
    - in clinical trials
      - *Rommer et al., 2018*
    - in observational studies
      - *Lebrun et al.2011; Alping et al., 2020*

Need for **complementary real-world evidence** from large comparative studies **to confirm the potentially higher risk of cancer with IS** in comparison to IM

Objective

- To assess the risk of cancer of IS in comparison with IM
  - in a large population of MS patients
  - using data from the French nationwide claims and hospital database

Methods (1)

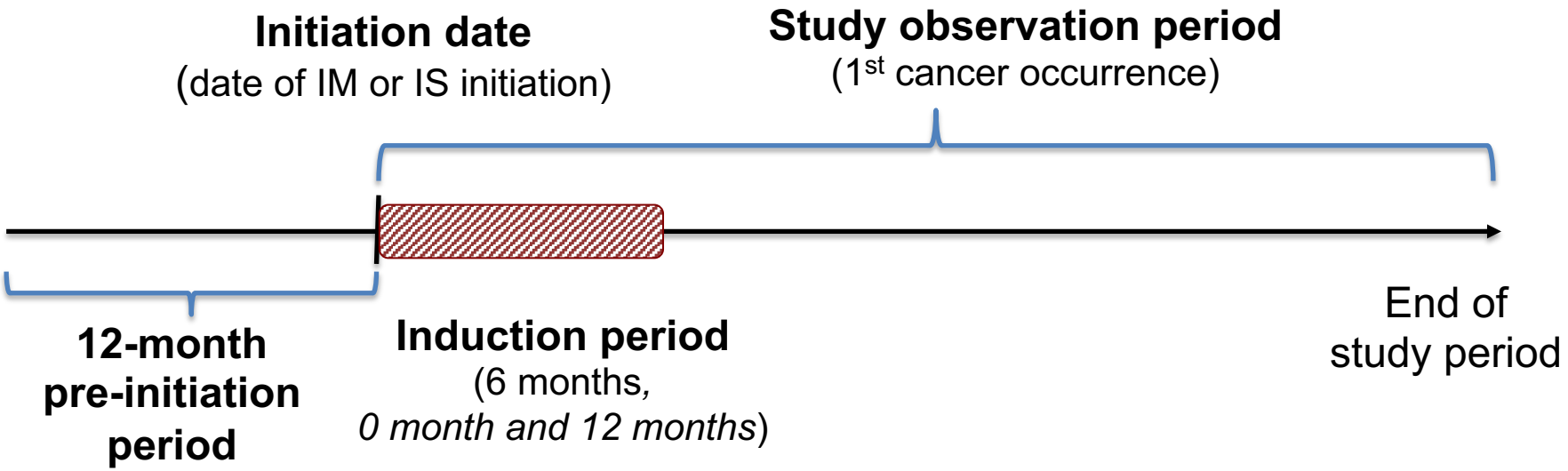
- ***Data source***
  - **SNDS database**
    - individual information on all reimbursed outpatient claims covering 99% of the French population
- ***Study population***
  - **MS patients** identified by
    - ICD-10 diagnosis code of hospitalization stay, LTD status or disability allowance
    - dispensing of DMT specifically indicated in MS
  - **New users of DMT**
    - *i.e.* no DMT during the 12 months preceding the first DMT dispensing

Methods (2)

- ***Exposure of interest***
  - **DMT use**
    - categorized as **IM or IS**
- ***Event of interest***
  - **1st occurrence of any malignancy**
    - identified by the earliest of the following events
      - hospitalization or LTD registration for cancer, excluding metastasis, cancer recurrences and secondary tumors
      - dispensing of prostate cancer specific treatment
    - confirmed by a 2nd occurrence of the same cancer

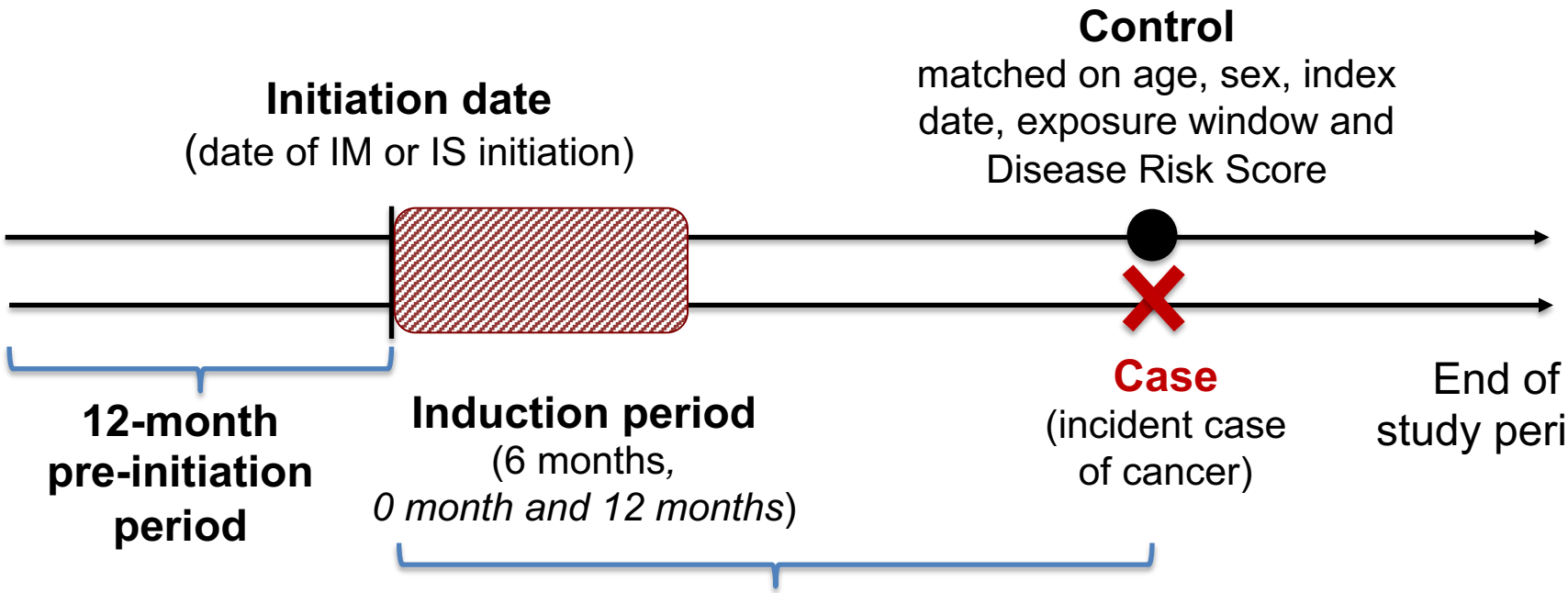
Study Designs

1) Cohort



Study Designs

2) Nested case-control



Exposure window

- Exclusive (ever use of IS, IM or both)
- Specific (≥ 1 dispensing of IM or IS)
- Cumulative (total period covered by IM or IS)

Statistical analysis

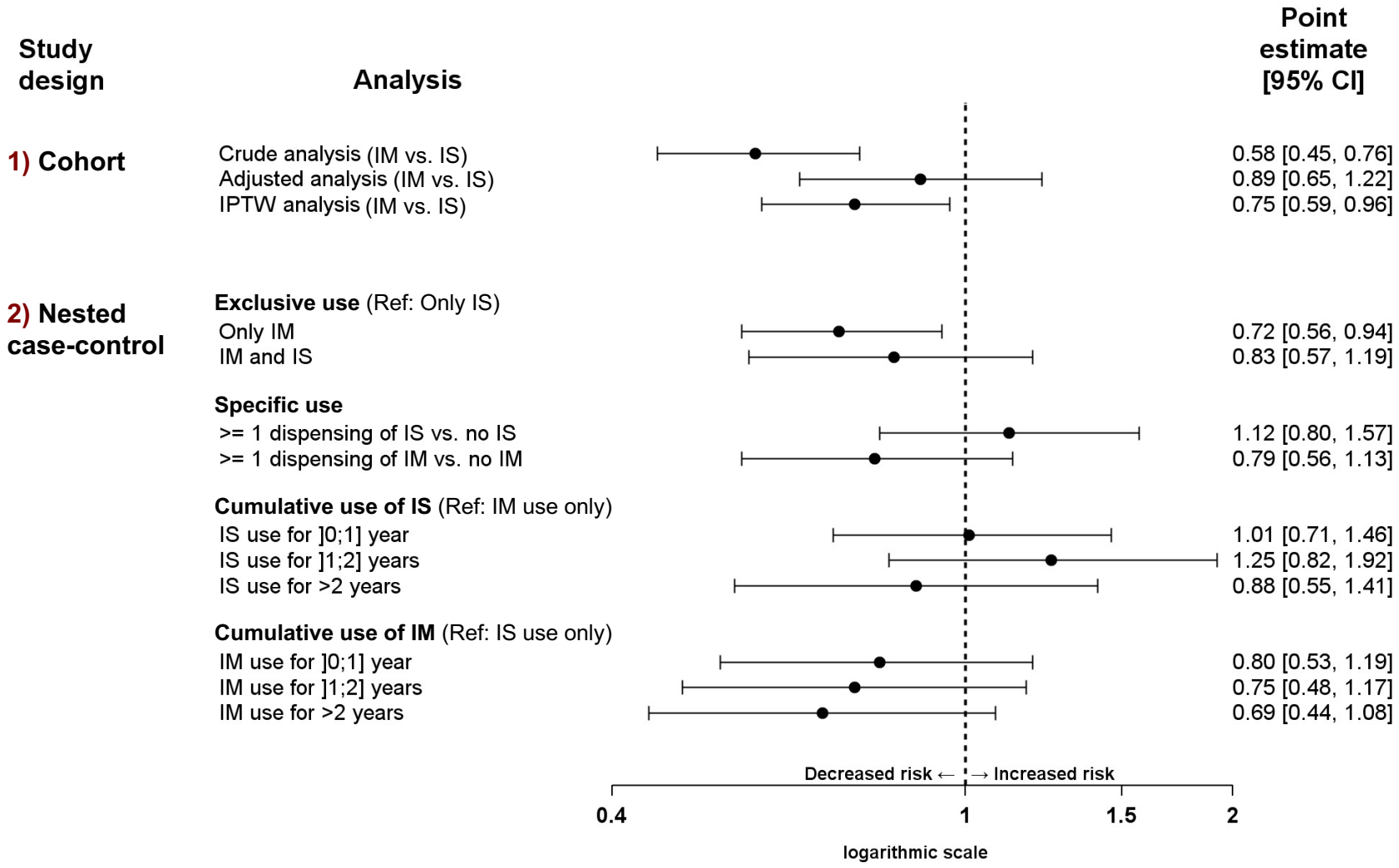
	Cohort	Nested case-control
Description of patients' characteristics	At initiation date	At index date
Association between DMT use and cancer	• Cox proportional hazards model • In intent-to-treat • Trimming and propensity score adjustment and IPTW	• Conditional logistic regression model • According to the various definitions of exposure (i.e. exclusive, specific and cumulative)

Results (1)

	Cohort			Nested case-control		
	IM n = 13988	IS n = 4607	Standardized difference (%) After adjustment	Cases n=416	Controls* n=416	Standardized difference (%)
Demographic characteristics						
Mean (SD) age at initiation date (years)	40.2 (10.9)	43.1 (12.1)	5.2	50.8 (11.5)	50.3 (4.7)	5.5
Mean (SD) age at index date (years)	-	-	-	53.9 (11.4)	53.4 (4.7)	5.6
Sex female, n (%)	10113 (72.3)	3263 (70.8)	-5.6	287 (69.0)	287 (69.0)	0.0
Mean (SD) drug exposure window [from initiation date to index date] (in years)	-	-		3.1 (1.7)	3.1 (0.7)	0
Mean (SD) duration of follow-up	4.5 (2.0)	3.6 (2.5)	-	-	-	
Main comorbidities, n (%)						
Autoimmune disease	647 (4.6)	248 (5.4)	-0.3	32 (7.7)	25 (6.1)	6.2
COPD	458 (3.3)	191 (4.1)	-0.4	19 (4.6)	16 (3.8)	3.7
Diabetes	346 (2.5)	164 (3.6)	-0.1	21 (5.0)	18 (4.4)	3.2
Conditions associated with chronic alcohol consumption	117 (0.8)	34 (0.7)	1.2	10 (2.4)	4 (1.0)	11.2
Within the 12 months of pre-index period						
Hospitalizations, median [IQR]	1.0 [1.0;2.0]	1.0 [1.0;2.0]	-8.9	1 [1.0;2.0]	1 [1.0;2.0]	7.1
Medical visits, median [IQR]	12.0 [8.0;17.0]	13.0 [8.0;18.0]	-4.3	13 [9.0;18.0]	13 [8.0;18.0]	3.5
Relapse, n (%)	5622 (40.2)	1875 (40.7)	-1.1	160 (38.5)	148 (35.6)	5.9
MS medical device, n (%)	1856 (13.3)	862 (18.7)	0.2	91 (21.9)	90 (21.5)	0.8
Female hormones use, n (%)	3398 (24.3)	1054 (22.9)	-0.5	94 (22.6)	74 (17.7)	12.2
Glucocorticoid use (excluding for relapse treatment)	5335 (38.1)	1750 (38.0)	-0.8	146 (35.1)	162 (38.8)	-7.8

*For controls, means median and percentages were weighted by the inverse number of controls matched to each case.
SD: Standard Deviation, IQR: Interquartile Range, COPD: Chronic Obstructive Pulmonary Disease, HIV: Human Immunodeficiency Virus, MS: Multiple Sclerosis

Results (2)


Study design
Analysis
Point estimate [95% CI]
1) Cohort
Crude analysis (IM vs. IS)
0.58 [0.45, 0.76]
Adjusted analysis (IM vs. IS)
0.89 [0.65, 1.22]
IPTW analysis (IM vs. IS)
0.75 [0.59, 0.96]
2) Nested case-control
Exclusive use (Ref: Only IS)
Only IM
0.72 [0.56, 0.94]
IM and IS
0.83 [0.57, 1.19]
Specific use
>= 1 dispensing of IS vs. no IS
1.12 [0.80, 1.57]
>= 1 dispensing of IM vs. no IM
0.79 [0.56, 1.13]
Cumulative use of IS (Ref: IM use only)
IS use for]0;1] year
1.01 [0.71, 1.46]
IS use for]1;2] years
1.25 [0.82, 1.92]
IS use for >2 years
0.88 [0.55, 1.41]
Cumulative use of IM (Ref: IS use only)
IM use for]0;1] year
0.80 [0.53, 1.19]
IM use for]1;2] years
0.75 [0.48, 1.17]
IM use for >2 years
0.69 [0.44, 1.08]
Decreased risk ← → Increased risk
0.4
1
1.5
2
logarithmic scale

Discussion

- No significant differences in risk of cancer between IM and IS according to the group classifications used
  - But trend towards risk reduction of cancer for IM in comparison with IS
  - Confirmed in the induction period sensitivity analysis (*0- and 12-months*)
  - Limitation: definition of IM and IS used in this analysis are general and include treatments with diverse mechanisms of action, further analysis is required to analyse effect of distinct mechanisms of action
- Similar magnitude of estimate in both designs
  - But NCC design permitted a clearer picture of the relationship between cumulative DMD exposure and malignancy

Discussion

	Cohort	Nested case-control
Strengths	• Consider **all exposed patients** (after trimming)	• Adapted for **rare events** such as cancer • Allows a good assessment of the **variations of the drug exposure over time**
Limitations	• Difficulty in assessing the **variations of the drug exposure over time**	• Selection of appropriate controls ➤ Matching on DRS and other relevant clinical variables • **Protopathic bias**: change of exposure may be due to progression of disease/comorbidities

Thank you

Bordeaux BPE PharmacoEpi

Bordeaux PharmacoEpi - http://www.pharmacoepi.eu
Plateforme de recherche en Pharmaco-épidémiologie
CIC Bordeaux CIC1401
INSERM - Université de BORDEAUX - CHU de Bordeaux - Adera
Bâtiment Le Tondu - case 41 - 146 rue Léo Saignat - 33076 Bordeaux Cedex
Acc. +33 (0)5 57 57 46 75 – Fax +33 (0)5 57 57 47 40