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Existing claims-based algorithm may overestimate relapses in multiple sclerosis (MS) patients using infusible disease modifying therapies (DMTs) that require steroid premedication

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SUMMARY

1 **The algorithm published by Boster et al[1] uses multiple sclerosis (MS)-related hospitalizations and outpatient steroid prescriptions to identify relapses, which may lead to overestimation, particularly in patients on disease-modifying therapies (DMTs) that require steroid premedication.**

2 **The current study assessed the strength of the algorithm published by the Boster et al[1] group and a revised algorithm for correctly identifying relapses in MS patients on intravenous (IV) DMTs requiring steroid premedication (ocrelizumab [OCR] and alemtuzumab [ALM]) compared with more commonly used therapies that do not require steroid premedication (dimethyl fumarate [DMF], or Betaseron, Rebif, Avonex, Copaxone, and Extavia [BRACE]).**

3 **The study results showed similar MS relapse rates in IV monoclonal antibodies (mAbs) and BRACE/DMF cohorts, despite revising the algorithm to extend the exclusion of steroid use. This is contrary to the observations seen in clinical trials and real-world practice, suggesting overestimation of MS relapses in IV mAbs due to unmeasured confounding.**

BACKGROUND

- Claim databases of MS patients lack information on clinical outcomes such as relapses, thus algorithms to estimate MS relapse events have been developed.[1,2]
- These algorithms use MS-related hospitalizations and outpatient steroid prescriptions to identify relapses, which may lead to overestimation, particularly in patients on DMTs that require steroid premedication.[3]

OBJECTIVE

- To assess the strength of a published algorithm[1] and a revised algorithm for correctly identifying relapses in MS patients on IV DMTs requiring steroid premedication (mAbs) compared with the most common therapies that do not require steroid premedication (BRACE/DMF). Natalizumab (NTZ), an IV mAb that does not require steroid premedication, was included as a reference.

METHODS

ALGORITHMS TO IDENTIFY MS RELAPSE

- MS relapse was identified via a published algorithm[1] and a revised algorithm which excluded steroid use from the relapse count when given within ±5 days for ALM and OCR, for which steroids are used as premedications (**Table 1**).

Table 1. MS relapse identification algorithms

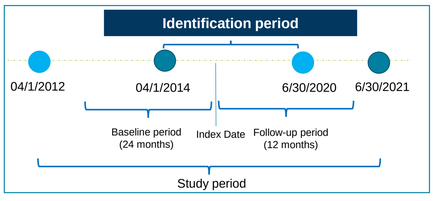
Boster et al.[1]	Revised Boster et al.
Inpatient A claim with an MS diagnosis code in the primary position at any time during an inpatient hospitalization. The relapse date was defined as the hospital admission date. **OR** **Outpatient** A claim with an MS diagnosis code in the primary or secondary position in an outpatient setting plus high dose oral corticosteroids (C500mg/day prednisolone or equivalent prednisone or methylprednisolone) or IV methylprednisolone or corticotropin or plasma exchange within 30 days of outpatient visit. The relapse date was defined as the service date of outpatient visit. A new relapse must begin at least 30 days after the beginning of the previous relapse.	In addition to Boster's definition[1], exclude IV corticosteroid use within a ±5-day window for ALM and OCR infusions, for which IV corticosteroids are recommended to be used as premedications.

ALM, alemtuzumab; DMTs, disease-modifying therapies; IV, intravenous; MS, multiple sclerosis; OCR, ocrelizumab

STUDY DESIGN

- This retrospective study used the Truven MarketScan® Commercial & Encounters database with adult MS patients who started OCR, ALM, NTZ, or BRACE/DMF from April-2014 through June-2020, with continuous enrollment ≥24 months before and ≥12 months after treatment initiation (index date) (**Figure 1**).

Figure 1. Study design



OUTCOMES

- The annualized relapsed rate (ARR) and proportion of patients having at least one relapse were estimated at 12-months post-index period.

ANALYSES

- Inverse Probability Treatment Weighting (IPTW) method was performed to control for potential confounding and selection bias at the class level. Baseline covariates were balanced in BRACE/DMF and mAbs cohorts after IPTW.

RESULTS

WEIGHTED AND UNWEIGHTED BASELINE CHARACTERISTICS

- A total of 2,791 patients were included, and baseline characteristics were comparable across groups after IPTW adjustment (**Table 2**).

Table 2. Baseline Demographics and Clinical Characteristics

	Unweighted		Weighted	
	BRACE/DMF (n=2,266)	mAbs (n=861)	BRACE/DMF (n=2,274)	mAbs (n=864)
Age, years				
Mean (SD)	44.6 (11.6)	46.1 (12.0)	44.9 (11.6)	44.8 (12.1)
Sex, n (%)				
Female	1,711 (75.5%)	576 (66.9%)	1,657 (72.9%)	631 (73.1%)
United States Region, n (%)				
Northeast	500 (22.1%)	205 (23.8%)	515 (22.7%)	190 (22.0%)
North Central	491 (21.7%)	197 (22.9%)	495 (21.8%)	188 (21.7%)
South	951 (42.0%)	340 (39.5%)	945 (41.5%)	366 (42.3%)
West	323 (14.3%)	116 (13.5%)	316 (13.9%)	120 (13.8%)
Unknown	1 (0.0%)	3 (0.3%)	2 (0.1%)	1 (0.1%)
Insurance Type, n (%)				
Fee for service	1,999 (88.2%)	760 (88.3%)	2,000 (88.0%)	764 (88.4%)
HMO and POS capitation	249 (11.0%)	81 (9.4%)	247 (10.9%)	90 (10.4%)
Unknown	18 (0.8%)	20 (2.3%)	27 (1.2%)	10 (1.2%)
With at least one relapse during pre-index period, n (%)	664 (29.3%)	398 (46.2%)	776 (34.1%)	288 (33.3%)
Number of relapses during pre-index period				
Mean (SD)	0.34 (0.61)	0.66 (0.96)	0.46 (0.89)	0.42 (0.73)
Charlson Comorbidity Index (CCI)				
Mean (SD)	0.83 (1.41)	0.77 (1.33)	0.81 (1.37)	0.83 (1.49)
Proxy disability level, n (%)				
No EDSS-related symptoms	417 (18.4%)	140 (16.3%)	403 (17.7%)	154 (17.8%)
Mild	512 (22.6%)	142 (16.5%)	475 (20.9%)	183 (21.2%)
Moderate	900 (39.7%)	387 (44.9%)	934 (41.1%)	353 (40.9%)
Severe	437 (19.3%)	192 (22.3%)	462 (20.3%)	174 (20.2%)
Had steroid use, n (%)	707 (31.2%)	399 (46.3%)	806 (35.4%)	296. (34.3%)

[a]Demographics were based on index date. Relapse, CCI, proxy disability level and steroid use were assessed during 2-year pre-index period. Mild disability level was defined as having only one functional system (FS) with severity level=1. Moderate disability level was defined as having more than 1 FS with severity level=1, or having any EDSS-related symptoms with severity level=2. Severe disability level was defined as having any EDSS-related symptoms with severity level=3; BRACE therapies: Betaseron (interferon beta-1b), Rebif (interferon beta-1a), Avonex (interferon beta-1a), Copaxone (Glatiramer acetate), and Extavia (interferon beta-1b); DMF, Dimetlyl Fumarate (Tecfidera); HMO, health maintenance organization; mAbs, monoclonal antibodies; POS, Point of service; SD, Standard deviation

OUTCOMES

- During 12-month post-treatment, MS relapse outcomes using both algorithms are presented in the **Table 3**.

Table 3. MS relapse outcomes in weighted cohorts

	BRACE/DMF (n=2,274)	GA (n=1,116)	INF β-1a (n=264)	INF β-1b (n=72)	DMF (n=822)	mAbs (n=864)	ALM (n=22)	NTZ (n=346)	OCR (n=495)
Relapse identified by Boster's definition									
With at least one relapse, n (%)	462 (20.3)	243 (21.8)	60 (22.9)	15 (21.4)	143 (17.4)	492 (56.9)	14 (63.4)	70 (20.1)	408 (82.4)
Time to first relapse, Mean (SD)	127.6 (112.6)	130.5 (108.7)	149.4 (106.2)	81.6 (101.1)	118.6 (121.8)	70.8 (87.9)	23 (68.5)	142 (103)	60.3 (80.0)
Post-pre relapse change#, %									
Improvement*	22.5	21.4	21.7	15.4	25.0	11.3	12.6	20.6	4.8
No change¶	65.1	64.7	64.5	71.2	65.3	42.5	52.9	65.2	26.1
Worsening†	12.4	13.9	13.8	13.5	9.7	46.2	34.5	14.2	69.1
Relapse identified by Revised Boster's definition									
With at least one relapse, n (%)	423 (18.6)	225 (20.1)	53 (19.9)	14 (18.8)	133 (16.1)	174 (20.1)	4 (19.0)	62 (18.0)	108 (21.7)
Time to first relapse, Mean (SD)	122.1 (113.2)	124.6 (108.8)	148.1 (108.2)	72.2 (106.1)	112.5 (121.7)	102.2 (92.3)	118.8 (85.7)	131.9 (98.6)	84.3 (85.3)
Post-pre relapse change#, (%)									
Improvement*	23.1	22.0	22.8	15.4	25.4	23.7	31.2	21.3	25.0
No change¶	65.9	64.9	66.4	73.8	66.4	61.4	62.8	67.1	57.4
Worsening†	11.0	13.1	10.8	10.8	8.2	14.9	5.9	11.6	17.6

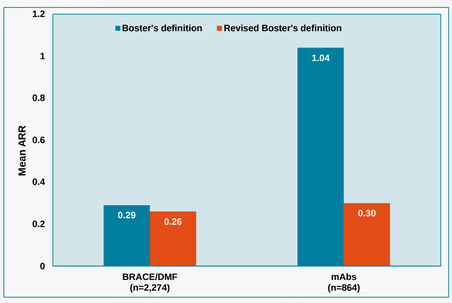
ALM, alemtuzumab; BRACE, (Betaseron (interferon beta-1b), Rebif (interferon beta-1a), Avonex (interferon beta-1a), Copaxone (glatiramer acetate), and Extavia (interferon beta-1b)); DMF, dimethyl fumarate; GA, glatiramer acetate; INF β-1a, interferon beta-1a; INF β-1b, interferon beta-1b; mAbs, monoclonal antibodies; MS, multiple sclerosis; NTZ, natalizumab; OCR, ocrelizumab; SD, Standard deviation. #Post-pre relapse change: relapse number during 1-year post-index - relapse number during 1-year pre-index; * improvement - post-pre relapse change < 0; ¶ no change - post-pre relapse change = 0; † worsening - post-pre relapse change > 0

- As per the published algorithm, the proportion of patients with a relapse was 82.4% in OCR, 63.4% in ALM, and 20.1% in NTZ cohorts compared with 20.3% in BRACE/DMF cohorts during 12-month follow up (**Table 3**).
- With the revised algorithm, these proportions decreased to 21.7% in OCR, 19.0% in ALM, and 18.0% in NTZ cohorts compared with 18.6% in the BRACE/DMF cohort (**Table 3**).

ANNUALIZED RELAPSE RATE

- ARR was lower with the revised algorithm compared with the published algorithm across all cohorts and sub-cohorts, but the extent of reduction was much more obvious in the mAbs cohort (**Figure 2**).

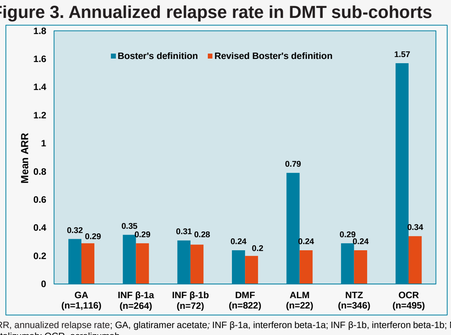
Figure 2. Annualized relapse rate in BRACE or DMF vs. mAbs cohorts



ARR, annualized relapse rate; BRACE, (Betaseron (interferon beta-1b), Rebif (interferon beta-1a), Avonex (interferon beta-1a), Copaxone (glatiramer acetate), and Extavia (interferon beta-1b)); DMF, dimethyl fumarate; mAbs, monoclonal antibodies

- The ARR was highest in the OCR cohort (1.57) followed by the ALM cohort (0.79) using the published algorithm. With the revised algorithm, ARR reduction was highest in these sub-cohorts (**Figure 3**).

Figure 3. Annualized relapse rate in DMT sub-cohorts



ARR, annualized relapse rate; GA, glatiramer acetate; INF β-1a, interferon beta-1a; INF β-1b, interferon beta-1b; NTZ, natalizumab; OCR, ocrelizumab

CONCLUSIONS

- **Despite adjusting for steroid use in the revised algorithm, we unexpectedly found similar relapse rates in IV mAbs and BRACE/DMF. These results are contrary to reporting from clinical trials and practice, suggesting continued overestimation of relapses in patients treated with IV mAbs, likely due to unmeasured confounding.**
- **This algorithm warrants further improvement/revision to accurately estimate relapses in the age of mAbs.**

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