Relapse Resolution and HCRU in Patients with MS: A Retrospective Study of Relapse Therapy Alternatives to Corticosteroids

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Introduction

Corticosteroids (CS), oral (OCS) or intravenous methylprednisolone (IVMP) are considered the first-line agents for managing relapses in patients with multiple sclerosis (MS).[1] Other, typically non-first-line relapse treatments include repository corticotropin injection (RCI; H.P. Acthar® Gel, approved in the US), intravenous immunoglobulin (IVIG; not approved), and plasmapheresis (PMP; procedure).[1] Supporting evidence for use of IVIG is limited.[1]

Few studies have evaluated the real-world effectiveness of MS relapse treatments other than CS.[2] Most relapse measures do not account for relapses which may be related; here, we do so using the terms: 1) 'relapse episode' uses a standardized 30-day[1] window to inter-relate relapse events, 2) 'unresolved relapse' uses a subsequent event occurring within 30 days[1] of a prior event to inter-relate relapse events. These provide important resolution and effectiveness information.

Also, where multiple administrations may be given as a course of therapy, as may be the case with PMP and IVIG, we sought to address this in our evaluation.[3,4]

Administrative claims data from Humana, a US health and wellness company, was used in this study. Humana's coverage policy requires experience of an acute MS relapse, or contraindications or intolerance to CS in order to receive second-line relapse treatment. CS trial and failure is not explicitly required.

Objective

- To compare the distribution of unresolved relapse rates for later-line MS relapse treatments RCI, PMP and IVIG, using fixed enrollment criteria and accounting for courses of therapy
- To compare healthcare resource use (HCRU) in patients initiating RCI, PMP, and IVIG

Methods

Study Design:

- Retrospective, observational, cohort study
- Study period: January 1, 2008 to July 31, 2015
- Patients ages >18 and < 90 years†
- 1 year pre-index enrollment in a Medicare Advantage or Commercial plan.
- No treatment change (RCI to PMP/IVIG or vice versa) within 30 days of index relapse.
- Cohort A or B was assigned based on 1- or 2- years post-index enrollment, respectively.

Data Source: Humana provides Medicare Advantage, stand-alone prescription drug plan, and commercial health insurance across the US. Humana administrative claims data is comprised of integrated medical, pharmacy, and eligibility files.

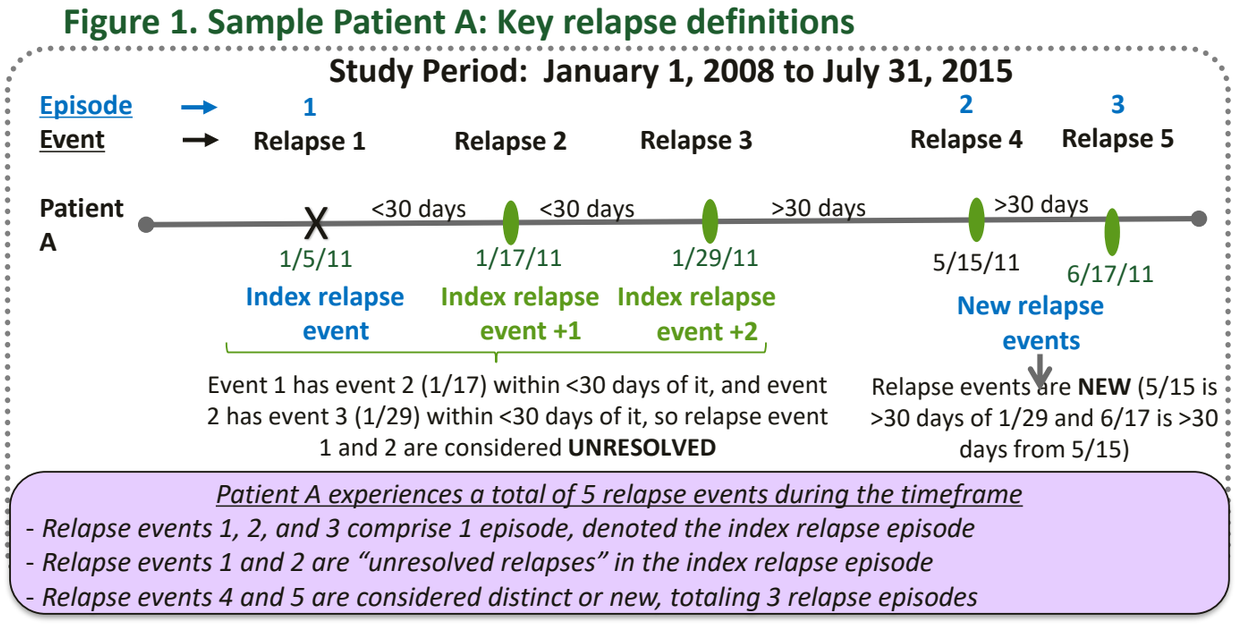
Measures:

- MS relapse event = inpatient admission or outpatient claim with a diagnosis of MS (ICD-9-CM code 340.xx) followed by a treatment of interest (RCI, PMP, IVIG) for relapse within 30 days.[5] Date of relapse event = date of treatment.
- The first relapse event observed = index relapse event; its date = index date.
- An "episode" comprised all relapse events occurring within 30 days of the first event. A relapse event was considered new (i.e. not part of the episode) if it occurred more than 30 days after the first event.

Methods (continued)

- A relapse event was considered an 'unresolved relapse' if the next relapse event occurred within 30 days (and new if >30 days).
- Based on the scientific literature[3,4], relapse events treated within 7 days of the index event with PMP or IVIG were considered purposeful administrations of PMP or IVIG, i.e. a course of therapy, not relapse events. This was also explored using data-driven methods.
- Patient characteristics included age, gender, race, geographic region, and plan type. MS functional impairment indicators included expanded disability status scale (EDSS) derived disability indicators (DDI), related neurological impairment indicators (RNII), and dalfampridine (Ampyra) use.[6]
- HCRU = inpatient (IP), outpatient (OP), emergency department (ED), and total visits (IP + OP + ED). Rehabilitation (Rehab) and magnetic resonance imaging (MRI) services were also examined.
- Disease-modifying therapies (DMT[1]) adherence was calculated using proportion of days covered (PDC).

Figure 1. Sample Patient A: Key relapse definitions



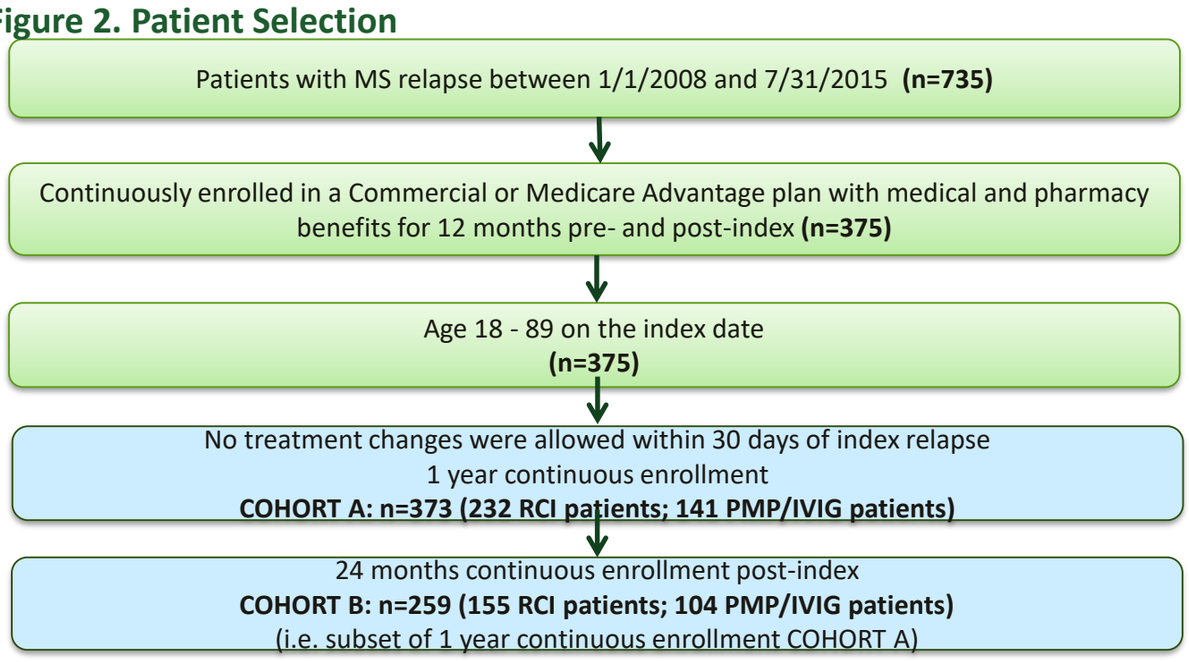
Analysis:

- All analyses were conducted by CHI using SAS Enterprise Guide version 7.1.
- PMP/IVIG groups were combined due to sample size.
- Chi square tests were used for categorical variables and t-tests were used for continuous variables.
- Pre-index analyses of patient characteristics and MS characteristics and post-index analyses of HCRU, Rehab, MRI, DMT PDC, Ampyra, EDSS-DDI and RNII were conducted groups in Cohorts A, B.
- Number and distribution of unresolved relapse events within the index relapse episode were assessed in RCI and PMP/IVIG groups in Cohort A.

Results

As shown in Figure 2, 373 patients were assigned to Cohort A [232 RCI, 141 PMP/IVIG]. Of these, 259 patients were assigned to Cohort B [155 RCI patients, 104 PMP/IVIG].

Figure 2. Patient Selection



Baseline characteristics of patients on RCI and PMP/IVIG indicated similar mean age (51.6 vs. 53.1 years, respectively). A larger proportion of patients on RCI was female (78.9% vs. 69.5%), in Medicare Advantage (88.4% vs. 64.5%), and had a higher mean number of functional impairment indicators EDSS-DDI (1.0 vs. 0.7) and RNII (2.2 vs. 1.9) and Ampyra use, vs. PMP/IVIG ***[Data not shown]***.

Table 1. Post-index HCRU, MS impairment, DMT use (Cohort A: 1 year)

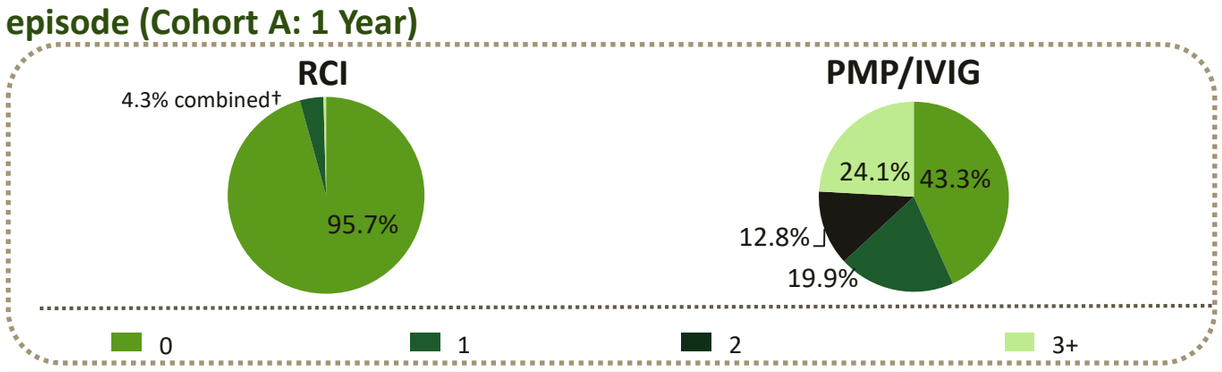
Measure, mean (SD)	RCI	PMP/IVIG	P value
Total service visits	**34.1 (27.0)**	**47.0 (34.4)**	**0.0001**
IP visits	**0.4 (0.8)**	**0.6 (1.2)**	**0.01**
OP visits	**32.7 (26.3)**	**45.4 (33.6)**	**0.0001**
ED visits	1.0 (1.6)	1.0 (2.2)	0.94
Rehab services	7.2 (18.2)	7.8 (15.5)	0.73
MRI services	0.9 (1.0)	0.8 (1.0)	0.36
EDSS DDI	**1.1 (0.8)**	**0.8 (0.9)**	**0.0019**
RNII	**2.3 (1.2)**	**1.8 (1.3)**	**0.0006**
DMT PDC	0.71	0.66	0.2625
Use of Ampyra, n (%)	**46 (19.8%)**	**<10**	**<0.0001**

Compared to patients on PMP/IVIG, patients on RCI had significantly lower total service visits, driven by slightly lower inpatient and much lower outpatient visits (all p≤0.01). Worse MS functional impairment indicators observed in patients receiving RCI vs PMP/IVIG pre-index (EDSS-DDI, RNII) remained in the 1-year post-index; higher dalfampridine use was also seen, in keeping (all post-index group differences, p<0.01). Notably, adherence to DMTs (PDC) appeared similar in both groups (RCI: 0.71 vs. PMP/IVIG: 0.66) (Table 1).

HCRU in Cohort B (2-year post-index), indicated similar trends . Patients on RCI had lower outpatient visits leading to lower total visits, greater number of EDSS-DDI and RNII, and greater dalfampridine use compared to patients on PMP/IVIG (all p<0.07) ***[Data not shown]***.

For Cohort A, mean (SD) unresolved relapse events in the one year post-index period for the RCI and PMP/IVIG groups were 0.06 (0.38) and 1.52 (2.03), respectively. For cohort B, mean (SD) annualized unresolved relapse events in the two years post-index for RCI and PMP/IVIG groups were 0.06 (0.43) and 1.66 (2.21), respectively ***[Data not shown]***.

Figure 3. Proportion of Patients with unresolved relapses within the index episode (Cohort A: 1 Year)



Unresolved relapses within the index episode (Cohort A)		Figure 3 Analysis (individual administration**)	Analysis as a course of therapy
PMP/IVIG	0	61 (43.3%)	**93 (66.0%)**
	1	28 (19.9%)	**42 (29.8%)**
	≥2	52 (36.9%)	**<10 (<4.2%)**

95.7% of patients on RCI had 0 (i.e. no) unresolved relapses vs. 43.3% in the PMP/IVIG group. The distribution of patients on RCI with 1, 2 and ≥3 unresolved relapses was also consistently lower than that of PMP/IVIG ***[Figure 3]***. Similar results were observed for both groups in Cohort B (2 year), where 96.8% of patients receiving RCI had no unresolved relapses vs. 42.3% receiving PMP/IVIG ***[Data not shown]***.

The table accompanying Figure 3 shows the unresolved relapse analyses when considering PMP/IVIG treatment as a course of therapy rather than as an individual administration. As course of therapy, the proportion of patients on PMP/IVIG having unresolved relapses improves, i.e. 66.0% have 0 unresolved relapses, 29.8% have 1 unresolved relapse, and 4.2% have >=2 unresolved relapses.

Conclusions

- When accounting for continuous enrollment and courses of therapy, we confirm: effectiveness differences exist by treatment, and unresolved relapse rates are lower with RCI vs. PMP/IVIG.
- Index relapse episode analyses in the 1 year- and 2 year- cohorts (A and B, respectively) indicate the vast majority of patients using RCI had no unresolved relapses (95.7%), vs. a lower proportion of patients using PMP/IVIG (66.0%).
- Patients on RCI appear more severe in their MS vs. those taking IVIG/PMP, with greater MS functional impairment indicators EDSS-DDI, RNII, and use of Ampyra in the pre- and post-index periods. In keeping, a higher proportion were enrolled in Medicare Advantage vs. those taking IVIG/PMP. No significant differences were found in age or DMT-adherence between groups.
- Significant differences were seen in all-cause HCRU post-index, consistent with a prior claims study, with the RCI group having slightly less IP use.[2]
- Given high relapse resolution rates, RCI should be considered for relapse treatment in patients with severe MS indicators, as characterized here. These patients (the patient type described here) experience strong relapse resolution benefit from RCI.
- Timely relapse resolution and relapse treatment burden are critical considerations. Future research should quantify the latter, for improved treatment selection and decision-making.
- We recommend including relapse resolution in future studies of relapse as an insightful measure.

Limitations

- Administrative claims data lack important clinical detail, such as disease severity. We implemented a number of definitions used in prior studies in order to mitigate this limitation.
- Relapses were identified based on treatment-seeking behavior using an established claims-based algorithm; treatment received outside a healthcare visit was not addressed.
- Index relapse events were first observed, which may/not be the actual first events. However, relapse resolution is based on the occurrence of subsequent relapses, not prior relapses.
- PMP and IVIG may differ in relapse resolution effectiveness; they are combined here. Since PMP/IVIG are administered as outpatient procedures, OP visits may inherently be higher.
- Treatment regimens involving use of PMP and IVIG in MS relapse are unclear.

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† In compliance with Humana privacy requirements