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Sub-analysis of geographical variations in the 2-year observational COPTIMIZE trial of patients with relapsing–remitting multiple sclerosis converting to glatiramer acetate

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Abstract

Background: Studies suggest that patients with relapsing–remitting multiple sclerosis (RRMS) who fail to benefit from a disease-modifying treatment (DMT) may benefit from converting to another DMT class. COPTIMIZE was a 24-month observational study designed to assess the disease course of patients converting to glatiramer acetate (GA) 20 mg daily from another DMT and the association of disease characteristics and reasons for converting. This sub-analysis was to determine if any findings varied by three geographic locations: Latin America (LA), Canada and Western Europe (CWE), and Eastern Europe (EE).

Methods: A total of 668 patients were included (263 LA, 248 CWE, 157 EE) in an analysis of annualized relapse rate (ARR) and annualized rate of deterioration (ARD), as well as secondary endpoints including reason for DMT switch and changes in disability and fatigue scores. Repeated-measures analysis of variance and log transformation were used to analyze ARR and ARD, whereas the Wilcoxon signed rank test was used for secondary endpoints.

Results: The sub-analysis of treatment outcomes stratified by region showed that Latin American patients had higher ARR before conversion to GA compared with patients from the other two areas and subsequently experienced the largest reduction in ARR. Latin American patients also had higher baseline rates of comorbidities and relapses with incomplete remissions and improved more than those in the other two regions based on measures of fatigue, quality of life, depression, and cognition scores. Latin American patients also generally had a better perception of the benefits associated with their conversion to GA in terms of efficacy and adverse events.

Conclusions: These findings indicate that, in RRMS patients, converting to GA is associated with positive treatment outcomes regardless of geographic location. However, the reasons for converting and the type and degree of any associated benefits appear to vary depending on various factors, including patients' geographical location.

Keywords: Multiple sclerosis, RRMS, Glatiramer acetate, Demographics

Background

Multiple sclerosis (MS) is a chronic relapsing disorder of the central nervous system characterized by inflammation, multifocal demyelination, and neuronal and axonal damage [1]. The majority of MS patients initially present with relapsing–remitting MS (RRMS) that frequently develops to a progressive disease course [1]. The prevalence of MS varies according to geographic location from 10 to 20 per 100,000 in Central and South America to >30 per 100,000 in northern Europe and North America [2].

Immunomodulating disease-modifying therapies (DMTs) have been shown to improve multiple measures of disease activity in RRMS patients, including the annualized relapse rate (ARR), proportion of relapse-free individuals, and accumulation of T2 lesion burden [3–5]. However, these agents are only partially effective in controlling disease progression; studies have reported treatment interruption or

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discontinuation because of lack of tolerability, progression of disability, or inadequate clinical response [6]. Additionally, the development of neutralizing antibodies, specifically with interferon β products (IFNs) and natalizumab [7], can interfere with the biologic response [8].

Converting to another DMT class represents one treatment strategy for MS patients with an inadequate response to first-line treatments or intolerant side effects [9]. Expert guidance on the specific steps of a conversion has been reported [10]; however, the lack of information on outcomes in different populations [11] results in limited guidance on regional patient considerations.

The COPTIMIZE study was designed to monitor clinical outcomes after converting from failing or ineffective DMT therapy for RRMS to glatiramer acetate (GA) in a prospective way. GA is approved in 57 countries as a 20 mg daily subcutaneous (s.c.) injection for reducing relapse frequency in patients with RRMS. It has long-term efficacy and safety data, with the longest continuous treatment exposure of more than 20 years [12, 13]. The primary results of COPTIMIZE, presented elsewhere [14], indicate that a conversion to GA is associated with positive treatment outcomes and that the benefits vary depending on patients' reasons for changing. The primary objective of the present sub-analysis is to determine whether benefits associated with converting to GA were affected by therapeutic strategies and patient selection in different geographic locations: Latin America (LA), Canada and Western Europe (CWE), and Eastern Europe (EE).

Methods

Study design

Study design, patient eligibility criteria, and conduct of the COPTIMIZE have been previously reported [14]. Briefly, this post-hoc subgroup analysis attempted to describe any variation in results that might exist between three predefined geographical areas: LA (Argentina, Brazil, Chile, Mexico, Venezuela), CWE (Belgium, Canada, Denmark, France, Greece, Ireland, Portugal, Netherlands, Norway, Sweden), and EE (Hungary, Romania, Slovakia). Countries were grouped into regions based on similarity of healthcare systems, physician approaches [15], available treatment options [10, 16], and epidemiological characteristics of the population (disease prevalence, demographics, etc.) [2]. All countries investigated in this observational study reported the use of IFN-β and GA at baseline, with no anticipated systematic differences between regions. This study was conducted in accordance with the 18th World Medical Assembly (Helsinki) recommendations and amendments, as well as guidelines for Good Epidemiology Practice. The study protocol was approved by the institutional review boards and independent ethics committees at all participating study locations in each individual country; each site ensured all necessary regulatory submissions in accordance with local regulations including local data protection regulations. All patients provided informed, written consent according to local independent review board ruling.

Study endpoints

The primary objective was to assess the disease course in RRMS patients converting from IFN treatment to GA as measured by the primary endpoints of ARR and annualized rate of deterioration (ARD) (confirmed progression of Expanded Disability Status Scale [EDSS]/worsening mobility scores). Secondary data collected included reasons for DMT conversion, characteristics of patients failing to benefit from previous DMT, and change in EDSS and modified fatigue impact scale (MFIS) scores. Also recorded were quality of life (QoL) changes following GA conversion as measured by the Functional Assessment of Multiple Sclerosis (FAMS), cognition changes as evaluated by the Paced Auditory Serial Addition Test (PASAT), depression as measured by Centre for Epidemiologic Studies Depression (CES-D) scale, and change in adverse events (AEs) following the conversion.

Statistical analyses

Statistical analyses of parameters in this observational study required comparison of at least two endpoint measures, pre- and post-GA conversion, with data represented by descriptive procedures and figures, if necessary. Adjustment for missing data was not required to maintain statistical integrity of the analyses, and annualized rates (primary endpoints) were calculated for each subject using all the available data. Other parameters, which provide additional data for evaluation of the patient status prior to and following conversion to GA, were reported in a non-obligatory manner. Tests of significance (signal rank test and binominal test) were used to measure changes in efficacy parameters from baseline to final examination. ARR and ARD pre- and post-conversion were analyzed using repeated measures analysis of covariance using the maximum likelihood ratio. Log transformation was implemented to the ARR and ARD to establish if there was a significant deviation from normality (i.e., $P < .001$ using the Shapiro-Wilk test). The Wilcoxon signed rank test was used within groups for EDSS, MFIS, FAMS, PASAT, and CES-D.

Results

Patient disposition

Overall, 672 patients from 148 centers across 19 countries were enrolled, with 668 patients included in the analysis (excluding four patients from Taiwan): 263 LA, 248 CWE, and 157 EE patients (Table 1). Patient characteristics were comparable at baseline between regions,

Table 1 Baseline patient demographics, disease characteristics, and DMT history

Characteristics	LA (*n* = 263)	CWE (*n* = 248)	EE (*n* = 157)
Female gender, *n* (%)	189 (71.9)	175 (70.6)	108 (68.8)
Mean age, years (± SD)	40.1 (10.1)	43.0 (10.2)	34.7 (8.4)
Patients with comorbidities at recruitment, *n* (%)	27 (10.3)	19 (7.7)	8 (5.1)
Depression	13 (4.9)	6 (2.4)	1 (0.6)
Anxiety	2 (0.8)	1 (0.4)	1 (0.6)
Hypertension	1 (0.4)	4 (1.6)	2 (1.3)
Patients with concomitant therapies at time of recruitment, *n* (%)	24 (9.1)	15 (6.1)	7 (4.5)
Psychoanaleptics	14 (5.3)	5 (2.0)	1 (0.6)
Antiepileptics	6 (2.3)	2 (0.8)	1 (0.6)
Thyroid therapy	3 (1.1)	3 (1.2)	N/A
Mean disease duration since onset, months (± SD)[a]	98.0 (82.9)	100.1 (84.4)	92.3 (63.9)
Mean disease duration since diagnosis, months (± SD)[b]	68.9 (59.6)	72.1 (70.7)	67.9 (48.5)
Mean ARR, events/year (± SD)[c]	1.0 (0.8)	0.8 (0.6)	0.7 (0.5)
Patients in ARR range, *n* (%*)			
0.00–1.25	166 (67.5)	193 (84.6)	130 (88.4)
1.25–3.25	78 (31.7)	35 (15.4)	17 (11.6)
>3.25	2 (0.8)	0 (0.0)	0 (0.0)
Data unavailable	17	20	10
Clinical type of MS, *n* (%[d])			
RRMS with incomplete remissions	171 (67.6)	117 (47.6)	91 (59.1)
RRMS with complete remission	80 (31.6)	122 (49.6)	62 (40.3)
Clinically isolated syndrome	0 (0.0)	0 (0.0)	1 (0.6)
Other	2 (0.8)	7 (2.8)	0 (0.0)
Data unavailable	10	2	3
Diagnosed with MS by criteria, *n* (%[d])			
McDonald	217 (83.8)	194 (78.5)	143 (92.3)
Poser	42 (16.2)	53 (21.5)	12 (7.7)
Data unavailable	4	1	2
Mobility, *n* (%[d])			
Asymptomatic	45 (19.8)	46 (20.0)	20 (14.9)
Able to walk unaided for >500 m	96 (42.3)	126 (54.8)	112 (83.6)
Able to walk unaided for <500 m	30 (13.2)	27 (11.7)	2 (1.5)
Walking with bilateral support	13 (5.7)	9 (3.9)	0 (0.0)
Walking with unilateral support	33 (14.5)	18 (7.8)	0 (0.0)
Need of a wheelchair outdoors	10 (4.4)	4 (1.7)	0 (0.0)
Data unavailable	36	18	23
Mean EDSS score (± SD)[e]	3.5 (2.2)	2.8 (1.9)	2.6 (1.0)
Mean CES-D score (0–60) (± SD)[f]	16.0 (11.7)	16.0 (10.3)	20.6 (19.5)
Mean MFIS score (0–84) (± SD)[g]	32.3 (19.7)	31.4 (19.1)	33.7 (27.9)
Mean FAMS score (0–176) (± SD)[h]	109.4 (37.8)	100.8 (34.3)	77.7 (59.4)
Mean PASAT score (0–60) (± SD)[i]	35.6 (13.6)	36.7 (15.7)	51.8 (5.9)

Table 1 Baseline patient demographics, disease characteristics, and DMT history *(Continued)*

Mean observation duration, months (± SD)[j]	20.5 (6.3)	18.6 (7.7)	19.2 (7.8)
Number of DMT classes used (%) (converters only)			
1	206 (85.5)	201 (83.4)	143 (92.9)
2	32 (13.3)	38 (15.8)	10 (6.5)
3	3 (1.2)	2 (0.8)	1 (0.6)
Non-converters	22	7	3
Previous type and mode of IFN-β used, %[k]			
IFN-β-1a (i.m.)	30.3	36.0	47.4
IFN-β-1b (s.c.)	30.3	25.9	30.5
IFN-β-1a (s.c.)	35.5	30.7	21.4
Reason for conversion to GA, *n* (%)[l]			
Lack of previous DMT efficacy	171 (71.0)	78 (32.4)	92 (59.7)
Presence of neutralizing antibodies	1 (0.4)	44 (18.3)	2 (1.3)
Intolerable adverse events associated with previous DMT	98 (40.7)	132 (54.8)	55 (35.7)
Flu–like symptoms	67 (27.8)	73 (30.3)	40 (26.0)
Subjective	29 (12.0)	37 (15.4)	17 (11.0)
Skin reactions	15 (6.2)	14 (5.8)	20 (13.0)
Blood work	7 (2.9)	18 (7.5)	4 (2.6)
Others	21 (8.7)	39 (16.2)	4 (2.6)
Not specified	1 (0.4)	1 (0.4)	0 (0.0)
Other	8 (3.3)	21 (8.7)	36 (23.4)
Non-converters	22	7	3
Discontinuation of GA, *n* (%)	66 (25.1)	77 (31.1)	30 (19.1)
Perceived lack of efficacy by physician	19 (7.2)	7 (2.8)	16 (10.2)
Perceived lack of efficacy by patient	7 (2.7)	14 (5.7)	6 (3.8)
Adverse events	9 (3.4)	17 (6.9)	4 (2.5)
Lost to follow-up	14 (5.3)	24 (9.7)	2 (1.3)
Other	15 (5.7)	8 (3.2)	3 (1.9)

[a]Missing data in 24 LA, 28 CWE, and 5 EE patients
[b]Missing data in 15 LA, 21 CWE, and 4 EE patients
[c]Missing data in 7 LA, 2 CWE, and 3 EE patients
[d]Adjusted percentage of patients with data available
[e]Missing data in 55 LA, 9 CWE, and 8 EE patients
[f]Missing data in 116 LA, 103 CWE, and 150 EE patients
[g]Missing data in 113 LA, 118 CWE, and 150 EE patients
[h]Missing data in 55 LA, 9 CWE, and 8 EE patients
[i]Missing data in 197 LA, 103 CWE, and 150 EE patients
[j]Missing data in 11 LA, 17 CWE, and 10 EE patients
[k]Missing data in 32 LA, 20 CWE, and 3 EE patients
[l]Adjusted percentage of patients with data available. Patients were allowed to cite ≥1 reason for conversion to GA. Therefore, the percentage may exceed 100 %

excluding EE patients, who were younger and reported fewer comorbidities and concomitant medications than LA and CWE patients. Baseline disease characteristics that were similar across regions (Table 1) included disease duration from onset, diagnosis, and mean ARR. Distribution of baseline ARR score varied slightly, with the majority of patients experiencing between 0 and 1.25 events/year. LA patients reported the highest disability (baseline EDSS) and the highest frequency of RRMS with incomplete remissions. At baseline, the majority of patients had received one previous DMT regimen in one class of agents (Table 1). Reports of flu-like symptoms were the most common reason for converting to GA. The majority of patients in all regions were converted from IFN-β therapy.

Annualized relapse rate

ARR was significantly decreased in all groups following the conversion to GA (Fig. 1). LA patients, who had the highest baseline ARR rate, also had the greatest ARR

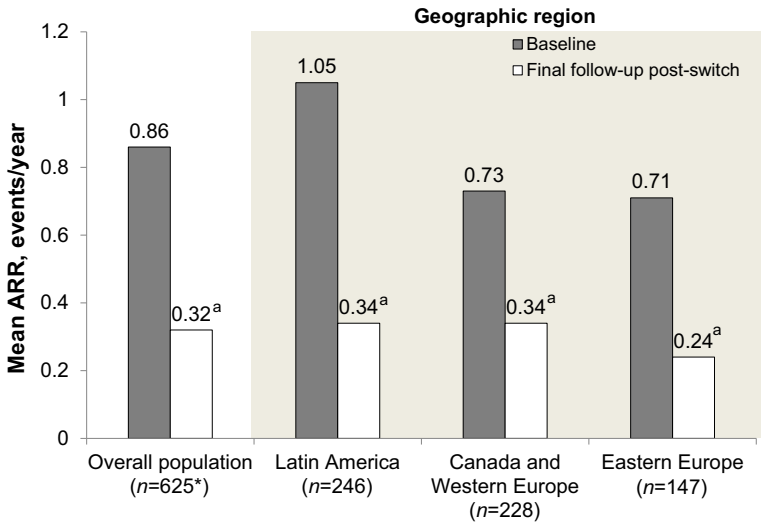

Fig. 1 Reduction of annualized relapse rate by geographic region. [a]$P < .0001$ vs. baseline. *The overall population size does not each the sum of the three individual regions due to four patients in Taiwan that excluded from the regional analysis. *ARR* annualized relapse rate

reduction (1.05 ± 0.78 pre-conversion to 0.34 ± 0.86 post-conversion; $P < .0001$, Shapiro-Wilk test). ARR went from 0.73 ± 0.58 to 0.34 ± 0.84 ($P < .0001$) in CWE patients and 0.71 ± 0.50 to 0.24 ± 0.92 ($P < .0001$) in EE patients.

Disease progression

In total, 499 patients had ≥1 EDSS assessment after baseline examination, with the overall population showing a significant increase in EDSS score (i.e., progression to worse disability) from 2.9 at baseline to 3.02 at final follow-up, post-switch ($P = .0256$). There was a significant difference between regions in the degree of change in EDSS score while on GA therapy ($P = .0230$, Wilcoxon signed-rank test), driven by a significant increase in CWE patients' EDSS score of 0.26 ± 1.18 ($P = .0016$). Neither LA nor EE patients had significant changes in mean EDSS score from baseline. Improved (i.e., numerically lowered) EDSS scores were seen in 32.5 %, 24.4 %, and 33.8 % of LA, CWE, and EE patients, respectively. There was no change from baseline in 35.8 %, 34.9 %, and 41.2 %, respectively. Deterioration was reported in 31.8 %, 40.7 %, and 25.0 %, respectively.

Disease activity

Disease activity while receiving GA varied. LA patients reported the highest incidence of frequent exacerbations and of fast progression of MS (Table 2). Fewer LA patients reported rarely experiencing exacerbations (27.9 %, vs. 43.5 % CWE and 66.0 % EE patients).

Change in mobility

The majority of patients showed no change in mobility scores (63.4 %, 62.8 %, and 67.5 % of LA, CWE, and EE patients, respectively). Mobility scores improved in 17.1 % LA and 18.9 % CWE patients, with a significant improvement in 23.0 % of EE patients ($P = .0079$). Mobility scores deteriorated in 19.4 %, 18.4 %, and 9.5 % of LA, CWE, and EE patients, respectively. Data were missing for 47 LA, 52 CWE, and 31 EE patients.

Table 2 MS disease activity over the 2-year study period

Patients, *n* (%)	LA ($n = 251$)	CWE ($n = 246$)	EE ($n = 153$)
Stable MS (Stage 1)	37 (14.7)	47 (19.1)	22 (14.4)
Rare exacerbations (≤1 per year, Stage 2a)	70 (27.9)	107 (43.5)	101 (66.0)
Slow progression (≤0.5 EDSS points per year, Stage 2b)	48 (19.1)	35 (14.2)	6 (3.9)
Frequent exacerbations (>1 per year, Stage 3a)	80 (31.9)	43 (17.5)	21 (13.7)
Fast progression (>0.5 EDSS points per year, Stage 3b)	11 (4.4)	3 (1.2)	1 (0.7)
Not classified/not available	5 (2.0)	11 (4.5)	2 (1.3)

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