Exploring the Relationship Between Serum GDF-15 and Disease Stability in Patients With a First Clinical Demyelinating Event Treated With Subcutaneous Interferon β-1a or Placebo in the REFLEX Study

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CONCLUSIONS

There was an association between GDF-15 and decreased inflammation in MS

GDF-15 levels were higher in patients treated with IFN than with placebo from 6 months after initiation. The difference was more profound in patients with higher GDF-15 at baseline

Patients aged >30 years had a reduced level of GDF-15 on study

INTRODUCTION

- Subcutaneous interferon beta-1a (sc IFN β-1a) is a disease-modifying therapy for multiple sclerosis (MS), with an estimated cumulative exposure of 1,889,156 patient-years (to 30 April 2022)
- In the REFLEX study (NCT00404352), sc IFN β-1a 44 µg three times weekly (tiw) led to stable disease activity in patients with a first clinical demyelinating event, compared with placebo. Stable disease activity was based on MS conversion, lesion counts, and relapse-free rates[1]
- Serum levels of the anti-inflammatory cytokine growth differentiation factor 15 (GDF-15) are shown to be higher in clinically stable MS patients receiving disease-modifying therapy (DMT) than patients not receiving DMT

OBJECTIVE

Explore findings for serum GDF-15 in patients from the REFLEX study who received either sc IFN β-1a or placebo, by using mixed models repeated measures (MMRM) to account for repeated GDF-15 measures over time

METHODS

- In the REFLEX study, patients were randomised to receive sc IFN β-1a 44 µg once weekly, 44 µg tiw, or placebo, for up to 24 months
- All randomised patients with ≥1 non-missing GDF-15 value at baseline (the start of the REFLEX study) and post-baseline were included
- A *post hoc* exploratory analysis was undertaken to investigate the relationship between serum GDF-15 over time and disease stability in MS, among patients from REFLEX
- Results of the REFLEX study showed higher clinical stability in MS patients of the sc IFN β-1a tiw group.[1] As such, this analysis used the latter treatment group as a proxy of disease stability
- The impact of multiple covariates or factors on serum GDF-15 were assessed using a multivariate approach, and MMRM was used to account for all time points simultaneously

Note: Per the REFLEX study protocol,[1] 58/161 patients in the placebo arm with CDMS conversion during the double-blind period were switched to open-label sc IFN β-1a 44 µg tiw.

RESULTS

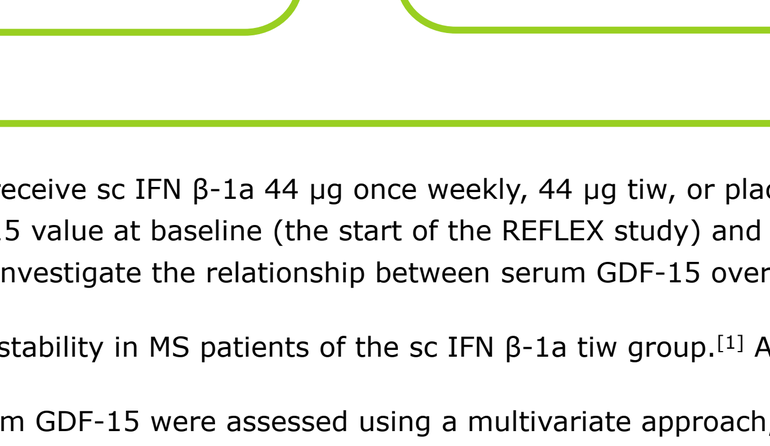
Table 1. Patient Demographic and Disease Characteristics (GDF-15 Analysis Set, N=318)

	Placebo (N=161)	sc IFN β-1a 44 µg tiw (N=157)
Age (years), mean ± SD	30.6 ± 7.6	30.6 ± 8.6
Female gender, n (%)	105 (65.2)	103 (65.6)
Time since first demyelinating event (days), mean ± SD	57.6 ± 4.3	57.6 ± 3.7
Multifocal classification by adjudication committee, n (%)	76 (47.2)	74 (47.1)
Use of steroid treatment, Yes, n (%)	113 (70.2)	111 (70.7)
Number of Gd+ lesions, mean ± SD	1.2 ± 2.6	1.3 ± 2.5
Number of T1 hypointense lesions, mean ± SD	5.5 ± 7.8	5.9 ± 6.9
Number of T2 lesions, mean ± SD	20.9 ± 20.1	22.4 ± 18.5
Normalised brain volume (cm^3), mean ± SD	1545.76 ± 63.09	1536.73 ± 75.18

Gd+, gadolinium-enhancing; **SD**, standard deviation

- Blood samples from 157 sc IFN β-1a tiw-treated and 161 placebo recipients were analysed
- Baseline demographics and disease characteristics were similar between cohorts (**Table 1**)
- **Figure 1** shows no differences in GDF-15 levels at baseline (median GDF-15 at baseline: 325.73 pg/mL)
  - After 6 months, least squares (LS)-mean serum GDF-15 was about 15% higher in treated vs placebo patients (396.87 vs 337.77 pg/mL; p=0.0002)
  - Higher LS-mean serum GDF-15 for treated vs placebo patients was also seen at Months 12 (390.46 vs 317.72 pg/mL; p<0.0001) and 24 (366.61 vs 321.36 pg/mL; p=0.0213)

Figure 1. GDF-15 Levels Over Time (GDF-15 Analysis Set, N=318)

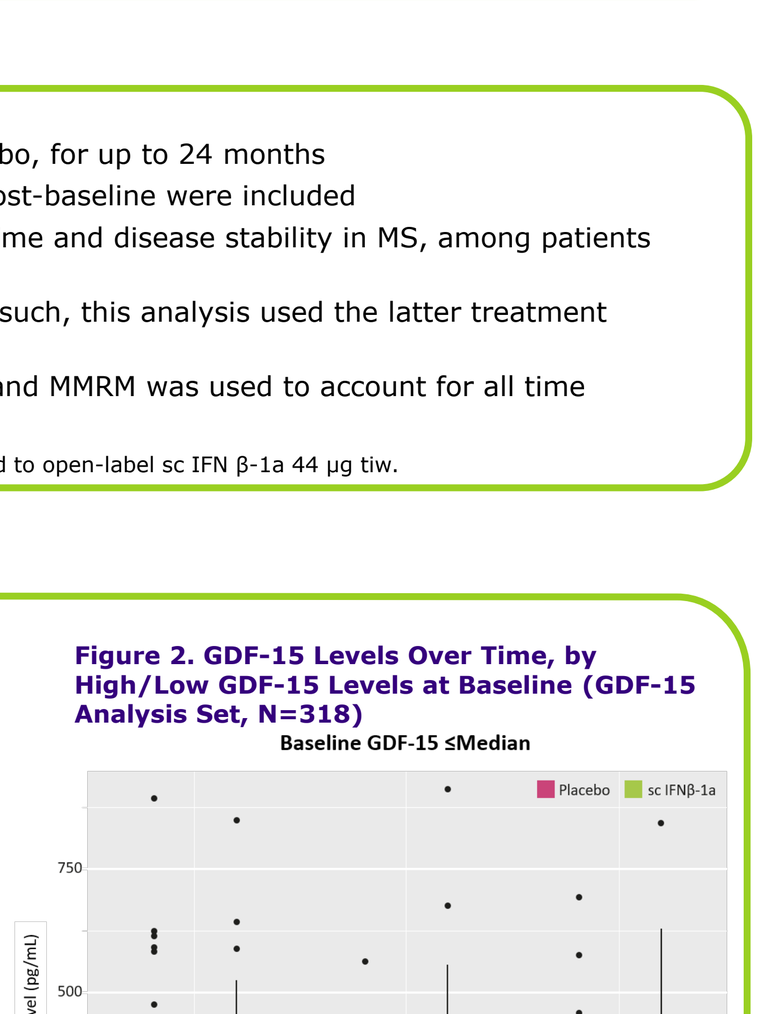


LS-means were estimated from a non-adjusted model
CI, confidence interval; **IFN**, interferon; **GDF-15**; growth differentiation factor 15; **LS**, least squares; **sc**, subcutaneous; **tiw**, three times weekly

- Differences between treatment groups were more prominent in patients who commenced the study at higher GDF-15 levels (**Figure 2**)
  - Among patients with high baseline GDF-15 levels: mean GDF-15 at 12 months was 485.30 pg/mL for patients treated with sc IFN β-1a vs 374.90 pg/mL for patients treated with placebo (p<0.0001)
- GDF-15 levels were 12% lower on study in patients aged >30 years at baseline (MMRM analysis of stratification variables: estimate 0.88, p=0.0006). Other stratification variables (multi/monofocal events, steroid use, and presence of T1-Gd+ lesions at baseline; see **Supplementary content**) had no significant effect on GDF-15 levels during the study.
  - MMRM analysis showed comparable results to non-adjusted model with respect to LS-mean estimates

SCAN HERE FOR ADDITIONAL CONTENT

Figure 2. GDF-15 Levels Over Time, by High/Low GDF-15 Levels at Baseline (GDF-15 Analysis Set, N=318)



Median GDF-15 at baseline = 325.73 pg/mL
CI, confidence interval; **IFN**, interferon; **GDF-15**; growth differentiation factor 15; **LS**, least squares; **sc**, subcutaneous; **tiw**, three times weekly

REFERENCE
1. Comi G, et al. *Lancet Neurol*. 2012;11:33–41.

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