Therapeutic effect of semaglutide on pulmonary function and fibrosis in a bleomycin-induced and spirometry-confirmed mouse model of IPF

Authors
Asbjørn Graver Petersen[1], Denise Oró[1], Alba Manresa Arraut[1], Martin Rønn Madsen[1], Ulf Simonsen[2], and Michael Feigh[1]

[1]Gubra, Hørsholm, Denmark
[2]Aarhus University, Aarhus, Denmark

Corresponding author
Michael Feigh - mfe@gubra.dk

BACKGROUND & AIM

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and fatal interstitial lung disease.

Presently, there are not efficient therapeutic tools for the treatment of IPF. Glucagon-like peptide-1 receptor (GLP-1R) activation exerts anti-inflammatory action and might play a role in pulmonary dysfunction and fibrotic development in IPF.

The aim of the present study was to study the therapeutic effects of the GLP-1R agonist, semaglutide, in a bleomycin-induced (BLEO) and spirometry-confirmed mouse model of IPF.

METHODS

10-12 weeks old C57BL/6JRj male mice received either a single intratracheal instillation of bleomycin (1.5 mg/kg, 50 µL) or saline (CTRL) at study day 1. To ensure correct bleomycin administration, only animals that showed a sustained ≥ 5% weight loss at day 7 were randomized into treatment groups.

Pulmonary terminal end-points included spirometry (Flexivent), hydroxyproline (HP) content, and quantitative histomorphometry for markers of inflammation and fibrosis. Histopathological Aschroft scoring was performed using Gubra Histopathological Objective Scoring Technique (GHOST).

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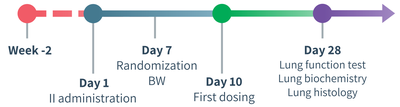
1 Study outline



Group	Animal model	Name	Number of animals	Dose [nmol/kg]	Route of administration	Dosing frequency
1	CTRL	CTRL Vehicle	12	NA	SC	QD
2	BLEO-IPF	BLEO-IPF Vehicle	10	NA	SC	QD
3	BLEO-IPF	BLEO-IPF Semaglutide	11	30	SC	QD

2 Improvement in metabolic and biochemical parameters

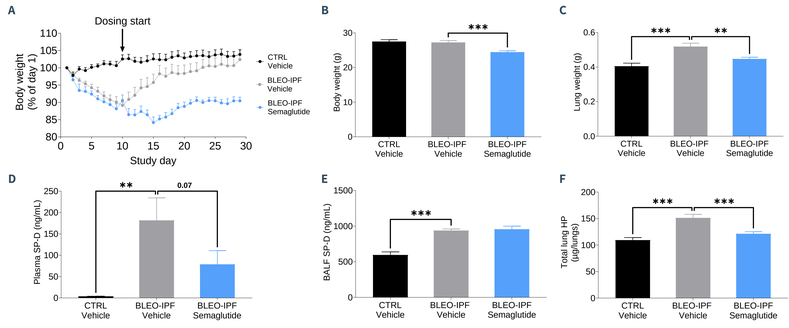


Figure 1. Metabolic and biochemical parameters in BLEO-IPF mice. **(A)** Body weight change relative to baseline (day 1). **(B)** Terminal body weight (g). **(C)** Terminal lung weight (g). **(D)** Plasma surfactant protein D (SP-D). **(E)** Bronchoalveolar lavage (BALF) SP-D. **(F)** Terminal lung total HP. Mean ± SEM. **p<0.01 and ***p<0.001 compared to BLEO-IPF Vehicle (Dunnett's test one-factor linear model).

3 No effect on parameters of pulmonary dysfunction

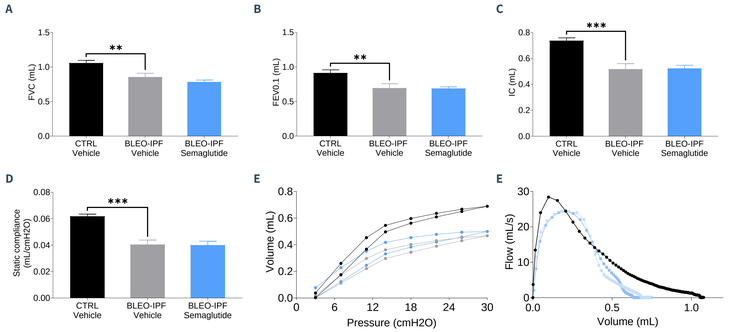
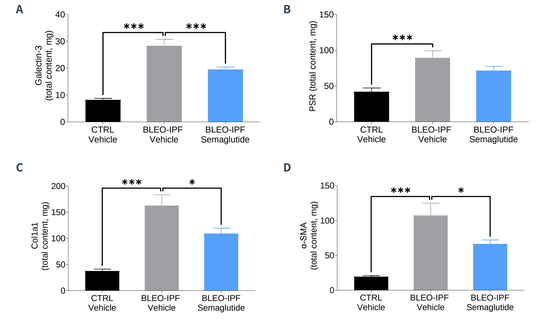


Figure 2. Pulmonary function testing in BLEO-IPF mice. **(A)** Forced vital capacity (FVC). **(B)** Forced expiratory volume in 0.1 seconds (FEV0.1). **(C)** Inspiratory capacity (IC). **(D)** Static compliance. **(E)** Pressure-volume curves. **(F)** Flow-volume curve. Mean ± SEM. **p<0.01 and ***p<0.001 compared to BLEO-IPF Vehicle (Dunnett's test one-factor linear model).

4 Improvement in histological markers of inflammation, fibrosis, and fibrogenesis



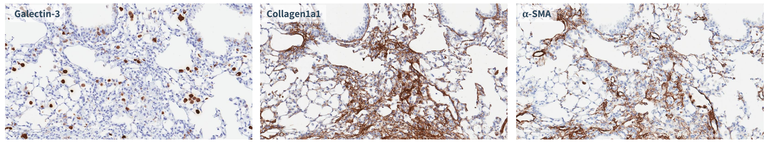


Figure 3. Lung quantitative histological markers in BLEO-IPF mice. Histomorphometric assessments were performed by conventional IHC image analysis (panels A-D). **(A)** Total galectin-3 content. **(B)** Total PSR content. **(C)** Total collagen-1a1 content. **(D)** Total alpha-smooth muscle actin (α-SMA) content. Mean ± SEM. *p<0.05 and ***p<0.001 compared to BLEO-IPF Vehicle (Dunnett's test one-factor linear model). Bottom panels: Representative galectin-3, collagen 1a1 and α-SMA photomicrographs for BLEO-IPF semaglutide (scale bar, 100 µm).

5 Improvement in histopathological Ashcroft scoring

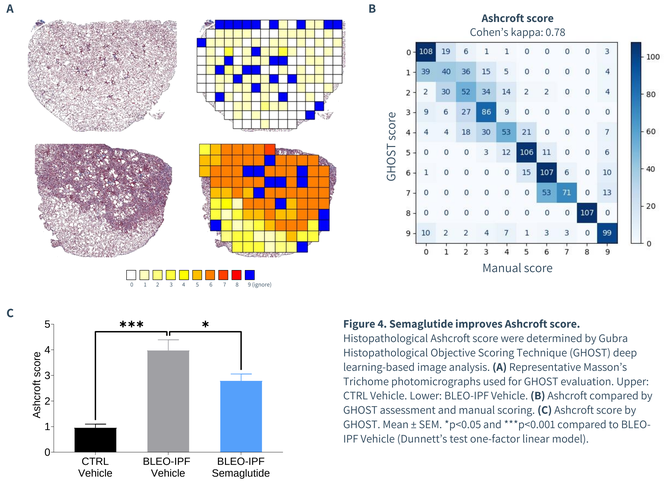


Figure 4. Semaglutide improves Ashcroft score. Histopathological Ashcroft score were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. **(A)** Representative Masson's Trichome photomicrographs used for GHOST evaluation. Upper: CTRL Vehicle. Lower: BLEO-IPF Vehicle. **(B)** Ashcroft compared by GHOST assessment and manual scoring. **(C)** Ashcroft score by GHOST. Mean ± SEM. *p<0.05 and ***p<0.001 compared to BLEO-IPF Vehicle (Dunnett's test one-factor linear model).

CONCLUSION

- Semaglutide reduces terminal body weight, lung weight, and lung total hydroxyproline content.
- Semaglutide reduces plasma SP-D levels.
- Semaglutide provides no improvements in pulmonary functions tests.
- Semaglutide reduces quantitative histological markers of fibrosis, inflammation and fibroblast cell activation.
- Semaglutide improves fibrosis severity evaluated by histopathological Ashcroft score.
- The BLEO-IPF mouse represent a translational preclinical model for exploring novel therapeutic agents for IPF.