#20449 Antifibrotic treatment with nintedanib restores bladder dysfunction in mice with spinal cord injury

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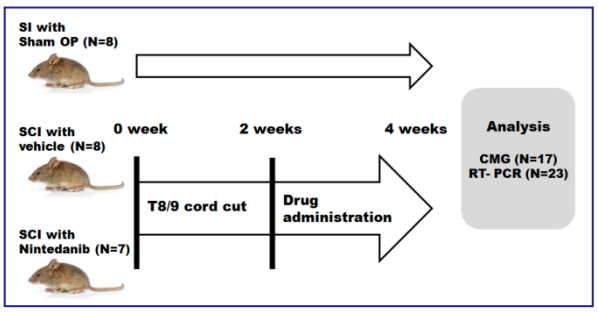
Introduction

- It has been revealed that bladder fibrosis induced by chronic bladder schemia, partial bladder outlet obstruction, or spinal cord injury (SCI) has a close relationship with bladder dysfunction in these disease conditions [1,2,3]
- Nintedanib, which has been approved as a therapeutic agent for idiopathic pulmonary fibrosis, blocks the receptors of pro-fibrotic growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF).
- Therefore, we investigated whether the anti-fibrotic treatment with nintedanib can restore lower urinary tract (LUT) dysfunction using mice with SCI

Materials and Methods

- Twenty-three female C57BL/6 mice were divided into 3 groups: In group A, spinal intact (SI) mice underwent sham operation; In group B, vehicle was administered for 2 weeks after 2-week SCI; and in group C, 100mg/kg of nintedanib was administered i.p. daily for 2 weeks after 2-week SCI. SCI was produced by complete transection of the spinal cord at the level of T 8/9
- At 4 weeks after SCI, filling cystometrograms (CMGs) were recorded under an awake condition. First, under 1.5-2.0% isoflurane anesthesia, a PE-50 tube was inserted into the bladder through the dome as a cystostomy catheter. After complete recovery from the anesthesia, CMGs were recorded by filling the bladder with saline (0.01 mL/min) to observe rhythmic bladder contractions for at least 120 min. After bladder activity stabilized, the data were collected
- Intercontraction intervals (ICI), non-voiding contractions (NVC), voided volume, and voiding efficiency were measured and compared. Then mRNA expression of HIF-1, VEGF, FGF-1, TGF-β, Collagen 1a (Col 1a), and Col 3a in bladder tissue were measured by RT-PCR

Fig. 1. Study design



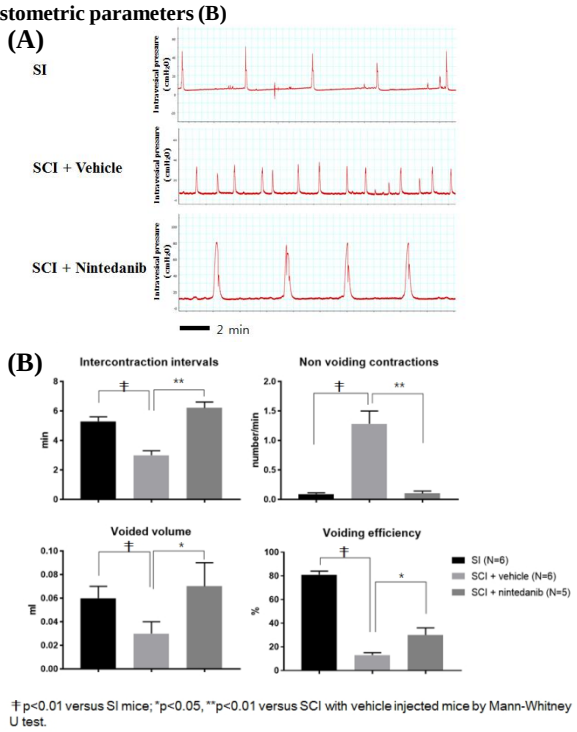
Resuls & Interpretations

- In CMGs, ICI, the number of NVC, voided volume, and voiding efficiency were significantly improved in group C compared to group B (Fig. 2)
- TGF-β1, FGF2, collagen 1a, fibronectin, vimentin was increased in group B, but decreased in group C (Fig. 3 B).
- Collagen 1a was significantly increased in seperated detrusor muscle in group B (Fig. 3 B) comparing with in whole bladder tissue (Fig. 3 A)
- The levels of FGF2 was increased in group B and decreased in group C, but VEGF was not increased in group B (Fig. 3 B).
- HIF-1 was increased in group B, but not changed by nintedanib (Fig. 3 A)

Interpretations

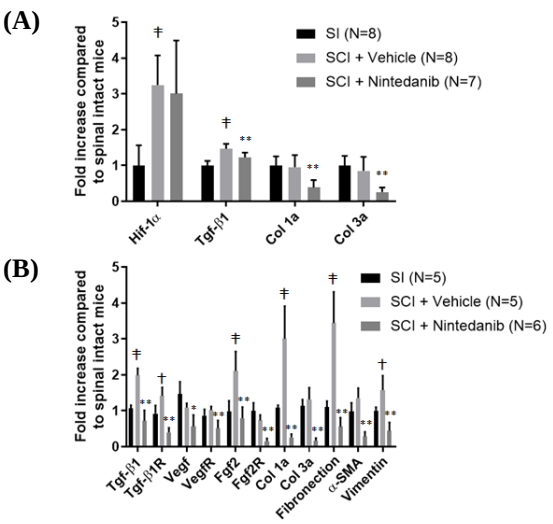
- Bladder distention induces chronic bladder ischemia, evident as upregulations of HIF-1 and TGF-β. TGF-β, which is known as an important regulatory factor that modulates the tissue fibrosis, is upregulated by HIF-1 or other pro-fibrotic growth factors such as FGF and PDGF
- Nintedanib induced functional improvements of both storage and voiding dysfunctions in SCI mice, which is associated with the changes in growth factors such as TGF-β1, and FGF2 as well as in the fibrosis evident as changes of transcripts such as collagen, fibronectin, vimentin, and α-SMA.
- However, nintedanib did not improve the HIF-1 level, indicating that nintedanib can have an antifibrotic effect without affecting bladder ischemia.
- Significant changes in collagen 1a in the seperated detrusor muscle than in the whole bladder indicate that fibrotic changes are more active in the detrusor muscle.
- Compared with changes in level of VEGF, the level of FGF2 changes more significantly before and after treatment, suggesting that FGF2 is more significantly involed in TGF-β1 production and fibrosis.

Fig. 2 Representative cystometrograms (A) and comparison of cystometric parameters (B)



†p<0.01 versus SI mice; *p<0.05, **p<0.01 versus SCI with vehicle injected mice by Mann-Whitney U test.

Fig. 3 mRNA expressions in whole bladder tissue (A), and seperated detrusor tissue (B) from SI mice, SCI with vehicle injected mice, and SCI with nintedanib injected mice.



†p<0.05 , ‡p<0.01 versus SI mice; *p<0.05, **p<0.01 versus SCI with vehicle injected mice by Mann-Whitney U test.

Conclusions

- Nintedanib induced functional improvements of both storage and voiding dysfunctions in SCI mice.
- Thus, inhibition of fibrosis-related growth factors could be an effective modality for the treatment of neurogenic LUT dysfunction and bladder remodeling after SCI.

References

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Conflict of Interest:
None

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