Masitinib for the treatment of amyotrophic lateral sclerosis (ALS)

Preclinical overview

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The phase 3 study of masitinib as an add-on therapy to riluzole in ALS was a success, with masitinib demonstrating a clinically meaningful retardation of disease progression.

- Masitinib orally administered at 4.5 mg/kg/day in ALS patients with a baseline ALSFRS-R progression rate of <1.1 points/month showed significant disease retardation in terms of:
  - \( \Delta \)ALSFRS-R and ALSFRS-R slope
  - Time elapsed between treatment initiation and decline in ALSFRS-R of nine points (PFS)
  - ALSAQ-40 score
  - FVC

These positive clinical findings are supported by equally compelling preclinical data.
Identification of aberrant glial cells that proliferate after paralysis onset in SOD1\(^{G93A}\) rats

Post-paralysis treatment with masitinib slows paralysis progression in SOD1\(^{G93A}\) rats

Tyrosine kinase inhibitors target aberrant glial cells via CSF1R

AB Science launches phase 2/3 clinical trial with masitinib
- Double blind
- 394 patients, 3 arms
- 48 weeks

Positive therapeutic effects

**Why post-paralysis tyrosine kinase inhibition in ALS?**

- Phenotypically aberrant astrocytes that promote motoneuron damage in a model of inherited amyotrophic lateral sclerosis

- Post-paralysis tyrosine kinase inhibition with masitinib abrogates neuroinflammation and slows disease progression in inherited amyotrophic lateral sclerosis

**REFERENCES**

PNAS


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Positive therapeutic effects

**REFERENCES**

PNAS

Isolation and characterization of aberrant glial cells (AbAs)

Symptomatic SOD1$^{G93A}$ rat

Spinal Cord culture

Relevant:

AbAs are the most toxic cells yet identified to embryonic motor neurons in cell culture

Díaz-Amarilla et al, 2011
Trias et al, 2013
Identification of aberrant glial cells in the degenerating spinal cord

• Appear around damaged motor neurons

• Express mixed astrocytic/microglial markers

AbA proliferation after paralysis onset

- Emerge only after paralysis onset (mediate rapid paralysis progression in SOD1G93A rats?)
- Active proliferation (targeted by antineoplastic drugs?)
- Lack of replicative senescence in vitro

Díaz-Amarilla et al, 2011
Trias et al, 2013
Masitinib as a prototypic inhibitor of type III growth factor receptors

- Anti-neoplastic drug (mast cell tumors & others)
- Currently in clinical trials for ALS, Alzheimer’s disease, MS, severe indolent mastocytosis and severe asthma.

Masitinib (AB1010)

Olivier Hermine

- Growth, Differentiation, Survival, Chemotaxis, Cytokine production
- Mast cells
- Stem Cell Factor (SCF)
- Growth, Differentiation, Survival, Chemotaxis, Cytokine production
- Macrophages/microglia
- Proliferation, Survival, Migration, Differentiation

M-CSF, IL-34

CSF1R

CSF-R1, PDGF-R, cKit, Lyn
Masitinib treatment after paralysis onset increases survival of SOD1<sup>G93A</sup> rats

Trias et al, JNI 2016

- Daily oral Masitinib (30mg/kg) or vehicle administration, starting after paralysis onset.
- Survival was increased even when treatment was started 7 days after paralysis onset.
- Masitinib prolongs post-paralysis survival with minor effects on overall survival.
- Well adapted to ALS clinical setting.
Hindlimb paralysis onset (day 1) (5-6 months old)

Vehicle (20d after onset)

Masitinib (30 mg/kg)
MOA-1:
Reduction of microgliosis and aberrant glial cells through CSF-1R inhibition

Trias et al, JNI 2016

Method:

• Treatment starting day 1 post-paralysis lasting 20 days.
• Masitinib 30mg/kg vs vehicle orally, 7/7 d
• Hindlimb onset only
Masitinib prevents motor neuron degeneration

Trias et al, JNI 2016
Alternative cellular targets for masitinib in the PNS
Mast cells cluster together with motor nerve endings and macrophages in EDL muscle.

Trias et al, Unpublished data
Mast cells cluster together with motor nerve endings and macrophages in EDL muscle

Trias et al, Unpublished data
MOA 2: Masitinib prevents mast cell and macrophage infiltration in the PNS
Masitinib prevents Schwann cells and vascular remodeling
Masitinib reduces mast cells accumulation in the sciatic nerve

Trias et al, Unpublished data
Masitinib reduces macrophages infiltration

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<th>Ventral Root</th>
<th>SOD1&lt;sup&gt;G93A&lt;/sup&gt; symptomatic</th>
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<th>Sciatic Nerve</th>
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Trias et al, Unpublished data
Conclusions

1 Multi-target

Multi-faceted

Further research needed
Masitinib reduces anomalous inflammatory response (neurotoxic environment) associated to rapid paralysis progression in both CNS and PNS.

- Targets microglial cells, macrophages and mast cells expressing CSFR1 or C-Kit.

- Masitinib could delay the dying-back of motor nerve endings and preserve NMJ innervation.

Conclusions

Tyrosine Kinase inhibitors: a hope for slowing paralysis progression in ALS patients?
THANKS !!

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