

IMPACT OF PROLONGED LINEZOLID TREATMENT ON MITOCHONDRIAL FUNCTION AND PROTEOME OF PERIPHERAL BLOOD MONONUCLEAR CELLS



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BACKGROUND

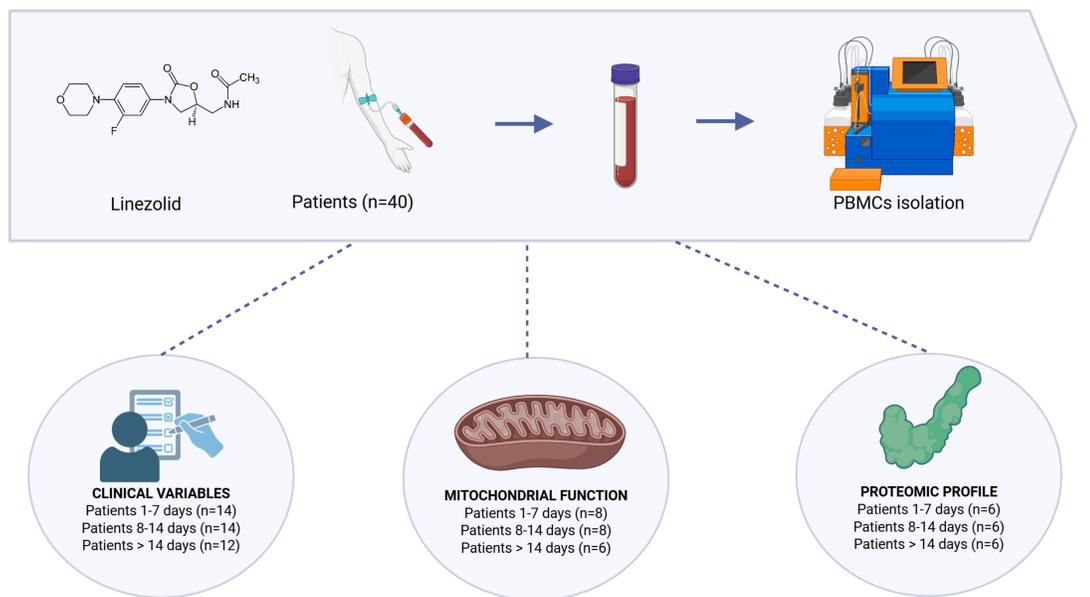
Linezolid is an oxazolidinone antibiotic active against resistant Gram- positive bacteria. Although **use beyond 28 days is not usually recommended**, extended treatments may be required. While linezolid does not affect human cytoplasmic ribosomes, **it can impair mitochondrial protein synthesis**, leading to side effects such as lactic acidosis and hypoglycemia. A reduction in mitochondrial protein synthesis has been documented in peripheral blood mononuclear cells (PBMCs), **mainly impacting complex IV of respiratory chain**.

OBJECTIVE

To **evaluate mitochondrial function** in PBMCs from patients treated with linezolid for different durations and to perform **proteomic analysis** of these cells.

MATERIAL AND METHODS

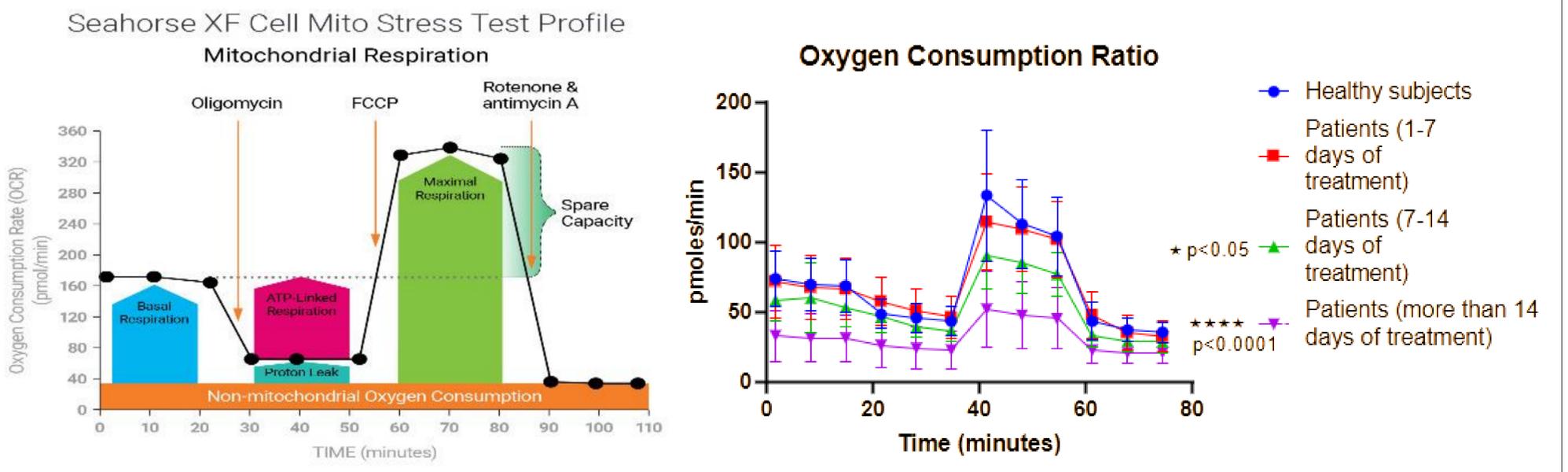
PBMCs were isolated from healthy subjects and linezolid-treated patients and stored for analysis. Mitochondrial respiration was measured using **Seahorse XF assays**, while proteomic profiling was performed via **LC-MS/MS**. Differential protein expression was analysed in **R**, with significant proteins identified based on \log_2 fold-change ≥ 0.58 or ≤ -0.58 and $p < 0.05$ and visualized using Volcano plots and STRING protein-protein interaction networks.



RESULTS

Mitochondrial function **declined progressively with longer treatment duration**, with maximal respiratory capacity as the most affected parameter. Proteomic analysis identified 6,587 downregulated proteins and 50 were common to all patient groups. Notably, 28 were related to mitochondrial ATP synthesis, **predominantly involving complexes I and IV**.

Graph 1: A) Seahorse XFp Cell Mito Stress Test profile, showing the key parameters of mitochondrial function. B) Mitochondrial function as determined in our study.



CONCLUSION AND RELEVANCE

Prolonged linezolid treatment causes progressive **mitochondrial dysfunction** in PBMCs, evident in both functional assays and proteomic profiles. Concordant **changes in respiration and protein expression** highlight mitochondrial involvement in linezolid toxicity, with this study uniquely identifying **complex I proteins** affected in treated patients.

