



Telomere length and immunosuppression in non-idiopathic pulmonary fibrosis interstitial lung disease

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Fibrotic hypersensitivity pneumonitis and unclassifiable ILD patients who have age-adjusted leukocyte telomere length <10th percentile may experience reduced survival when exposed to immunosuppression, similar to IPF patients <https://bit.ly/3DJJLYg>

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Abstract

Background Studies suggest a harmful pharmacogenomic interaction exists between short leukocyte telomere length (LTL) and immunosuppressants in idiopathic pulmonary fibrosis (IPF). It remains unknown if a similar interaction exists in non-IPF interstitial lung disease (ILD).

Methods A retrospective, multicentre cohort analysis was performed in fibrotic hypersensitivity pneumonitis (fHP), unclassifiable ILD (uILD) and connective tissue disease (CTD)-ILD patients from five centres. LTL was measured by quantitative PCR for discovery and replication cohorts and expressed as age-adjusted percentiles of normal. Inverse probability of treatment weights based on propensity scores were used to assess the association between mycophenolate or azathioprine exposure and age-adjusted LTL on 2-year transplant-free survival using weighted Cox proportional hazards regression incorporating time-dependent immunosuppressant exposure.

Results The discovery and replication cohorts included 613 and 325 patients, respectively. In total, 40% of patients were exposed to immunosuppression and 22% had LTL <10th percentile of normal. fHP and uILD patients with LTL <10th percentile experienced reduced survival when exposed to either mycophenolate or azathioprine in the discovery cohort (mortality hazard ratio (HR) 4.97, 95% CI 2.26–10.92; $p < 0.001$) and replication cohort (mortality HR 4.90, 95% CI 1.74–13.77; $p = 0.003$). Immunosuppressant exposure was not associated with differential survival in patients with LTL ≥ 10 th percentile. There was a significant interaction between LTL <10th percentile and immunosuppressant exposure (discovery $p_{\text{interaction}} = 0.013$; replication $p_{\text{interaction}} = 0.011$). Low event rate and prevalence of LTL <10th percentile precluded subgroup analyses for CTD-ILD.

Conclusion Similar to IPF, fHP and uILD patients with age-adjusted LTL <10th percentile may experience reduced survival when exposed to immunosuppression.

