Dienogest impact on DIE lesions and prognostic treatment selection through gene expression and histological presentation

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Introduction/Background

Progestins are a heterogeneous group of compounds with varying affinities for steroid hormone receptors, leading to variation in patient response. Dienogest is a fourth-generation progestin with highly selective binding to progesterone receptors. A direct impact on lesions that contributes to its effectiveness has been postulated and leveraged for treatment selection.

Materials and Methods

Using 33 DIE lesions from 10 untreated, 13 Dienogest responders and 10 non-responders we generated sequences from 40,015 nuclei of archival tissue. Cellular composition and gene expression were compared between groups and the impact of treatment and markers of non-response identified. The CMAP database was interrogate with gene signatures to identify therapeutics for non-responders and high throughput drug screening performed on organoid to determine the impact of these drugs on patient derived tissue.

Results

Untreated DIE lesions have a strong inflammatory phenotype with high lymphocyte content (18.5%), that was significantly reduced after Dienogest treatment. This mechanism was mediated through the suppression of epithelial CXCL1, 2 and 4, stromal CXCL12 and 14 and lymphocyte CXCR4 expression. Patients' refractory to DNG had increased gene expression markers for fibrosis mediated by stromal TGFB and epithelial SDC4. Increased fibrosis and non-response could be identified prognostically by H&E staining. Interrogation of the CMAP database strongly support the use of glucocorticoid agonists to target stromal and lymphocyte cells in non-responding lesions. NFKB and HSP90 inhibitors were implicated to target epithelial cells. The impact of NFKB and HSP90 inhibitors Triptolide and Luminespib on endometrial epithelial cells was validated in high content screening of organoids.

Conclusion

Gene signatures and histological appearance of DIE lesions can be utilized for prognostic treatment selection. Glucocorticoid agonist activity was strongly indicated for Dienogest refractory patients. Novel compounds for epithelial dominated endometriotic lesions were identified. Together this study provides a genuine pathway to stratify the current approach to endometriosis treatment.

Key words

Treatment, Progestins, personalized treatment