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Summary

REGULATORY IMMUNE CELLS MODULATE THE INTESTINAL IMMUNE RESPONSE TO GLUTEN CHALLENGE IN CELIAC DISEASE – EFFECT OF THE TG2 INHIBITOR ZED1227: RESULTS FROM THE CEC-3 CLINICAL TRIAL

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RNAseq analysis of CEC-3 trial biopsies shows that the transglutaminase 2 inhibitor Zed1227 upregulated 93% of the top 100 regulatory T cell-related genes in celiac disease patients challenged with 3 g gluten daily, potently activating anti-inflammatory immune modulation.

KEY POINTS

- In 100 mg/d Zed1227-treated patients versus placebo, 93% of the top 100 most significant regulatory genes were upregulated, including TGF-beta signaling genes (Smad7, MERTK), cholesterol and fatty acid genes (ACAT1, NPC1L1), autophagy/apoptosis genes (VPS35, SQSTM1, BMF), and inhibitory genes (SOCS2).
- Zed1227-treated patients with maintained post-challenge villous height to crypt depth ratio showed upregulated induced regulatory T cell genes.
- In placebo-treated subjects, upregulated Treg genes correlated with better inflammatory control under gluten challenge.
- Pre-challenge biopsies identified protective genes (RNF167, BAD, FOXN3, BAG1, CLAUDIN15) predictive of maintained tolerance and detrimental genes (IRF9, CD96, HLA-/TAP1) predictive of more pronounced villous atrophy after gluten exposure.
- The data demonstrate largely Treg-mediated anti-inflammatory immune modulation in celiac disease patients prior to and during gluten challenge, and support future Treg-based therapies to attenuate inflammation in celiac disease and other intestinal autoimmune diseases.

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