BARICITINIB TREATMENT IN A PATIENT WITH GAIN-OF-FUNCTION MUTATION IN SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 1 (STAT1)

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STAT1 GOF Mutation

Clinical manifestations of STAT1 gain-of-function (GOF) mutation

- Chronic mucocutaneous candidiasis
- Bacterial and/or viral infections
- Autoimmunity

Immunological phenotype

- Enhanced STAT1 phosphorylation
- Overexpression of programmed death ligand 1 (PD-L1)
- Abolishes T-helper 17 (Th17) responses: decreased production of IL-17A, IL17F, and IL-22

Baricitinib

- Novel oral JAK 1/2 inhibitor
- Recently approved for treatment of rheumatoid arthritis
- Diminishes interferon (IFN) induced JAK-STAT1 signaling

Research Question

Can baricitinib improve clinical symptoms and immunological phenotype of a patient with STAT1 GOF mutation?

Conclusion

- Previously required prophylactic systemic antifungal and immunosuppressive treatments could be terminated
- No reoccurrence of candidiasis or immune-mediated ulcers during 12 months of treatment
- No clinical or biochemical complications were reported
- Improvement in immunological phenotype

Patient and Brief Method

The patient is a 24-year-old Dutch female diagnosed with heterozygous STAT1 GOF mutation at p.V653I of the SH2 domain. Over the years, main clinical problems included recurrent oral and esophageal *Candida albicans* infections and immune-mediated oral and vaginal ulcers. Candidiasis repetitively erupted within two weeks after termination of a course of antifungal therapy. Therefore, prophylactic antifungal therapy was required. In vitro study of baricitinib (BRN) was performed before baricitinib treatment (2 mg once daily) was initiated in the patient. Blood samples, collected before start of baricitinib and every 2 - 4 weeks afterwards, were examined for STAT1/STAT3 phosphorylation, STAT1-regulated gene expression, and cytokine production.

Flow cytometry of phosphoSTAT1:
hyperphosphorylation of STAT1 in the patient was decreased during baricitinib treatment

- Healthy controls
- Patient before treatment
- Patient during BRN treatment

Flow cytometry of phosphoSTAT3:
phosphorylation of STAT3 in the patient was decreased during baricitinib treatment

- Healthy controls
- Patient before treatment
- Patient during BRN treatment

In vitro study of STAT1 regulated genes:

baricitinib significantly reduced expression of CXCL9, CXCL10, and CD274 (PD-L1) after IL-27 stimulation in long-term T lymphocyte cultures.

- Healthy control
- Healthy control + BRN 20nM
- Patient
- Patient + BRN 20nM

STAT1 regulated genes during treatment:

The remarkably high expression levels of CXCL9 and CXCL10 from patient PBMCs before baricitinib treatment were strongly decreased, approaching those of healthy controls.

- Patient before treatment
- Patient after 2 wks of BRN
- Patient after 4 wks of BRN
- Patient after 8 wks of BRN
- Patient after 12 wks of BRN

Cytokine production (ELISA):

PBMCs obtained during baricitinib treatment displayed higher production of IL-17A, IL-17F, and IL-22 (pg/ml) upon stimulation. However, these levels were much lower than those observed in healthy controls (n=5).

(US, unstimulated, PMA + I = phorbol 12-myristate 13-acetate and ionomycin, HKCA = heat-killed *Candida albicans*)

- Healthy controls
- Patient before treatment
- Patient during BRN treatment