Utility of Ruxolitinib in a Child with Chronic Mucocutaneous Candidiasis Caused by a Novel STAT1 Gain-of-Function

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Abstract

PURPOSE: Signal transducer and activator of transcription 1 gain-of-function (STAT1 GOF) mutations are the most common cause of chronic mucocutaneous candidiasis (CMC). We aim to report the effect of oral ruxolitinib, the Janus kinase (JAK) family tyrosine kinase inhibitor, on clinical and immune status of a 12-year-old boy with severe CMC due to a novel STAT1 GOF mutation.

METHODS: Clinical features and laboratory data were analyzed, particularly
lymphocyte subsets, ex vivo IFNγ- and IFNα-induced STAT1, 3, 5 phosphorylation dynamics during the course of JAK1/2 inhibition therapy, and Th17-related, STAT1- and STAT3-inducible gene expression before and during the treatment. Sanger sequencing was used to detect the STAT1 mutation. Literature review of ruxolitinib in treatment of CMC is appended.

RESULTS: A novel STAT1 GOF mutation (c.617T > C; p.L206P), detected in a child with recalcitrant CMC, was shown to be reversible in vitro with ruxolitinib. Major clinical improvement was achieved after 8 weeks of ruxolitinib treatment, while sustained suppression of IFNγ- and IFNα-induced phosphorylation of STAT1, STAT3, and STAT5, as well as increased STAT3-inducible and Th17-related gene expression, was demonstrated ex vivo. Clinical relapse and spike of all monitored phosphorylated STAT activity was registered shortly after unplanned withdrawal, decreasing again after ruxolitinib reintroduction. No increase of peripheral CD4+ IL17+ T cells was detected after 4 months of therapy. No adverse effects were noted.

CONCLUSION: JAK1/2 inhibition with ruxolitinib represents a viable option for treatment of refractory CMC, if HSCT is not considered. However, long-term administration is necessary, as the effect is not sustained after treatment discontinuation.


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