demands there is benefit to using combination products in the asthma population.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2019-2461HHHH

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**Lung–Restricted Inhibition of Janus Kinase 1 Is Effective in Rodent Models of Asthma**


**PURPOSE OF THE STUDY:** Multiple type 2 cytokines, including interleukin-4, interleukin-5, interleukin-9, interleukin-13, and thymic stromal lymphopoietin, drive the pathophysiology of an important subset of asthma. These and other cytokines, such as interleukin-6 and type I and type II interferons, depend on Janus kinase 1 (JAK1) for signal transduction. iJak-381 is a synthesized, small, and inhalable molecule that was specifically designed for lung-restricted JAK1 inhibition. The purpose of this study was to conduct preclinical studies to test whether local inhibition of JAK1 can inhibit allergic inflammation in the lungs.

**STUDY POPULATION:** The study tested iJak-381 in mice and guinea pigs. Guinea pigs are an ideal species to study lung inflammation because their lung anatomy is similar to humans, and they mount a robust response to inhaled challenges.

**METHODS:** The authors developed a dry powder inhalation system for iJak-381 and tested its ability to suppress inhaled ovalbumin-induced pulmonary inflammation and airway hyperresponsiveness in murine and guinea pig models.

**RESULTS:** iJak-381 suppressed signal transducer and activator of transcription 6 activation by interleukin-13. iJak381 also suppressed ovalbumin-induced lung inflammation in both murine and guinea pig asthma models. Using human allergens (*Aspergillus, Alternaria*, and house dust mite *Dermatophagoides farinae*), iJak-381 had a strong suppressive effect on neutrophilic inflammation compared with systemic corticosteroids. Lastly, iJak-381 reduced lung pathology without inhibiting systemic JAK1 activity.

**CONCLUSIONS:** The authors concluded that lung-restricted inhibition of JAK1 suppressed asthma-related lung inflammation in 2 rodent models without systemic JAK inhibition. Because iJak-381 also suppressed neutrophilic inflammation in the lungs, the authors suggest that a combination of inhaled JAK1 inhibition with corticosteroid administration may be an efficacious approach to asthma treatment.

**REVIEWER COMMENTS:** This study highlights the importance of JAK1 signaling in asthma pathogenesis and suggests a therapeutic benefit to lung-restricted JAK1 inhibition. JAK1 inhibition may improve lung function by inhibiting both type 2 cytokine signaling and antigen-driven eosinophilic and neutrophilic inflammation in the lungs. More importantly, the inhaled route may provide clinical relief without systemic side effects. These promising preclinical findings suggest that clinical studies should be pursued to test iJak-381 efficacy and safety in asthma.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2019-2461II

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**Immunology**

**Newborn Screening for Severe Combined Immunodeficiency and T–Cell Lymphopenia in California, 2010–2017**


**PURPOSE OF THE STUDY:** To evaluate the diagnostic capability of the T-cell receptor excision circles–(TRECs) based newborn screen (NBS) for severe combined immunodeficiency disease (SCID) in California.

**STUDY POPULATION:** The population studied includes all infants born in hospitals in California from 2010 to 2016, with the exception of families opting out for religion.

**METHODS:** Dried blood spot specimens were obtained from the infants via heel punch for DNA extraction and evaluation of TREC count as a part of the NBS. TREC testing was initially performed at a single facility in California until 2015 and then in regional laboratories across the state starting in 2015, using a new neonatal TREC kit. Threshold values for positive screening results were therefore adjusted after the change of methods. Infants with positive screen results or 2 indeterminate screen results obtained laboratory testing for complete blood count and lymphocyte subsets. Infants with <300 absolute T cells per microliter were referred to SCID medical centers, and those with up to 1500 T cells per microliter were managed by pediatric immunologists. All patients continued to be monitored by their general practitioners for the next 6.5 years.

**RESULTS:** A total of 3 252 156 infants underwent SCID newborn screening from August 2010 to March 2017. A total of 562 infants had abnormal screen results, and 213 infants (1 in 15 300 [95% CI: 1 per 13 500 to 1 per 17 700]) were confirmed to have T-cell lymphopenia (TCL) (<1500 cells per microliter). Fifty cases of SCID (1 per 65 000 births [95% CI: 1 per 51 000 to 1 per 90 000]) were identified with TREC screening. The remaining 162
cases of TCL were due to congenital abnormalities, other primary immunodeficiencies, self-limiting TCL, or idiopathic TCL. Infants who were premature or small for gestational age were more likely to demonstrate positive or indeterminate TREC screening results and subsequently noted to have TCL. Forty-nine of 50 children identified with SCID were referred to centers for further management, with 47 children presenting to medical care before any infectious complication (2 developed infection and rash). Forty-six infants (94%) with SCID received a bone marrow transplant, gene therapy, or enzyme replacement therapy and survived. Two of the 50 SCID patients had delayed diagnosis after toddlerhood and were not identified by the TREC screening. Urgent positive test results requiring immediate call back for lymphocyte screen (<4 TRECs) identified 90% of infants with SCID.

CONCLUSIONS: TREC screening in California has proven to be highly sensitive and specific in the identification of SCID in newborn infants. The test allows infants with SCID and other TCLs to be identified in a timely manner, allowing for early intervention and treatment of these infants.

REVIEWER COMMENTS: The study demonstrates that identification of patients with TCL is accurate and shows the benefits of early detection of patients who are likely to have SCID. Early management has led to high survival rates posttreatment, likely because most interventions occurred before serious infection. Similar incidences of disease and outcomes were seen in the first 2 years of TREC NBS in California, (J Allergy Clin Immunol. 2013;132 [1]:140–150), thus supporting the long-term reliability of TREC testing and its addition to the NBS panel.


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T-Cell Receptor Excision Circles in HIV-Exposed, Uninfected Newborns Measured During a National Newborn Screening Program for Severe Combined Immunodeficiency

PURPOSE OF THE STUDY: To assess the level of T-cell receptor excision circles (TRECs) in HIV-exposed, uninfected (HEU) infants as well as assess the variables associated with lower TRECs in the study population.

STUDY POPULATION: Researchers in the study reported on 158 HEU infants born to mothers positive for HIV who were ≥32 weeks’ gestational age between January 2015 and July 2016 from 10 birthing centers in France. They were unable to determine if control of maternal HIV viral replication had any effect on HEU infant TREC level. This study also noted that infants with sub-Saharan African or Caribbean decent had a significantly lower TREC level when compared with both HEU infants of other origin and the infants with seronegative mothers in the DEPISTREC cohort. The 126 infants with sub-Saharan African or Caribbean decent had significantly lower TREC levels than the infants with seronegative mothers, whereas the 32 infants of other origin had no significant difference in TREC levels when compared with the infants with seronegative mothers.

CONCLUSIONS: Researchers in the study concluded that when controlling for gestational age, overall, the HEU newborns had a lower TREC level than unexposed infants. They were unable to determine if control of maternal HIV viral replication had any effect on HEU infant TREC level. This study also noted that infants with sub-Saharan African or Caribbean decent had a significantly lower TREC level when compared with both HEU infants of other origin and the infants with seronegative mothers in the DEPISTREC cohort. Importantly, a previous study completed on New York State severe combined immunodeficiency disease and T-cell immunodeficiency newborn screening showed that infants of African American decent had lower TREC levels than infants of other origins in the general population.

REVIEWER COMMENTS: This study used the newborn screening program for severe combined immunodeficiency disease and T-cell immunodeficiency to assess the level of TRECs in HEU infants. When the study cohort was separated on the basis of origin, HEU infants of sub-Saharan African or Caribbean decent had a significantly lower TREC level than HEU infants of other origins. This suggests that patients with African
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Pediatrics 2019;144;S58
DOI: 10.1542/peds.2019-2461JJJJ

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DOI: 10.1542/peds.2019-2461JJJJ

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