4.0 Abstract

Title

Pregnancy Exposures and Outcomes in Women with Psoriasis Treated with Risankizumab: A Cohort Study Utilizing Large Electronic Healthcare Databases with Mother-Baby Linkage in the United States

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Keywords

Psoriasis; pregnancy; risankizumab; electronic healthcare databases; mother-baby linkage

Rationale and Background

Risankizumab is an interleukin (IL)-23 antagonist approved for the treatment of moderate to severe plaque psoriasis. Limited information can be obtained from risankizumab clinical trials on the safety of risankizumab exposure during pregnancy. Therefore, information about the association between risankizumab exposure during pregnancy and maternal, fetal and infant outcomes is limited.

Research Question and Objectives

The study aim is to evaluate the safety of risankizumab during pregnancy in women with psoriasis. The risk of pre-specified pregnancy, birth and infant outcomes will be estimated in pregnant women with moderate-to-severe psoriasis exposed to risankizumab and in a comparator population of pregnancies exposed to comparator biologics (anti- tumor necrosis factor (TNF), interleukin (IL)-17 biologics or their biosimilars [comparator biologic-exposed group]).

The primary outcome of this cohort study is major congenital malformations of the infant among live birth pregnancies.

Secondary outcomes include the following:

- Pregnancy outcomes: live birth, spontaneous abortion, elective abortion, stillbirth
- Infant outcomes: premature birth, small for gestational age (SGA), neonatal deaths, serious infections

Study Design

The study will be a population-based, non-interventional, cohort study of pregnant women. The primary comparison will be among women with moderate-to-severe psoriasis exposed to risankizumab versus those exposed to a comparator biologic during pregnancy (comparator biologic-exposed group). Secondary descriptive analyses will estimate rates of major congenital malformations and other adverse pregnancy and birth outcomes in a population of women diagnosed with psoriasis and not treated with risankizumab or other biologics indicated for the treatment of psoriasis (untreated psoriasis group) for a frame of reference. The study will be conducted using US administrative claims databases that have longitudinal capture of medical encounters and prescription medication exposures for large cohorts. Medical charts will be reviewed by board certified teratologists to confirm major congenital malformations, the primary outcome of interest.

Population

This study will be conducted in several secondary data sources in the US that participate in the Innovation in Medical Evidence Development and Surveillance Distributed Data Network (IMEDS-DDN).

The study population will include adult pregnant women (ages 15 to 55 years at the start of pregnancy). Pregnancies with outcomes occurring during the period 01 May 2019 to 31 December 2026, and infants born to the women, will be included. Additional eligibility criteria will include continuous health plan enrollment with medical and pharmacy benefits for at least 272 days prior to estimated start of

pregnancy until the pregnancy end date, allowing gaps of up to 45 days in coverage. The 272-day pre-pregnancy period will allow identification of potential confounders of interest in the electronic healthcare databases.

Pregnancies ending in gestational trophoblastic disease or ectopic pregnancy will be excluded from the analysis. Additional exclusion criteria will include exposure to both risankizumab and comparator biologics during pregnancy, or exposure to medications that present a known increased risk for fetal malformation. For the risankizumab-exposed group and the comparator biologic-exposed group, evidence of moderate-to-severe-psoriasis will be required, defined as both documentation of a diagnosis code for psoriasis and an administration or dispensing of systemic therapy for psoriasis in the period 272 days prior to the estimated start of pregnancy until the pregnancy end date.

For analyses evaluating infant outcomes (major congenital malformations and other infant outcomes), pregnancies for which the infant is identified with a chromosomal or genetic anomaly will also be excluded.

For eligible pregnancies ending in a live birth, mothers will be linked to their infants using the FDA Sentinel Initiative mother-infant linkage methodology which utilizes health plan administrative claims data and birth certificate data (as available).

The study will examine pregnancy outcomes in the entire IMEDS-DDN population of pregnant women meeting eligibility criteria. Infant outcomes will be assessed in the subset of live birth pregnancies linked to infant records. Among all eligible pregnancies and among the subset of pregnancies resulting in a live birth, three specific cohorts of pregnancies will be included in the study: 1) pregnancies for which the woman was diagnosed with psoriasis and exposed to risankizumab during pregnancy (risankizumab-exposed cohort); 2) a matched sample of two pregnancies for which the woman was diagnosed with psoriasis and exposed to an anti-TNF-α or IL-17 inhibitor biologic comparator drug during pregnancy (comparator biologic-exposed group [primary comparison group]); and 3) a matched sample of

two pregnancies for which the woman was diagnosed with psoriasis and was not exposed to risankizumab or other biologics (indicated for the treatment of psoriasis) during pregnancy (untreated psoriasis group [reference group for descriptive purposes]).

Variables

Information about demographics, maternal age, pregnancy start and trimester (estimated using claims-based algorithms), maternal comorbidities and early complications of pregnancy, psoriasis treatments during pregnancy (90 days before pregnancy and during pregnancy), psoriasis treatment history (biologic systemic drugs, nonbiologic systemic drugs, and phototherapy), concomitant (non-psoriatic) medications, healthcare utilization, pregnancy outcomes (live birth, spontaneous abortions, stillbirths, elective abortions) and infant outcomes (major congenital malformations, premature birth, SGA, neonatal deaths, serious infections) will be collected from the healthcare electronic databases (health plan enrollment and claims data and integrated healthcare systems data), supplemented with medical records to confirm major congenital malformations. All conditions used to define the population, exposures, comorbidities, and outcomes will be identified using validated algorithms, where available.

Data Sources

This study will be conducted using health plan administrative claims data in the Innovation in Medical Evidence Development and Surveillance System (IMEDS) Distributed Databases (IMEDS-DD). IMEDS provides a framework for private-sector entities (e.g., regulated industry, academic institutes) to leverage the FDA Sentinel Distributed Databases (SDD) and analytic tools. FDA Sentinel is a national electronic system for active surveillance of the safety of drugs, biologics, vaccines, and medical devices in the US, established under the Sentinel Initiative. The SDD uses a common data model for standardization of demographic and clinical data elements and has routine analytical tools to permit rapid queries, including descriptive analyses and

complex methodologies (e.g., comparative analyses), across Data Partners. IMEDS-DD is a subset of SDD and expected to be largely representative of the commercially-insured population in the US. Across all 9 participating IMEDS Data Partners, the IMEDS-DD currently includes approximately 111 million patient-lives. Health plan claims and integrated healthcare systems data included in the IMEDS-DD will be supplemented with medical records to confirm major congenital malformations.

Study Size

The sample size will be influenced by the uptake of risankizumab and comparators (biologic therapies for psoriasis), among pregnant women in the study population. All pregnant women who are exposed to risankizumab and meet the study inclusion/exclusion criteria will be included in this study.

Assuming a two-sided test, a type 1 error of 0.05 for a two-group Chi-square test of equal proportions, a 4% prevalence of major congenital malformations in the comparator biologic-exposed group, and a 1:2 ratio of risankizumab to comparator biologic users, 200 live birth infants (live birth pregnancies linked to infant records) from the risankizumab-exposed group (exposed during the first trimester) and 400 live birth infants from the comparator biologic-exposed group will allow us to achieve 80% power to detect a risk ratio (RR) of 2.5 for the primary safety outcome, major congenital malformations.

Based upon available Sentinel data estimating the prevalence of first trimester anti-TNF exposures among pregnant women diagnosed with psoriasis, the estimated sample size of risankizumab-exposed live birth pregnancies linked to an infant may range from 108 to 220 during a 6-year period. Thus, the sample size during the follow-up period may be sufficient to achieve a target RR = 2.5, depending on the uptake of risankizumab among pregnant women. If target numbers of exposed pregnancies are not reached, AbbVie will continue the study until such time as the target numbers are obtained. Conversely, if target numbers of exposed are achieved

earlier than the proposed Q4 2026 cut off to identify pregnancy outcomes, AbbVie will complete data collection at such time the target sample size is reached and stop the study earlier than proposed.

Data Analysis

Descriptive analyses will be performed to estimate the prevalence of use of risankizumab and comparator treatments during pregnancy among women with psoriasis and among women with psoriatic arthritis. Use will be described overall and by trimester, maternal age, and calendar year of pregnancy outcome.

AbbVie will conduct comparative analyses of pregnancy and birth/infant outcomes between risankizumab-exposed and comparator biologic-exposed pregnancies (primary analysis of interest). Separate cohort analyses will be conducted depending on the outcomes of interest (pregnancy outcomes among all eligible pregnancies and infant outcomes among live birth pregnancies). To assess and compare outcomes for risankizumab-exposed and comparator treatment-exposed pregnancies, analyses will be stratified by stage of pregnancy: early pregnancy stage (women receiving an administration of risankizumab/comparator during the period 90 days prior to pregnancy through less than 14 weeks gestation) and mid to late pregnancy (women receiving an administration of risankizumab/comparator during the period 14 weeks gestation through the end of pregnancy). Secondary analyses will also be conducted stratifying the analyses by exposure in the 90 days prior to pregnancy and exposure in the first trimester (the first day of the last menstrual period [LMP] through < 14 weeks gestation).

Logistic regression will be used to estimate propensity scores. AbbVie will match comparators on propensity score and other baseline variables, including maternal age, presence of psoriatic arthritis, and timing of exposure to adjust for confounding by baseline risk factors for adverse outcomes. Separate propensity scores will be estimated for analyses conducted among all eligible pregnancies and among the subset of live birth pregnancies linked to infant records.

The prevalence of infant outcomes (major congenital malformations, premature birth, SGA, neonatal deaths, serious infections) among liveborn infants in the risankizumab-exposed group compared to those in the comparator-biologic exposed group will be assessed and compared. To estimate the relative risk (prevalence/risk ratios and 95% confidence intervals) of major congenital malformations associated with risankizumab exposure in early stage pregnancy, a log binomial distribution with robust variance using generalized estimating equations will be used.

This study will estimate the incidence (cumulative risks) of pregnancy outcomes, including live births, spontaneous abortions, elective abortion, and stillbirths and will compare the occurrence of these events among risankizumab-exposed women with those among the matched comparator biologic-exposed women. AbbVie will use a log binomial distribution with robust variance using generalized estimating equations to estimate the effects of exposure (cumulative risk ratios and 95% confidence intervals) to risankizumab.

Secondary analyses will include a descriptive analysis of women diagnosed with psoriatic arthritis.

Additional secondary analyses will include estimation of the prevalence of major congenital malformations and other infant outcomes and the incidence of pregnancy outcomes among the untreated psoriasis group to serve as a frame of reference for descriptive purposes.

These methodologies and additional secondary and sensitivity analyses will be described in detail in a Statistical Analysis Plan (SAP).

Milestones

The use of risankizumab and comparator treatments will be evaluated annually throughout the duration of the study surveillance period. The start of data collection will be Q1 2021 (the start date for surveillance of exposure and outcome data). The end of data collection will be Q3 2029 (the end date for collection of all health plan

and chart review/adjudication data). Interim annual surveillance reports will summarize the counts of risankizumab and comparator biologic exposures overall and by trimester in the live birth pregnancy cohort (to be submitted Q2 2022 and Q2 2023). Subsequent annual surveillance reports will summarize counts of risankizumab and comparator biologic exposures in all pregnancies and in the live birth pregnancy cohort. A study progress report will be completed in September 2024. This report will summarize the counts of risankizumab and comparator biologic exposures among all pregnancies and among live birth pregnancies. Sample size calculations, participation of specific Data Partners (and potential inclusion of additional Data Partners), and the expected duration of the study period will also be determined based upon the reported use of risankizumab and comparator biologics at this time. Annual reports for calendar years 2028 and 2029 will provide updates on the status of the comparative safety analyses. A final study report will be submitted to the EMA and FDA by October 2030.

Marketing Authorisation Holder(s)

EU: AbbVie Deutschland GmbH & Co. KG

US: AbbVie Inc.

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