Title

The safety assessment of a variety of stage-4 medications during pre-conception and pregnancy in IBD patients.

Background and Rationale

Little human data is available on the use of a variety of stage-4 IBD medications such as Entivio, Stelara and so on during pregnancy. This study has been designed to provide information to clinicians and patients on pregnancy outcomes in women exposed to a variety of stage-4 IBD medications during pregnancy. Improved understanding of the effects of IBD and the use of these medications in pregnant patients on rates of congenital malformations, spontaneous abortions, preterm birth, and SGA infants will be of great benefit to prospective mothers with IBD and the physicians taking care of this population.

This cohort study will utilize information available from the institutional prospective pregnancy registry from the IBD MOM clinic in the Digestive Disease Institute, Shaare Zedek Medical Center, Jerusalem, Israel.
The IBD MOM clinic was established in June 2011 in response to the vast need of IBD female patients in their reproductive years. This is a unique clinic in which a gastroenterologist and a fetal maternal medicine expert consult together. Since the establishment of this clinic we have a prospective cohort data registry of 200 women till June 2015.

Objective

The primary objective of this study is:

1. To quantify incidence of major structural birth defects and other birth outcomes in infants born to women with UC/CD with exposure to a variety of stage-4 medications compared to women with exposure to other biological agents or conventional IBD therapy during pregnancy

2. To assess the health and developmental status of infants up to 4yr of age.

Study Design

The IBD MOM clinic currently follows women with IBD from the preconception stage through postpartum period. In addition, we have now started following the offspring for 1 year with an option of extending the follow up until 4 years after birth with participation of the family health center. Data is collected longitudinally on use of stage-4 IBD medications, non-immunomodulator AZA/6MP, biologic therapy infliximab, adalimumab, certolizumab, and natalizumab. Corticosteroids,5-ASA and Methotrexate), disease activity during gestation, complications of pregnancy and delivery, and infant birth outcomes during the first year of the child's life because from population-based data, including the Kaiser sample[1] and studies from Europe[2-4] women with IBD clearly have an increased risk of adverse pregnancy outcomes such as preterm birth and/or low birth weight infants, even with inactive disease.[10].

Study duration: September 2015- September 2022

This is a non-interventional observational prospective cohort study to be conducted in an actual clinical practice setting.

This is an exposure-based cohort study in which there will be 3 reference groups. Women on conventional therapy only, women on Vedolizumab and women on other biologics.

The source database contains information collected from our IBD MOM clinic in Shaare Zedek Medical Center in Jerusalem, Israel.

Study Population

The source population is women attending the IBD MON clinic at Shaare Zedek Medical Center in Jerusalem, Israel. The Shaare Zedek Medical Center is located on a vast, 11-acre campus directly opposite Mount Herzl, making it Jerusalem's only major, centrally located hospital. The hospital complex, completed in 1979, comprises ten interconnected buildings and an expansive parking area. Since occupying the current location, Shaare Zedek has transformed itself from a respected regional hospital into a major multi-disciplinary medical center with an international reputation for excellence in many areas of expertise.

With a constant commitment to developing increasingly innovative means to provide patient care, the 700-bed facility treats hundreds of thousands of patients per year in its thirty inpatient departments and 70 departments and units comprising its out-patient clinics.

The cohort will prospectively recruit women attending the IBD MOM clinic who meet the study inclusion/exclusion criteria. In addition, the cohort will be supplemented with women who attended the IBD MOM clinic after the commercial launch of stage 4 IBD medications but prior to the study.

Inclusion Criteria for the UC/CD Prospective Cohort:

- The subject is a currently pregnant woman with UC or CD
- The subject considers pregnancy (pre-conception stage)
- The subject agrees to the conditions and requirements of the study including the interview

schedule, release of medical records, and the physical examination of live born infants.

Exclusion Criteria for the UC/CD Prospective Cohort:

- The subject has had an exposure to the known or suspected human teratogens:
  - Chlorambucil
  - Cyclophosphamide
  - Mycophenylate mofetil

Any stage 4 IBD drugs exposed mother who does not meet the entry criteria will be entered into case series, which will be used to provide support data to cohort study.

Study participants will be categorized into one of the following exposure groups:

Group 1: STAGE-4IBD medication Cohort (Each medication will be analyzed separately)

- **Group 1a** Mothers exposed to stage-4 IBD medication at any time during pregnancy and pre-conception.
- **Group 1b** Infants born to Group 1a patients.

Group 2: Anti-TNF Agents Cohort

- **Group 2a** Patients with IBD who were exposed to anti-TNFs at any time during pregnancy and pre-conception.
- **Group 2b** Infants born to Group 2a patients.

Group 3: Conventional therapy only Cohort

- **Group 3a** Patients with IBD who were exposed to conventional therapy only (such as Thiopurines) at any time during pregnancy and pre-conception.
- **Group 3b** Infants born to Group 3a patients.

Number of Patients:

The IBD MOM clinic sees approximately 15 pregnant women on Entyvio and 150 pregnant women on conventional therapy or other biologic agents each year.

The sample size is based on anticipated recruitment at the IBD MOM clinic, rather than on the sample size needed for a specific minimum detectable relative risk. Like most similar drug exposure pregnancy registries, this study by itself is underpowered to detect specific birth births. The intent is for the information generated from this study to be used in conjunction with information from several other stage 4 medications pregnancy registries in helping to identify or rule out potential risks.

Based on previous experience of the OTIS Autoimmune Diseases in Pregnancy Project, it is estimated that subjects will be an average of 7-10 weeks post-LMP at the time of enrollment. Given this mean gestational timing at enrollment, the anticipated spontaneous abortion and stillbirth rate is 10%, the estimated elective abortion rate is 10%, the estimated lost-to-follow-up rate is 5% (based on previous OTIS experience) resulting in approximately 75 live born infants in each group at the end of recruitment. Experience with the current OTIS Autoimmune Diseases in Pregnancy Project has demonstrated a yield of approximately 80% live born infants from the total proportion enrolled; therefore the estimated yield of 75% in this proposal is conservative.

Estimates of baseline rates of major structural defects, spontaneous abortion, premature delivery, and SGA and the standard deviation for mean birth weight of full-term infants are based on previous OTIS studies and on general population data. With this sample size, α of 0.05, 2-tailed test of significance (except as noted for pattern of minor anomalies), the minimum effect sizes and power shown in Table 0.a will be detectable. The primary comparison group for all analyses will be "exposed to other biologic drugs" exposure category.

Table 0.a Sample Size and Power for a Specified Effect Size

Endpoint	N of Live Births in Each Exposure Group	Baseline Rate	Minimum Detectable Relative Risk	Power (a)
Major structural defects (b)	75	3%	5.8	80%
Specific pattern of 3 or more minor structural defects	75	1%	10.0	71%
Spontaneous abortion	85	10%	2.8	80%
Premature delivery	75	6%	3.8	80%
Small size for gestational age	75	7%	3.5	80%

(a) Based on Fisher exact test, 2 tailed, and α=0.05, except specific pattern of 3 or more minor structural defects, which is based on a 1-sided test. For preterm delivery and SGA, although the population baseline rate is typically 10%, OTIS healthy comparison group is typically 6% and 7% incidence of preterm and SGA respectively, thus providing a more conservative estimate of power than other registries.
(b) Primary endpoint.

With respect to the evaluation of minor malformations, the strength of this study design is in the ability to examine the data for a pattern of minor and/or major structural defects, given that the known human teratogens are typically associated with a pattern as opposed to isolated major birth defects. The baseline prevalence of a specific pattern of 3 or more minor structural defects is estimated to be essentially zero, as the occurrence of the same 3 low baseline frequency minor structural defects in any 2 children in a sample of 75 would be an extremely unlikely event. However, for purposes of the power calculation, a hypothetical baseline prevalence estimate of 1% has been used. The minimum detectable relative risk (MDRR) with this sample size (10.0) has an approximately 71% power based on an alpha of 0.05 using a 1-tailed Fisher exact test. A MDRR of 10 with a baseline rate of 1% represents a 10% birth prevalence of a specific pattern, which is comparable to the birth prevalence of a specific pattern in other known human teratogens of moderate risk such as the anticonvulsant medications.

As the study may be underpowered for some endpoints and individual specific birth defects, study results will need to be interpreted with respect to both lower and upper bounds of the 95% confidence interval of the relative risk with caution. The following guide will be used:

(a) If the CI lower bound >1 then risk is detected;

(b) If the CI lower bound <1 and,

- If the CI upper bound >MDRR, then MDRR is not detected but cannot be ruled out.
- If the CI upper bound <MDRR , then MDRR is ruled out.

Study Procedures:

Data will be included from patients currently enrolled in the registry and from patients who will be enrolled in the registry in the future. Data collection in the first year of pre-conception, conception, pregnancy, and delivery will be taken at Shaare Zedek and will include:

Blood samples for CBC, CRP, ESR and others, Urine , stool and saliva samples

From the infants: Blood tests at birth, 3 months, 6 and 12 months old for both study and control group.

Stool samples will be taken from the infant's first meconium and in the age of one month, 3 months, 6 months and 12 months, in order to examine the influence of the medications used during pregnancy on the infant's bowel microbiome. These samples will be taken from both study and control group.

Two ml of mother's milk sample will be taken before the first stage-4 IBD medication infusion after birth and every second day during the two weeks later. Mother's milk samples will be taken from the control groups as well.

The data collected during the follow up will include the gestational age, sex, delivery date, weight, live or still birth, and birth defects.

Data collection for infants up until age four will be taken in cooperation with the Family Health Center (known as"Tippat Halav"). This will be done with the approval of the mom from the infant's vaccine notepad.

The infants' health status will include:

- Antibiotic use
- Hospitalizations
- Infections, including type of infectious pathogen (viral, bacterial, fungal, parasitic)
- Other important diagnoses, including all congenital malformations

The infants' developmental status will include:

- Turning over from back to stomach or stomach to back at around 6 months
- Sitting up without adult help between 9 and 12 months
- Saying a word or significant sound between 9 and 12 months
- Walking without adult help at 18 months until 2 years of age
- Running without falling between 2 and 3 years of age
- Forming sentences of at least 3 words between 2 and 3 years of age
- Counting at least 3 objects until 4 years of age

The study will assess pregnancy complications and birth outcomes with respect to IBD medications taken during pregnancy as well as disease activity. In addition, infants will be followed for 1 year to assess hospitalizations, infections, and emerging

disorders and developmental milestones.

This study is non-interventional.. All decisions on clinical management are independent of participation in the study.

The categorization of a patient to an exposure cohort is determined by the medication exposure status between 3 month prior to LMP and delivery for the pregnant women, using the following rules:

Note that each pregnant woman will be included in only one cohort
Blood tests for disease activity(CRP,ESR), Fecal calprotectin and lactofferin and serum levels for future performing through levels and ab will be taken for each patient every trimester and post partum Trough levels and ab will also be taken from cord blood and from the newborn at 3 and 6 months and 12 months of age. As part of the routine evaluation of IBD pregnant women in our clinic.

Outcome Variables:

Primary Outcome: Major structural defects

Definition: a major structural defect is defined as a defect that has either cosmetic or functional significance to the child (eg, a cleft lip), as defined by the Centers for Disease Control and Prevention (CDC; [4]). These defects in aggregate typically occur in <4% of the general population. Over 100 specific structural defects are considered to be major [4].

Secondary Outcome: Minor structural defects

Definition: a minor structural defect is defined as a defect that has neither cosmetic nor functional significance to the child (eg, complete 2,3 syndactyly of the toes) and is identified using a study-related checklist incorporated into the study dysmorphology examination of live born infants.

Inclusion Criteria for Structural Defects

- *Time period for identification:* major structural defects identified up to 1 year of age by the mother, the HCP, or identified in the dysmorphological examination will be included in the primary analysis. Defects identified after that time frame will be described and considered separately.
- *Confirmation of defects:* independent confirmation of certain defects will be required. For example, a heart murmur thought to represent a ventricular septal defect that is ascertained by the examining dysmorphologist prior to 1 year of age will be included if it is confirmed as a heart defect by cardiac ultrasound. Similarly, a midline cutaneous marker at L2-L3 noted in the dysmorphological examination will be included as occult spinal dysraphism only if confirmed by appropriate imaging studies. In addition, minor structural defects that are reported only by the mother or medical record but not confirmed by the dysmorphological examination will not be included as valid defects.
- *Body measurements:* only those growth parameters for which actual measurements are available will be considered in the analysis. Measurements of head circumference, length, weight, palpebral fissure length, inner canthal distance, ear length, and philtrum length will be taken. These will be compared to mean values for infants of the same age and sex (where sex-specific normative data are available). Less than or greater than 2 standard deviations from the mean will be used to define such terms as microcephaly, hypertelorism, etc.

Exclusion Criteria for Structural Defects

- *Birthmarks:* isolated birthmarks will not be included.
- *Variations of normal:* features on the physical examination which typically occur in greater than 4 percent of the population and have no cosmetic or functional significance for the child, eg, 2,3 syndactyly of the toes less than one-third of the distance to the tip of the 3rd phalanx, will not be included.
- *Deformational defects:* Those deformational defects that do not require casting or surgery will not be included.
- *Time period for identification:* structural defects ascertained after 12 months of

age will not be included in the analysis, but will be considered separately in the context of a possible pattern.

- *Defects identified in spontaneous abortions or elective terminations:* Defects identified by prenatal ultrasound or examination of the products of conception following elective or spontaneous abortion will be not be included in the primary analysis of defects in live born infants due to potential bias involved in non-uniform use of prenatal diagnosis and pathology evaluation for all abortuses; however, these defects will be considered in a separate analysis including all defects in the numerator over all pregnancies with known outcome in the denominator, and in the context of pattern.

Additional Secondary Outcomes:

Spontaneous abortion is defined as non-deliberate embryonic or fetal death that occurs prior to 20 weeks' gestation post-LMP.

Elective abortion is defined as deliberate termination of pregnancy at any time in gestation. Reason for elective abortion will be ascertained.

Stillbirth is defined as a non-deliberate fetal death that occurs at or after 20 weeks' gestation post-LMP, but prior to delivery.

Premature delivery is defined as live birth prior to 37 completed weeks' gestation post-LMP. Elective caesarian deliveries or inductions prior to 37 completed weeks are not considered premature deliveries, and will be considered separately.

SGA is defined as birth size (weight, length or head circumference) less than or equal to the 10^{th} percentile for sex and gestational age using standard pediatric CDC growth curves for full term or preterm infants [5,6].

Postnatal growth deficiency is defined as postnatal size (weight, length or head circumference) less than or equal to the 10^{th} percentile for sex and age using National Center for Health Statistics (NCHS) pediatric growth curves, and adjusted postnatal age for premature infants if the postnatal measurement is obtained at less than 1 year of age.

Lost-to-follow-up is defined as an enrolled subject where follow-up information on the outcome (live birth, fetal loss) is not obtainable, or for a live birth if the birth defect status is designated as "unknown" as of 12 months following the estimated due date. The OTIS Autoimmune Diseases in Pregnancy Project has experienced extremely low losses to follow-up (<5% of enrolled subjects) by virtue of maintaining consistent contact with the pregnant woman. Before a subject is designated as lost to follow up, the subject or reporter receives at least 3 reminder telephone calls (documented in the database) followed by written correspondence and alternative contact information that is requested upon enrollment is utilized. Voluntary subject withdrawals will be considered separately.

Serious or opportunistic infections are defined as commonly accepted, and identified in newborn infants up to 1 year of age, or infections that require hospitalization up to 1 year of age. Pediatric records will be requested with specific requests for documentation of hospitalizations and opportunistic infections.

Malignancies are defined as any malignancy reported in an infant up to 1 year of age. Pediatric records will be requested with specific requests for documentation of

malignancies.

Pregnancy history variables: maternal age, parity, outcomes of previous birth outcomes; medication used in pregnancy, smoking in pregnancy, alcohol, etc. Pregnancy complications

IBD variables
IBD medications during pregnancy
IBD sites
Extraintestinal manifestations
IBD flares during pregnancy
IBD severity scores, such as Mayo score) during pregnancy, etc

All variables will be collected by the IBD mom clinic team.

Management and Reporting of adverse events

Serious Adverse Events in the Fetus/Infant

If the investigators becomes aware adverse events occurring in a participant enrolled in the study with exposure to any stage-4 medication tested, the event will be reported to the regulatory authorities, IRBs and Takeda in accordance with national regulations, regardless of expectedness or causality. All SAEs and pregnancy reports will also be reported in English by facsimile to Takeda Pharmacovigilance or designee:

Fatal and life threatening SAEs within 24 hours of the sponsor-investigator`s observation or awareness of the event

All other serious (non-fatal/non-life threatening) events within 4 calendar days of the sponsor-investigator`s awareness of the event

SAEs are of the following:

- Major birth defect.
- Spontaneous abortion.
- Still birth.
- Elective termination of pregnancy.
- Neonatal death.
- Serious or opportunistic infection in infant.
- Malignancy in infant.
- Reports of adverse drug reactions in a newborn/neonate that are fatal, life-threatening, resulting in persistent or significant disability/incapacity or resulting in or prolonging hospitalization, except prolongation of hospitalization due to pre-specified study endpoints such as preterm delivery and small for gestational age birth weight, or delivery by caesarian section.

Other Adverse Events in the Infant

Any other adverse event occurring during the 1st year of life in an infant where the investigator is of the opinion that the adverse event is related to vedolizumab exposure, the adverse event will be reported to the sponsor within 24 hours of becoming aware of the event, using the Medwatch form.

Serious Adverse Events in the mother

If the investigators or research staff becomes aware of any adverse event in the mother that meets the following Serious Adverse Event criteria, and the investigator is of the opinion that the adverse event is related to vedolizumab exposure, the event will be reported to the sponsor within 24 hours of becoming aware of the event, using the Medwatch form:

- Results in death
- Is life-threatening. Life-threatening in this context refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if more severe
- Results in persistent or significant disability or incapacity. Disability is defined as a substantial disruption of a person’s ability to conduct normal life functions.
- Requires inpatient hospitalization or prolongation of an existing hospitalization. Hospitalization for underlying disease progression will constitute an SAE. Hospitalization for an elective or

planned procedure to treat a pre-existing condition is not considered an SAE, unless it results in one of the other outcomes listed above.

- Suspected transmission of an infectious agent via a medicinal product

Any other important medical event that may not result in death, be life-threatening or require hospitalization, but based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Reporting to Regulatory Agencies

Takeda will be responsible for reporting of adverse events to regulatory agencies, according to regulatory requirements.

Statistical Analysis

Groups 3a and 3b will serve as the control groups for the study.
Baseline demographics and disease characteristics will be summarized for the 3 disease cohorts at the time of enrollment.

Descriptive statistics, such as mean, median, standard deviations, and range for continuous variables, and counts and percentages for categorical variables will be used to summarize data. All statistical testing will be 2-sided and will use a 0.05 level of significance. Incidence rates by exposure cohort will be estimated and compared using Fisher's exact test. Crude and adjusted odds or risk ratios comparing Vedolizumab and reference will be estimated along with 95% confidence intervals. Logistic regression will be used to compare birth outcomes for Vedolizumab and control cohort. General linear models will be used to compare infant health status between Vedolizumab and control cohorts. The covariates that will be included in models to estimate the adjusted risk ratios are provided in the Group Analyses Section. As a main rule subjects with missing values of a particular endpoint or covariate will not contribute to the analyses. Because missing data are minimal in the data sets, observed data will be used in the analysis without imputation.

Data Management
Data will be obtained and analyzed with the collaboration and assistance of Dr. Ariella Shitrit and/or her designees, There will be limited access only to study team. who will be responsible for data management and statistical analysis.
Shaare Zedek Medical Center affiliated with the Hebrew University will serve as the Data Management Center and the site for all data management activities.
Upon completion of data collection it will be presented in GI conferences noting that this study was supported by takeda.

Schedule for Data Extraction

Data to be Extracted	At Registry Entry	3-Month Period Prior to Estimated LMP	During Pregnancy and at Delivery				Infant/Child Follow-up Period
			Trimester			At Delivery	At 4, 9, 12 months
			1st (LMP to Week 13)	2nd (>13 weeks until Week 26)	3rd (>26 weeks until Week 40)		
Maternal age at pregnancy		x					
Maternal smoking		x					
Maternal substance use (alcohol and/or recreational drugs)		x					
Maternal diagnosis		x					
Maternal duration of disease		x					
Prior surgeries performed on mother		x					
Maternal disease location		x					
Maternal disease activity (HBI, SCAI, and modified PDAI)[a]		x	x	x	x	x	x
Maternal medications		x	x	x	x	x	x
Maternal IBD disease history	x						
Maternal pre-pregnancy BMI	x						
Maternal Parity	x						
Pregnancy type (singleton or multiple)		x					
Route of delivery							
Elective C-section						x	
Emergency C-section						x	
Vaginal						x	
Duration of pregnancy						x	
Gestational age						x	

Spontaneous preterm birth						x	
Pregnancy outcome							
Live birth, normal						x	
Live birth, abnormal						x	
Preterm birth						x	
SGA						x	
Congenital malformations						x	x
Perinatal morbidity						x	
Fetal death						x	
Induced abortion, including reason for abortion						x	
Spontaneous abortion						x	
Stillbirth (intrauterine death)						x	
Neonatal death						x	
Infant's birth weight						x	
Infant's sex						x	
Infant's APGAR at 5 minutes						x	
Infant's hospitalizations up to 4 years							x
Indication for hospitalization							x
Duration of hospitalization							x
Outcome							x
Infant's infections up to 4 years							x
Type and location of infection							x
Pathogen information, if available							x
Antibiotic use							x
Parental socioeconomic status [b]		x					x
Infant's/Child's vaccinations							x
New diagnoses that are chronic or severe							x
History of breast feeding [c]							x

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