SAFETY OF IBD DRUGS DURING PREGNANCY AND BREASTFEEDING: MOTHERS AND BABIES' OUTCOMES (DUMBO REGISTRY)

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1. INTRODUCTION

Most patients with inflammatory bowel disease (IBD) are affected during their peak reproductive years, when many female patients affected by Crohn's disease (CD) or ulcerative colitis (UC) wish to have children. Although a diagnosis of IBD does not pose a risk to pregnancy, it has been shown that active disease or a disease flare-up is associated with poor obstetrical outcomes[1]. As a result, effective control of disease activity is vital both prior to conception and during pregnancy[2].

Biologic drugs have been increasingly used for the treatment of IBD[3]. Therefore, many women wishing to become pregnant may be exposed to these drugs. In this respect, taking anti-TNF drugs during pregnancy has been considered safe in several registries and observational studies. Nevertheless, their presumed safety is based on short-term data (at delivery or during the first few months postpartum).

The human placenta seems to be impermeable to all antibodies from the maternal immune system except immunoglobulin G (IgG)[4]. Infliximab, adalimumab, and golimumab are IgG1 monoclonal antibodies, whereas certolizumab is a Fab fragment of IgG1 antibody. Materno-fetal transfer of IgG takes place via binding to a specific receptor known as the neonatal Fc or Brambell receptor (FcRn). The FcRn of placental syncytiotrophoblasts is not detected before 14 weeks of gestation[5, 6].

Case series have reported clinically significant infliximab and adalimumab levels in cord blood when these drugs were administered at the end of the second trimester or during the third trimester, although this was not the case for certolizumab pegol[7]. A number of case reports indicate that placental transfer of infliximab leads to prolonged exposure in the neonate. Indeed, serum levels in neonates are often higher than those in maternal serum and remain detectable up to six months after birth, probably as a result of the immaturity of the reticuloendothelial system, which leads to slow antibody clearance[8]. The effects of these high drug levels on the developing immune system are unknown. In fact, only few studies have evaluated the safety of anti-TNF in the

offspring. The TEDDY study showed that the risk of severe infections (causing hospitalization) is not increased in children exposed *in utero* to anti-TNF drugs[9]. However, Julsgaard et al suggested that the combined treatment with anti-TNF and immunosupressants during pregnancy could increase the risk of infections (severe but also mild) in the children in comparison with those exposed to anti-TNF in monotherapy[7].

On the other hand, vedolizumab is an IgG1 monoclonal antibody that has been recently approved for the treatment of IBD either as first line or after failure of other biologic agents[10, 11]. Vedolizumab is also transported across the placenta by FcRn receptor. Recent studies have demonstrated that vedolimumab is present in cord blood of neonates exposed to this drug during pregnancy[12]. In addition, vedolizumab can be detected in breast milk, although at very low concentrations (100-fold lower than the therapeutic levels of drug in the serum)[13, 14]. Although experience is limited, it is unlikely that this exposure has any negative effect on the baby[15]. Finally, Ustekinumab, recently approved for the treatment of CD[16], is also an IgG1 monoclonal antibody and, therefore, able to cross the placenta by the receptor FcRn. In consequence, fetuses from mothers treated with ustekinumab during pregnancy will be exposed *in utero* to the drug[17].

Data about the safety of those agents during pregnancy and during the first years of life of the offspring is scarce, making it unable to make any recommendation with respect to maintaining or interrupting the treatment during pregnancy or lactation. In this respect, pivotal trials specifically exclude pregnant women, preventing to obtain any information on their safety during gestation. Furthermore, several new drugs are in the pipeline for approval for IBD treatment and information about their safety during pregnancy will be an urgent uncovered need.

In summary, most patients with IBD are affected during their peak reproductive years. This fact, together with the increase in the incidence of IBD (especially in western countries) has lead to a higher number of pregnant women attended in IBD clinics. A number of new drugs are being added to the therapeutic armamentarium of IBD and we expect to have more in the near future. To know the safety of these drugs (during pregnancy and for the children development) is an urgent uncovered need. Registries based on clinical practice are crucial to obtain this information.

2. OBJECTIVES

2.1. Main objective

To assess the safety of drugs used for IBD treatment both for pregnancy and for the offspring mainly focused on the risk of serious infections (from birth and in the first 4 years of life).

2.2. Specific objectives

- To know the risk of serious adverse events (including abortions) during pregnancy and delivery associated with drugs used for the treatment of IBD.
- To asses the developmental status of children born from IBD mothers during the first 4 years.
- To compare the relative risk of serious adverse events in children born from mothers with IBD who have been exposed *in utero* to different drugs to treat IBD with the risk in children who were not exposed.
- To compare the prevalence of malformations in children exposed to drugs to treat IBD *in utero* with the prevalence in children who were not exposed.
- To evaluate the relative risk of developing neoplasm in children exposed to drugs to treat IBD.

3. SOURCE OF INFORMATION AND SCOPE

The information will be obtained by recording from pregnant IBD women. To reach the aims of the study, treatments, disease activity and complications during pregnancy and infections, malformations, developmental milestones, neoplasia and any other complications over the first 4 years of life of the offspring will be recorded.

4. METHODS

4.1. Study design

This is a prospective, observational, multicenter registry, which will enrol pregnant women with IBD (CD, UC, or unclassified IBD) over 5 years in Spain.

In addition, each incident gestation will be followed-up during pregnancy, and children born to those mothers will be followed-up over 4 years to determine the incidence of serious adverse events (such as alteration of developmental status, infections, neoplasia or any other serious adverse events) during the study period. In order to harmonize the inclusion of adverse events and complications, only serious adverse events will be registered (see the definition of serious adverse events in the Annex 1 of the protocol). The main variable will be the development of serious infection in children —as this is the outcome that had controversial results in previous studies.

The assignment of a patient to a specific therapeutic strategy will not be established in advance by the protocol of the study. Patients will be classified depending on the treatment they are receiving at conception (before study entry). The therapeutic strategy adopted during pregnancy will be decided by the clinician responsible for the patient. Therefore, the decision to prescribe a particular drug will be clearly dissociated from the decision of including the patient in the study. No intervention will be applied to patients, either diagnostic or follow-up, other than those recommended in clinical practice.

4.2. Timetable and scheduled end date

Start of recruitment: January 2019.

End of recruitment: January 2024.

End of study: September 2028.

4.3. Study population

4.3.1. Inclusion criteria

- Patients over 18 years of age diagnosed with IBD.
- Confirmed pregnancy.
- Awareness of the pregnancy (by the researcher) before week 28th of gestation (the end of the second trimester).

4.3.2. Exclusion criteria.

- Patients who do not accept to participate in the study.

4.4. Study cohorts

- Biologics exposed cohort: Children born from mothers treated with biologic drugs (with or without immunomodulators) at any time during pregnancy or the three months before conception. Biologic drugs are IgG monoclonal antibodies able to cross the placenta.
- Immunomodulators exposed cohort: Children born from mothers treated with immunomodulators (without biologics) during pregnancy or the three months before conception.
- Non-exposed cohort: Children born from mothers treated neither with biologic drugs nor with immunomodulators at any time during pregnancy or the three months before conception.

4.5. Tasks and responsibilities

IBD specialists from the participating centers will be responsible for identifying the patients, obtaining the informed consent and registering them in the database.

Each participating investigator will register all the demographic and clinical data

of the mother at the time of entering in the study and will contact the pregnant woman at the end of first trimester, the end of second trimester, the end of third trimester and one month after delivery to prospectively include information about disease activity, treatments and serious adverse events (if any) during pregnancy and delivery. If the mother contacts the clinician (researcher) after the end of the first trimester but before the end of the second trimester of gestation, the case can be included and data up to the entry date registered retrospectively. In order to ensure data quality, patients who inform about the pregnancy after the end of the second trimester of gestation will be excluded.

After birth, the mother will be contacted every 3 months to include information about the child development and serious adverse events (mainly malformations, infections, hospital admissions or neoplasias such as developmental tumors). After consenting, contact information of the mother will be shared with the research team in Hospital Universitario de La Princesa in order to complete the information every 3 months. On a yearly basis, the mothers will provide the site investigator with the reports that support the information given in the remote contact. In addition, in the first visit after birth, mothers will be provided with the Ages and Stages Questionnaire (ASQ 3, annex 2) that should be completed during follow-up (2, 4, 6, 8, 9, 10, 12, 14, 16, 18, 20, 22, 24, 27, 30, 33, 36, 42, 48 months of age). The mother should give the questionnaire she has completed once per year. External monitoring of cases included in the registry will also be performed by review of some cases selected at random by the research team of Hospital Universitario de La Princesa.

4.6. Definitions

1. Disease location and phenotype: IBD location and phenotype will be defined according to the Montreal classification.

2. Date of conception: It will be defined as the date of last menstruation before becoming pregnant.

3. Smoking: Smoking status will be categorized as “non-smoker”, “smoker”, or “ex-smoker”, and will be considered at the time of conception. Patients will be considered “smokers” if they smoked more than 7 cigarettes per week for at least 6 months prior to conception. Patients will be considered “ex-smokers” if they quit smoking before conception. Patients will be considered “non-smokers” if they never smoked.

3. Diagnosis of pregnancy: Elevated human chorionic gonadotropin (hCG) hormone in blood or urine (biochemical pregnancy).

4. Miscarriage: Natural death of an embryo or fetus before it is able to survive independently.

5. Elective abortion: The removal of an embryo or fetus from the uterus in order to end a pregnancy.

6. Comorbidities: Mother’s diseases, with special mention to hypertension, diabetes mellitus, seizure disorders, thyroid disorders, allergic disorders, heart diseases, connective tissue diseases, autoimmune diseases, hepatitis.

7. Known risk factors for adverse pregnancy outcomes, including environmental or occupational exposure, among others.

8. Treatments: Treatments received by the mother in the 3 months before conception, during pregnancy and breastfeeding will be recorded.

9. Serious adverse events: In order to harmonize the inclusion of adverse events and complications, only serious adverse events will be registered (see the definition of adverse events in the Annex 1 of the protocol). Nevertheless, we have predefined the most frequent serious adverse events during pregnancy and in the offspring. In this respect, the main variable in our study will be the development of serious infection

in the offspring (infection meeting criteria of serious adverse event).

9.1. Serious adverse events during pregnancy: Any event that meets the criteria of serious adverse event will be registered in the database. Some of the most frequent serious adverse events during pregnancy are specifically defined and inquired by the registry: abortion, stillbirth, growth retardation, serious infection, eclampsia, placenta previa, chorioamnionitis, or abruptio placenta. Abnormalities found in the 20th week ultrasound will be registered (although malformations should be confirmed after birth and included in the Serious Adverse Events section of the newborn). Fetal malformations that lead to abortion or stillbirth will be included as cause of abortion or cause of stillbirth in their specific sections (Serious adverse events of the mother).

9.2. Serious adverse events during delivery: Serious adverse events, such as instrumental delivery or preterm delivery will be registered in the Serious adverse events of the mother section. The admission for delivery will not be considered as a serious adverse event, but any event causing prolongation of the admission will be considered as a serious adverse event and registered in the specific section.

9.3. Serious adverse events in the newborns and children: Serious adverse events in the newborn and children, such as congenital malformations, admission to the intensive care unit, low birth weight, hypoxic-ischemic encephalopathy, neonatal stroke or low Apgar score, severe infections and tumors will be included.

10. Preterm delivery: Delivery before week 37 of gestation[18, 19].

11. Low birth weight: <2,500 mg[18, 19].

12. IBD activity: The IBD activity will be assessed at conception (when the physician is aware of the pregnancy) and in each trimester of gestation based on the Harvey-Bradshaw for CD and Partial Mayo Score for UC patients.

13. Low Apgar score: Apgar scores lower than 7 are considered low, and scores of 7 or higher are considered normal at ten minutes after birth[20].

14. Serious infection: Only infections that meet the criteria of serious adverse event will be included. The inclusion of any infection, irrespective of its seriousness, would be very heterogeneous among investigators, leading to reporting bias which might affect the interpretation of the results. This variable will be the main outcome.

15. Developmental status: The developmental status will be assessed by the ASQ-3 questionnaire (annex 2). The mothers will complete the questionnaire at home and send the completed forms yearly to their treating clinicians.

4.7. Data collection and follow-up

After the case is registered, four other visits will be recorded during pregnancy, coinciding with the routine visits of the patient for the follow-up of her disease. After delivery, the children will be followed-up until the age of 4 years. In case of multiple gestations, each child will be considered as a case with his/her own follow-up. Only live newborns will be considered cases. Abortions or stillbirths will be registered as mothers' adverse events. In multiple gestations, the number of fetuses affected by a certain serious adverse event will be indicated in the CRF. During the child's follow-up period, the mother (that is the patient, indeed) will be contacted remotely every-three months to complete information about child complications (if any). The visits over the study are described below. The variables included in the eCRF are listed in Annex 3.

- Visit 0 (baseline): inclusion of patient in the study (after confirmed pregnancy) and registration of clinical data (characteristics of the disease, disease activity and treatments).
- Visit 1 (end of first trimester of gestation): Updating of data related to treatment, disease activity and serious adverse events (if any).
- Visit 2 (end of second trimester of gestation): Updating of data related to

treatment, disease activity and serious adverse events (if any).

- Visit 3 (end of third trimester of gestation): Updating of data related to treatment, disease activity and serious adverse events (if any).

- Visit 4 (1 month after delivery): Updating of data related to treatment, disease activity and serious adverse events (if any). In addition, in this visit, the child will be registered in the database as a case. Information of the newborn, such as date of birth, sex, birth weight, Apgar score (at 5 and 10 minutes), vaccines, breastfeeding, serious adverse events, etc., will be included.

- Visit 5 (3 months of age, 2 months after visit 4) to 20 (4 years of age): Updating of data related to children development, vaccines, breastfeeding, date of schooling, infections, hospitalizations, allergies or any other complications. The same data will be queried to the mother every-three months after the age of 4 years. Remote contacts will be allowed to complete the children information, as we believe that this way of obtaining information will not have impact on the quality of data and will improve the adherence to the protocol. Nevertheless, once per year data should be confirmed with medical reports provided by the mothers.

Study data will be collected and managed using an electronic data capture tool (Research Electronic Data Capture [REDCap][1, 18, 19]), which is hosted at Asociación Española de Gastroenterología (AEG; www.aegastro.es)[21], a non-profit scientific and medical society focusing on gastroenterology. AEG provides this service free of charge, with the sole aim of promoting independent investigator-driven research. REDCap is a secure, web-based application designed to support data capture for research studies that provides the following: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

4.8. Sample size

The sample size was calculated based on the main comparison that is the incidence rate of severe infections in children exposed to biologics in comparison with non-exposed children (children non-exposed to immunomodulators or biologics). In a previous study from our group (the TEDDY study)[9], the incidence rate of severe infections in the non-exposed group was 1.6% per person-year of follow up. We have considered that a 2-fold higher incidence rate of severe infection in the biologic exposed group would be clinically relevant (3.2% per person-year of follow-up). Considering a significance level α of 5% and a power of 80%, the sample size needed to demonstrate statistically significant differences would be 1433 person-years in each group. The percentage of loses of follow-up is estimated to be 5%; therefore, the final sample size would be 1,500 person-years in each study group. As the follow-up will be 4 years, we will need to follow 375 children during 4 years in each group.

Approximately 70 IBD Units across the country have agreed to participate and will be involved in the registry. After a previous survey performed in these Units, we anticipate that the mean number of pregnancies per year will be 5 (2 of them with biologics) in each center. Therefore, we expect to include approximately 350 pregnancies per year, which means 1,750 pregnancies in 5 years. This information reassures the factibility of the project.

5. STATISTICAL ANALYSIS

For quantitative variables, the mean and standard deviation or median and interquartile range, depending on whether they are normally distributed or not, will be calculated. Comparisons between means will be performed using Student's t test for independent samples. Qualitative variables will be compared using the chi-square

($\chi 2$) test and the Fisher's exact test. Statistical significance will be considered at $p < 0.05$ for the overall comparison of the groups (non-exposed, exposed to immunomodulators, and exposed to biologic agents alone or in combination with immunomodulators). If the comparison of the three groups is statistically significant, then, exposed groups will be compared with the non-exposed group. P value for these comparisons will be considered statistically significant if <0.025, after adjustment by Bonferroni correction for multiple comparisons.

A binary logistic regression model will be used to estimate the effect of the different variables on the risk of serious infections. All the variables which reach the statistical significance in the univariate analysis and those who are considered clinically relevant will be included in the multivariate analysis. Thus, in the multivariate analysis, the dependent variable will be the presence of serious infections and the independent variables will be: type of IBD, maternal age at conception, consumption of toxic substances during pregnancy, IBD activity at the moment of conception, activity disease during pregnancy, low birth weight, prematurity, exposure to immunomodulators, and exposure to biologic drugs, among others. To evaluate the statistical interaction between the treatment with immunomodulators and biologic drugs a product of these two variables will be included in the regression model.

In addition, intermediate analyses will be carried out on an annual basis to know, in a descriptive way, the incidence of serious adverse events with each group of medicines.

6. ETHICAL ASPECTS AND CONFIDENTIALITY

6.1. General and specific rules for researchers

Researchers will strictly comply with the provisions of this protocol, completing the data collection sheets, which will be sent in due time to the sponsor or the

collaborating entity designated by the sponsor to analyze the data.

The trial will be carried out according to the recommendations for clinical trials and evaluation of drugs in humans that appear in the Declaration of Helsinki, revised in Tokyo, Venice, Hong Kong, South Africa, Edinburgh, Washington, Tokyo and Seoul (2008) and in the current Spanish Legislation on clinical trials.

The auxiliary personnel will follow the instructions given by the researcher.

Prior to the study, patients should receive oral and written information regarding the design, study purposes and possible risks that may arise from it. If they subsequently agree to participate, they must sign their consent, which will not prevent them from revoking it and abandoning the study at any time and for any reason.

Patients will receive instructions regarding the need to strictly follow the instructions of the investigators. Patients will be informed of the need to contact the researchers if any incidence arises during the study, which will be facilitated during the study's outpatient period.

If during the study any patient suffers a disease or adverse event that in itself or for requiring pharmacological treatment modifies the disposition of any of the drugs under study, or makes its administration unwise, the patient will be excluded from the study and the cause will be detailed. If the adverse reaction is mild or moderate, requiring or not treatment, and does not imply the suspension of the drug, this reaction will be recorded in detail and the follow-up within the study will continue as planned.

As per current pharmacovigilance legislation, investigators are asked to report any suspected adverse reactions recorded in the study via the web page of the national reporting system (Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano: www.notificaRAM.es).

6.2. Ethics Committee for investigation with medicinal products (CEIm)

The investigator will be responsible for obtaining from the CEIm the prior approval of the study protocol, the amendments to the protocol, the informed consent documents and other relevant documents, if applicable. All correspondence maintained with the CEIm will be kept in the investigator's file. Copies of CEIm approvals will be sent to the sponsor. An amendment can only be initiated without the prior approval of the CEIC when the change is necessary to prevent obvious immediate risks to patients. In this case, the investigator must notify the CEIm and the sponsorsponsor, in writing, immediately after its application.

6.3. Informed Consent (IC)

The IC document must be in accordance with the ICH's GCP, local administrative regulations and legal requirements.

The informed consent document used in this study and any changes made to it during the study must be approved in advance by the CEIC and by the sponsor before its use.

The investigator must ensure that all study patients, or their legal representatives, are fully informed of the nature and objectives of the study and the possible risks associated with participation. The investigator or his/her designee will obtain the written informed consent of each patient or their legal representative before carrying out any specific activity of the study and a copy of it will be delivered to the patient or his/her legal representative to be kept.

The researcher will keep the original of all the consent documents signed by the patients.

6.4. Amendments to the protocol

Neither the principal investigator nor the sponsor will modify this protocol without first obtaining the consent of the other parties. The modification must be documented in writing. Any change in the research activity, except those necessary to eliminate an immediate apparent risk to the patient must be reviewed and approved by the CEIm, before its implementation. The sponsor must send the amendments to the protocol to the health authorities, and the modifications may require the review and approval of the CEIm.

6.5. Security and confidentiality devices

The information obtained and disseminated by the implementation of this study is considered confidential and should be treated at all times as such. The subjects of the study will be identified by an identification number. All processed data will be identified with the identification number to ensure that patient identity remains unknown to the sponsor.

If data is transferred to third parties, such as entities of our group, service providers or scientific researchers who collaborate with us, the data of the participant will be protected by safeguards such as contracts or other mechanisms established by the data protection authorities and they will not be disclosed at any time except by legal requirement. The principal investigator will be responsible for maintaining said confidentiality.

The researchers participating in the study are responsible for keeping the identification of the codes of the subjects in each center during a period of 5 years after the finalization of the study.

Access to personal information of participating patients will be restricted to the study physicians / collaborators, health authorities (Spanish Agency for Medicines

and Medical Devices), Research Ethics Committee and personnel authorized by the sponsor, when they need to verify the data and study procedures, but always keeping their confidentiality in accordance with the provisions of Regulation (EU) 2016/679 of the European Parliament and the Council of April 27, 2016 on Data Protection (RGPD).

The results of the study may be communicated or disseminated in scientific meetings or publications, but at no time shall it be done in such a way that the identity of the patients can be revealed.

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