ORIGINAL ARTICLE

BJCP BRITISH PHARMACOLOGICAL SOCIETY

# Reported congenital malformations after exposure to non-tumour necrosis factor inhibitor biologics: A retrospective comparative study in EudraVigilance

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**Funding information**
Dutch Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen; CBG-MEB)

**Aims:** To evaluate the number and nature of reported congenital malformations (CMs) after intrauterine exposure to non-tumour necrosis factor inhibitor biologics (non-TNFi biologics) compared to certolizumab pegol (CZP).

**Methods:** A retrospective comparative study was conducted in the EudraVigilance (EV) database. A safe biologic (CZP) was considered as the reference group. Odds ratios (ORs) for CMs were calculated for each non-TNFi biologic (including abatacept, anakinra, belimumab, ixekizumab, rituximab, secukinumab, tocilizumab, ustekinumab and vedolizumab), versus CZP (quantitative assessment). Then, CM patterns were reviewed in consultation with a clinical geneticist (qualitative assessment).

**Results:** ORs were not statistically significant except for belimumab and vedolizumab (similar in magnitude). Except for vedolizumab, no specific CM patterns were observed for the included non-TNFi biologics. Three cases of corpus callosum agenesis (CCA) were identified for vedolizumab (versus none in CZP and other investigated non-TNFi biologics). Two of the CCA cases were associated with other neurological CMs (one cerebral ventriculomegaly with microcephaly and one polymicrogyria). This may indicate that these CCAs are related to undiagnosed genetic alterations or are associated with the underlying maternal disease, although a definite relationship with vedolizumab exposure cannot be ruled out.

**Conclusion:** No special safety signal was identified regarding the occurrence of CMs after exposure to abatacept ($n = 64$), anakinra ($n = 20$), belimumab ($n = 93$), ixekizumab ($n = 29$), rituximab ($n = 57$), secukinumab ($n = 128$), tocilizumab ($n = 124$) and ustekinumab ($n = 215$). Regarding observed CCAs in the vedolizumab group ($n = 113$), no firm conclusions can be made based on available information.

**KEYWORDS**
autoimmune diseases, EudraVigilance database, non-TNFi biologics, pregnancy

# 1 | INTRODUCTION

The prevalence of immune-mediated inflammatory diseases (IMIDs) is estimated to be twice as high in women, among whom many cases occur during the childbearing period.[1] Active disease may have a negative impact on both mother and fetus. It has been reported that uncontrolled IMIDs can result in spontaneous abortions, pre-term birth and intrauterine growth restriction.[2–4] Therefore disease control with safe medications during pregnancy is of utmost importance.[5]

Biologics are one of the main groups of medications indicated for the management of IMIDs. Based on the mode of action, biologics are classified into tumour necrosis factor-α inhibitors (TNFis) and non-TNFi biologics.

In recent years, various studies have been conducted to investigate the safety of TNFis during pregnancy. Based on prospectively acquired data, **adalimumab**, **etanercept**, **certolizumab pegol** (CZP) and **infliximab** are approved by regulatory authorities for use during pregnancy if clinically needed.[6–9] Among these, CZP crosses the placenta in very scarce amounts due to the lack of the Fc part.[10] Data from more than 500 prospectively followed pregnancies exposed to CZP did not indicate higher rates of congenital malformations (CMs) compared to the general population. CZP is generally considered to be safe for use during pregnancy.[7–9,11–21]

The strength of information and the amount of data available on the occurrence of adverse events after exposure to non-TNFi biologics during pregnancy is very limited (among which is the incidence of CMs).[22] Non-TNFi biologics are widely used in the management of IMIDs such as systemic lupus erythematosus, rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, Crohn's disease and ulcerative colitis. Due to lack of data, the use of non-TNFi biologics is not recommended during pregnancy. Yet, unintended exposure during the early stages of pregnancy is possible. Furthermore, the decision on changing or stopping the medication during pregnancy is difficult, since the risk of a flareup and consequent adverse events during pregnancy is high. Hence, there is a clinical need for studies on the safety of non-TNFi biologics during pregnancy. Due to the scarcity of prospective data for non-TNFi biologics, extracting retrospective data from available pharmacovigilance databases such as EudraVigilance (EV) could be helpful—to some extent—in an attempt to fill this knowledge gap.

This study aimed to evaluate the number and nature of reported CMs in the EV database, after intrauterine exposure to non-TNFi biologics compared to CZP.

## 2 | METHODS

### 2.1 | Data source

This was a retrospective comparative study using the EV database. This pharmacovigilance database is used for collecting the reports of suspected adverse drug reactions (ADRs) to medications that have been authorized by the European Medicines Agency (EMA).[23] The

**What is already known about this subject**

- Numerous prospective and retrospective studies have succeeded in demonstrating the safety of main tumour necrosis factor inhibitor biologics (TNFi biologics) (including certolizumab pegol [CZP]) during pregnancy.
- The strength of information and the amount of data available on the occurrence of adverse events (including the incidence of congenital malformations [CMs]) after exposure to non-TNFi biologics during pregnancy is very limited.
- The use of non-TNFi biologics during pregnancy is discouraged due to lack of safety data.

**What this study adds**

- Except for vedolizumab, no specific CM patterns were observed in pregnancy reports of non-TNFi biologics (including abatacept, anakinra, belimumab, ixekizumab, rituximab, secukinumab, tocilizumab and ustekinumab) in the EudraVigilance database.
- Three cases of corpus callosum agenesis (CCAs) were found in reported pregnancies exposed to vedolizumab (versus none in CZP and other non-TNFi groups).
- Based on consultation with a clinical geneticist, reported CCAs may be related to undiagnosed genetic alterations or association with the underlying maternal disease, although a definite relationship with vedolizumab exposure cannot be ruled out.

purpose of this database, which was launched in 2001, is to enable the early detection of possible safety signals from marketed drugs.[24] An important source of data collection for post-marketing pharmacovigilance is spontaneous reports, which are submitted on a voluntary basis (spontaneously) by healthcare professionals and patients. Regarding pregnancy, ADRs after exposure to medications have been reported to EV, both from observational studies (including non-pregnancy studies) and spontaneously. It should be noted that data acquisition in EV is heterogeneous, and spontaneous reports have a tendency to only report the adverse outcomes and underreport the normal outcomes.

Disproportionality analysis is used for quantitative assessment of the data in pharmacovigilance databases. This analysis consists of comparing the observed reported ratios with expected ratios (the proportion that is expected if no association existed between the drug and the ADR).[25] Due to the limitation of disproportionality analysis in extrapolating the results to the patient population outside of the database, identified potential safety signals and increased reporting rates

should be further assessed clinically. External validation and consideration of the other important factors such as the mechanism of action are also crucial in the interpretation of the recognized safety signals.

## 2.2 | Inclusion/exclusion process

A search was performed in the EV database among pregnancy-related ADR reports (all reports until 11 March 2021). An overlap exists between the biologics used for the indications of rheumatologic, gastroenterological, and dermatologic IMIDs. Thus, initially, all pregnancy reports with known IMID indications and exposed to CZP, abatacept, anakinra, belimumab, ixekizumab, rituximab, secukinumab, tocilizumab, ustekinumab and vedolizumab (non-TNFi biologics group), were extracted (for the list of indications, see Table S1 in the Supporting Information). Exposure was considered as any intake from 3 months before conception until delivery, due to the relatively long half-life of biologics and uncertainties about the conception dates in some cases.

Multiple versions of cases were detected with similar EV "World Wide Unique Case Identifier" or after reading the full texts. In the case of multiple versions of the same case, the most recent one was included. Exposures only via breast milk and paternal exposures were excluded. Cases with genetic disorders were also excluded from the final calculations, as exposure to biologics is unlikely to cause genetic alterations.[26] This was determined first based on the narrative of the reports and then based on the assessment by a clinical geneticist.

To be eligible for this study, a report must also have described the outcome of the pregnancy. This was defined as stating if the pregnancy had resulted in an abortion (spontaneous or induced, before the 20th week of gestation), stillbirth (after the 20th week of gestation) or live birth (with or without the date of birth).[22,27–29]

Major CMs are anomalies that are life-threatening or cause morbidities and disabilities. Minor CMs have minimal impact on overall health and mainly have cosmetic importance.[30] Both minor and major CMs were extracted after reading the narratives. This decision was made to improve the detection of potential abnormal CM patterns in qualitative assessment (see below). Termination of pregnancy due to fetal anomaly was also included as a CM. Data analysis was conducted using STATA Statistics software (version 17).

Considering the limitations of pharmacovigilance databases and the heterogeneity of data collection,[31] we have decided to analyse the reported CMs with both quantitative and qualitative measures. If a potential association between a specific non-TNFi biologic and a CM exists, it is expected to observe a pattern in CMs reported for exposed pregnancies.

## 2.3 | Quantitative assessment

Considering the nature of data acquisition in pharmacovigilance databases (here EV) and the absence of pure control subjects, no control group could be used, but instead, a safe biologic (CZP) was considered

as the reference group. Crude odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for total reported minor and major CMs in non-TNFi biologics compared to the CZP group (as the reference group). Crude OR is the ratio of odds reporting CMs versus all other pregnancy reports exposed to non-TNFi biologics (cases) compared with the odds reporting CMs versus all other pregnancy reports exposed to CZP (reference group). The statistically significant difference with the reference group was considered as the lower limit of 95% CI.[32]

It has been reported that mothers in higher age groups have an increased risk of specific CMs such as congenital heart malformations.[33] Furthermore, women in higher age groups have a longer disease duration and a higher chance to be exposed to biologics, which are the second and third lines in the treatment of IMIDs. Therefore, age is associated with both outcome and exposure and was considered to be a possible confounder in this study. To be able to adjust for maternal age, we extracted reported maternal ages (at the time of conception) from the full texts. If not provided in the full text, this was calculated based on the time gap between the mother's birth date and conception date. To adjust for confounding by maternal age (explanatory variables), logistic regression analysis was performed. The presence of CMs was considered as the outcome (dependent covariate). Adjusted ORs were calculated for each non-TNFi biologics. A $P$-value of ≤0.05 was considered statistically significant.

Exposure to teratogens can interfere with embryonic development.[34] It is expected that the use of teratogens is associated with exposure to specific non-TNFi biologics. For example, there is a higher possibility that belimumab is administered together with mycophenolate (known teratogen) for systemic lupus erythematosus (SLE). Therefore, also exposure to teratogens was considered a potential confounder. Concomitant medications reported for each pregnancy were scanned for the presence of known teratogens. The teratogenicity of each concomitant medication was determined based on its official Summary of Product Characteristics (SmPC) (see the final list of recognized teratogens in Table S2 in the Supporting Information).

As explained, the probability of exposure to known teratogens is not similar for different non-TNFi biologics (confounding by indication). Because exposure to teratogens was not normally distributed in different non-TNFi groups, instead of logistic regression, stratification was considered to control for possible confounding, after adjustment for maternal age. This was calculated for each non-TNFi group separately. Due to low numbers in various non-TNFi groups, the pregnancies exposed to known teratogens could not be reliably analysed.

## 2.4 | Qualitative assessment

To be able to get detailed insight into the data after quantitative assessment, the patterns of detected CMs were compared between non-TNFi biologics and CZP. ADRs in EV are coded using the MedDRA dictionary (the Medical Dictionary for Regulatory Activities terminology). MedDRA® is the international medical terminology.[7,35] The MedDRA dictionary has different hierarchical levels. Individual cases

are usually coded for data entry in EV at the most specific level (lowest level terms [LLTs]). Related LLTs are grouped into more general categories, "high level terms (HLTs)" and "high level group terms" (HLGTs) based upon anatomy, pathology, physiology, aetiology or function. For example, a CM can be reported with LLT "ventricular septal defect". This will be categorized as the HLT "septal defects" and the HLGT will be "cardiac and vascular disorders". We have used HLGT, HLT and LLT levels for comparison of CM patterns on both general and detailed levels.

After categorization, patterns of both minor and major CMs (including TOFAs) were compared between pregnancies exposed to included non-TNFi biologics and CZP. A table was made for this purpose at each MedDRA hierarchal level. A clinical geneticist (J.E.H.B.) reviewed the tables and full report texts of the suspected cases to recognize possible clusters.

## 2.5 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.

## 3 | RESULTS

In total, 2030 pregnancy reports were included, of which 1179 pregnancies were exposed to CZP and 851 were exposed to non-TNFi biologics, including abatacept, anakinra, belimumab, ixekizumab, rituximab, secukinumab, tocilizumab, ustekinumab and vedolizumab (Table 1). The biggest group among the non-TNFi biologics belonged to ustekinumab with 215 pregnancy reports. The smallest group was sarilumab with only one reported pregnancy.

For sarilumab, initially 266 reports were found. However, after reading the full texts it was noticed that all the submitted reports to EV were from one particular patient. This case was reported under numerous case numbers, with several concomitant medications as suspected medication and with numerous ADRs, possibly due to an administrative error. All these reports originated from Canada. Only one case was included in the sarilumab group and the remaining reports were considered repeated cases.

Pregnancy outcomes (spontaneous abortion, induced abortions, stillbirth and live birth) for each biologic are provided in Table S3 in the Supporting Information.

## 3.1 | Quantitative analysis

The number of total reported CMs was calculated based on reported CMs in live births and stillbirths or termination of pregnancies as a result of a fetal anomaly. No CMs were reported after exposure to canakinumab and sarilumab. Crude ORs for the rest of the included non-TNFi biologics were calculated.

Since exposure to teratogens was considered a confounder in the occurrence of CMs, we have calculated the stratified ORs for each included non-TNFi biologic in patients without reported exposure to teratogens (Table 2; see also Table S5 in the Supporting Information).

Considering CZP as the reference group, anakinra, rituximab, belimumab, ustekinumab and vedolizumab had higher crude ORs. This was statistically significant only for belimumab and vedolizumab.

After adjustment for maternal age, ORs were statistically significant for belimumab, rituximab and vedolizumab. However, after stratification for exposure to teratogens, OR was only statistically significant for belimumab and vedolizumab, though the ORs remained similar (Table 3). Due to the limitations of pharmacovigilance databases in the calculation of incidence rates, we have further investigated the results qualitatively.

## 3.2 | Qualitative analysis

To study observed differences in the clinical presentation of reported CMs between the included non-TNFi biologics and the CZP group (as reference), patterns of reported CMs were categorized and compared. First, patterns of reported CMs were categorized based on affected organs (HLGT level of the MedDRA dictionary, Table 3). In some reported cases, patients were also exposed to known teratogens such as methotrexate, mycophenolate or alcohol. These cases are indicated in red in Table 3 and Table S4 in the Supporting Information. A clinical geneticist (J.E.H.B.) reviewed both tables and narratives of suspected cases.

The most frequently reported CMs in the CZP group on the HGLT level were cardiac and vascular disorders, gastrointestinal tract disorders and musculoskeletal and connective tissue disorders. A comparable pattern was also observed for the included non-TNFi biologics, except for belimumab and vedolizumab. For belimumab, higher proportions of reported CMs were cardiac or neurological disorders. For vedolizumab, higher rates of neurological malformations were reported. To further investigate the observed differences in affected organs, specific CMs in each organ were compared to the CZP group at the LLT level.

On the LLT level, no specific patterns were observed in CMs reported for the belimumab-exposed group (Table S4 in the Supporting Information). From eight reported cardiac malformations, one septal defect and one valve defect had been exposed to known teratogens (possible association with exposure to methotrexate and mycophenolate[36–38]). Reported cardiac malformations were mostly septal defects and were associated with other disorders ($n = 5 +$ other valve and great vessels disorders, $n = 1 +$ Dandy-Walker syndrome, $n = 1 +$ hydrops fetalis, $n = 1 +$ hydronephrosis). From a total of five neurologic anomalies, one case was reported for each of the following CMs: spinal cord anomaly (possible association with exposure to methotrexate[36,38]), Arnold-Chiari malformation type I, hydrocephalus, mega cisterna magna ($+$ patent foramen ovale) and Dandy-Walker syndrome ($+$ unspecified cardiac anomaly). No cumulative

**TABLE 1** Flowchart of report selection

| | Certolizumab pegol | Abatacept | Anakinra | Belimumab | Canakinumab | Ixekizumab | Rituximab | Sarilumab | Secukinumab | Tocilizumab | Ustekinumab | Vedolizumab |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| The initial number of reports | 3725 | 904 | 72 | 343 | 15 | 79 | 784 | 266 | 331 | 1074 | 591 | 268 |
| Multiple versions of a unique case[a] | 2223 | 802 | 44 | 238 | 6 | 18 | 712 | 265 | 118 | 920 | 286 | 135 |
| Cases without reported pregnancy outcome | 283 | 35 | 5 | 12 | 2 | 8 | 13 | 0 | 58 | 22 | 73 | 12 |
| Paternal exposures | 18 | 0 | 3 | 0 | 0 | 23 | 0 | 0 | 24 | 6 | 13 | 5 |
| Exposure only via breast milk | 12 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| CMs due to genetic disorders | 10 | 3 | 0 | 2 | 0 | 1 | 2 | 0 | 3 | 2 | 3 | 3 |
| Included number of pregnancy reports in the analysis | 1179 | 64 | 20 | 93 | 7 | 29 | 57 | 1 | 128 | 124 | 215 | 113 |

CM: congenital malformation.
[a]Included only once.

**TABLE 2** Reported number, crude and adjusted ORs [95% CIs] for CMs after intrauterine exposure to non-TNFi biologics compared to certolizumab pegol

| Medication | Reported CMs, n/N (%) | Crude ORs [95% CIs] | Adjusted ORs (for maternal age) [95% CIs] | Stratified ORs (teratogen unexposed cases only) [95% CIs][a] |
|---|---|---|---|---|
| Certolizumab | 95/1179 (8.05) | Reference | Reference | Reference |
| Abatacept | 2/64 (3.12) | 0.36 [0.08, 1.52] | 0.35 [0.08, 1.47] | 0.69 [0.16, 2,96] |
| Anakinra | 3/20 (15.00) | 2.01 [0.57, 6.99] | 2.81 [0.77, 10.20] | 3.39 [0.91, 12.63] |
| Belimumab | 17/93 (18.27) | 2.55 [1.44, 4.49][b] | 2.63 [1.40, 4.93][b] | 2.65 [1.35, 5.20][b] |
| Ixekizumab | 1/29 (3.44) | 0.40 (0.05, 3.02] | 0.39 [0.05, 2.96] | 0.42 [0.05, 3.16] |
| Rituximab | 8/57 (14.03) | 1.86 [0.85, 4.04] | 2.47 [1.05, 5.80][b] | 2.55 [0.94, 6.95] |
| Secukinumab | 4/128 (3.12) | 0.36 [0.13, 1.01] | 0.34 [0.10, 1.11] | 0.37 [0.11, 1.19] |
| Tocilizumab | 10/124 (8.06) | 1.00 [0.50, 1.97] | 0.79 [0.37, 1.68] | 0.62 [0.22, 1.76] |
| Ustekinumab | 19/215 (8.83) | 1.10 [0.66, 1.85] | 0.92 [0.51, 1.66] | 1.01 [0.56, 1.82] |
| Vedolizumab | 23/113 (20.35) | 2.91 [1.76, 4.82][b] | 2.66 [1.53, 4.61][b] | 2.27 [1.24, 4.15][b] |

OR: odds ratio; CI: confidence interval; CM: congenital malformation.
[a]After adjusting for maternal age, stratified ORs are presented for patients who had no reported teratogen exposure during pregnancy. For results in teratogen-exposed cases, please see Table S5 in the Supporting Information.
[b]Statistically significant.

pattern was reported for the reported neurological CMs in the belimumab group.

For vedolizumab, three cases of corpus callosum agenesis (CCA) were reported versus none in the reference group or other biologics (Table S4 in the Supporting Information). Two of the CCA cases were associated with other neurological CMs including cerebral ventriculomegaly + microcephaly in one case and polymicrogyria in the other case. In none of the CCA cases was exposure to known teratogens reported. Two of the newborn's mothers were diagnosed with Crohn's disease and one with ulcerative colitis. Two of the pregnancies resulted in induced abortions, and one in a live birth. No exposure to teratogens or genetic abnormalities was reported in the fetuses. One case was exposed to vedolizumab 2 months before pregnancy (live birth), and two cases had exposure during the first trimester (induced abortions). Considering the long half-life of vedolizumab (24 days), the case with exposure during the pre-conception was also included in this study. No information was provided regarding the severity of CCAs.

## 4 | DISCUSSION

To our knowledge, this is the first study to compare the pattern of CMs for different non-TNFi biologics to CZP. Except for belimumab and vedolizumab, differences in CMs after exposure to abatacept, anakinra, ixekizumab, rituximab, secukinumab, tocilizumab and ustekinumab and CZP were not statistically significant. Except for vedolizumab, no specific CM patterns were observed.

The prevalence of the total CMs in our reference group was around 8%. This prevalence included both major and minor CMs. It should be taken into account that normal pregnancy outcomes are underreported in the EV database compared to adverse pregnancy outcomes.[39–41] Therefore, higher rates of ADRs compared to the general population are expected.

After adjusting for maternal age and correcting for exposure to known teratogens, ORs for CMs after exposure to belimumab and vedolizumab remained the same and were still statistically significant. High disease activity can increase the incidence of CMs. However, it was not possible to adjust for disease activity using the EV database as this information is usually not provided. Considering that non-TNFi biologics (such as belimumab) are mainly used as add-on therapy in severe forms of IMIDs, the role of disease activity in increased numbers of reported CMs cannot be excluded.

It must also be noted that in our study the number of exposures for rituximab and anakinra was low and therefore our data are insufficient to rule out a possible teratogenic effect since the ORs are consistently around or above 2.5.

### 4.1 | Belimumab

Regarding belimumab, its only indication (SLE) should be considered in the interpretation of the results. High activity of SLE during pregnancy is a risk factor for CMs in the offspring.[42] Results of a meta-analysis have shown a risk ratio of 2.63 (95% CI: 1.93–3.58) for CMs in neonates born to SLE patients.[43] This is comparable to the results from our study. In a large population-based study, Vinet et al. found increased rates of congenital heart defects (OR: 2.62; 95% CI: 1.77–3.88), mainly cardiac septal defects, in children born to 719 SLE patients compared to 8493 matched controls from the general population.[44] Comparable results were observed in qualitative assessment at HGLT and HLT MedDRA hierarchical levels in our study, for the belimumab group. Furthermore, two of the cases with cardiac septal defects in the belimumab group had been exposed to known teratogens: ventricular septal defect (VSD) + patent foramen ovale (PFO) after exposure to methotrexate and tricuspid valve incompetence after exposure to mycophenolate. This is in line with cardiac

**TABLE 3** Summarized pattern of CMs after exposure to certolizumab pegol (reference group) and non-TNFi biologics, based on organs, based on prevalence, MedDRA High Level Group Terms (for details, see Table S4 in the Supporting Information)

| Malformations by affected organs | Certolizumab pegol | Abatacept | Anakinra | Belimumab | Ixekizumab | Rituximab | Secukinumab | Tocilizumab | Ustekinumab | Vedolizumab |
|---|---|---|---|---|---|---|---|---|---|---|
| Number of included pregnancy reports; n [part of pregnancies exposed to known teratogens]; [n] | 1179 [68] | 64 [31] | 20 [3] | 93 [16] | 29 [1] | 57 [17] | 128 [5] | 124 [43] | 215 [13] | 113 [9] |
| Total cases with any CMs[a], n [part of CMs exposed to known teratogens]; [n] | 95 [7] | 2 | 3 | 17 [3] | 1 | 8 [2] | 4 | 10 [4] | 19 [1] | 23 [4] |
| Cardiac and vascular disorders; n | 21 [2] | 1 | | 8 [2] | | 2 | 1 | 3 [1] | 9 | 10 [2] |
| Gastrointestinal tract disorders; n | 16 | 1 | 2 | 2 | | 2 [1] | 1 | 1 [1] | 3 [1] | 3 [2] |
| Musculoskeletal and connective tissue disorders; n | 15 | | | 3 [1] | 1 | 3 [1] | 1 | 4 [2] | 1 | 2 |
| Renal and urinary tract disorders; n | 14 [2] | 1 | 1 | 2 [1] | | | | | 3 | 1 [1] |
| Reproductive tract disorders; n | 8 [2] | | | 1 | | | | 1 [1] | 1 | 1 |
| Neurological disorders; n | 6 [1] | | | 5 [1] | 1 | 2 | | 2 [2] | 1 | 5 |
| Eye disorders; n | 6 [2] | | | | | | 1 | 1 | | |
| Ear disorders; n | 3 | 1 | | | | | | | | |
| Respiratory system disorders; n | 2 | | | | | | | | 1 | 1 |
| Blood and lymphatic system disorders; n | 2 | | | | | | | | | |
| Endocrine disorders congenital; n | | | 1 | | | | | | | 1 |
| Skin and subcutaneous tissue disorders; n | | | | | | 1 | | | | |
| Not specified/other; n | 7 | | | | | | | 1 | 3 | |

Red colour: number of cases also exposed to known teratogens; CM: congenital malformation.

[a]Sometimes more than one malformation was reported in a case. Termination of pregnancy due to fetal anomaly was also included as a CM.

malformations reported in association with exposure to methotrexate and mycophenolate in the literature.[36–38]

No specific pattern on LLT level was observed for belimumab during qualitative assessment (including for neurological disorders). We also investigated the association between duration of use during pregnancy and occurrence of major CMs in another study to get a better insight, using the same data. In this study, we observed lower rates of major CMs if belimumab was continued during pregnancy, at least during the first trimester. These findings indicate a lower possibility of an association between belimumab exposure during pregnancy and the occurrence of major CMs. As explained above, confounding by disease activity can implicate a bias, which is not possible to correct for, with the data available from the EV database. Differences in indication can also have resulted in higher rates in the belimumab group compared to CZP, which is not indicated for SLE.

## 4.2 | Vedolizumab

In our study, the rate of (major and minor) CMs in the vedolizumab group was around 20%, compared to 8% in CZP (adjusted OR [95% CIs]: 2.27 [1.24–4.15]). From limited published data on vedolizumab exposure during pregnancy, rates of reported major CMs vary from 4–5% (retrospective studies)[45–47] to 12.5% (three CMs in 24 prospectively followed pregnancies: hip dysplasia, pulmonary valve stenosis and Hirschprung's disease).[48]

Vedolizumab is indicated for the treatment of inflammatory bowel diseases (IBD).[7] Different studies have shown no/slightly higher risk of CMs in IBD patients.[49] In a meta-analysis of 11 studies, OR of CMs in IBD patients compared to non-diseased controls, was calculated to be 1.29 (95% CI: 1.05–1.58).[50] A recent retrospective cohort has shown a higher risk of central nervous system (CNS) anomalies in patients with IBD, especially ulcerative colitis.[51] The authors of this study concluded that the increased risk of CNS anomalies is not related to vedolizumab use, but might be related to IBD activity and sensitivity of the fetus to pro-inflammatory cytokines. This may also explain the high rates of neurological anomalies (including CCA) observed in cases exposed to vedolizumab in our study.

For vedolizumab, three cases of CCAs from three different countries (Italy, Ireland and Canada), are reported in the EV database. No CCA cases were found for other included non-TNFi biologics or the reference group. In patients with CCA, the largest white matter structure connecting the two hemispheres of the brain is underdeveloped. Formation of the corpus callosum starts around the 10th week of gestation and lasts till the 20th week, although it continues to thicken and grow in a caudal direction for several months thereafter.[52] The incidence rate of CCA is estimated to be between 0.5 and 7 per 10 000 in the general population.[52–55] When symptomatic, it will present during the first 2 years of life, with mental retardation, vision problems, delay in language development, seizures and other neurodevelopmental disabilities. Several environmental and genetic factors, such as maternal alcohol consumption, prenatal infections, chromosomal aberrations or single-gene disorders have been described in the

aetiology of CCA.[56,57] No information on the severity of CCAs was provided in narratives of detected cases.

Two of the CCA cases were associated with other neurological CMs including cerebral ventriculomegaly + microcephaly and polymicrogyria. This may indicate that these CCAs are related to undiagnosed genetic alterations.[58] Unfortunately, the results of genetic tests were not available in the EV database. Alternative explanations are factors such as IBD activity[51] or susceptibility to specific infections (e.g., cytomegalovirus, toxoplasmosis, rubella and influenza[58]), although a definite relationship with vedolizumab exposure cannot be ruled out. Larger studies and pregnancy registries are needed to confirm either normal or abnormal results.

## 4.3 | Limitations

The interpretation of the calculated ORs is limited only to comparison with CZP (reference group) and not to the general population. As normal pregnancy outcomes are not considered an ADR and are not amended for submission in EV, there is a risk of underreporting of healthy pregnancy outcomes in this database.[39] Normal pregnancy outcomes are still reported to EV in some cases; for example, when an adverse event occurs only in the mother and does not affect the fetus (e.g., gestational hypertension in mothers with healthy offspring). An increased OR can only express the increased reporting rates in the database and is not extrapolatable to the patient population in general. The results should be interpreted with caution and both quantitative and qualitative assessments should be taken into consideration together.

Additionally, there are known limitations regarding spontaneous reporting. The analysis of these types of data relies upon individual cases and measures of disproportionate reporting and information bias. This includes the concept of voluntary reporting, whereby various factors may influence the reporting rate and data quality.[41]

Some reports were limited in their value by lack of data for pregnancy outcome, incomplete report of exposure to concomitant medications, or the lack of data on possible risk factors. Due to the lack of these data, we were not able to adjust for some of the additional potential confounders (concomitant drugs other than teratogens, comorbidities such as disease activity and maternal infections during pregnancy). Any signal from spontaneous reports needs to also be verified clinically (in pregnancy registries) and in combination with other information (such as the mechanism of action).[59]

Furthermore, all the biologics involved in the analysis were authorized at different times and so had different amounts of time to accrue suspected ADRs, including reports of pregnancy. The included biologics have different (multiple) indications and different market shares and so the number of patients exposed to each drug and hence the potential for reporting ADRs is vastly different. This also should be considered in the interpretation of quantitative results.

Considering these limitations, we cannot give any concrete advice in favour or against use of non-TNFi biologics during pregnancy in clinical practice. Our results give only a direction on safety of these

medications. In clinical practice an individuated benefit–risk balance assessment for each non-TNFi biologic and for each indication should be applied case by case.

# 5 | CONCLUSION

Except for vedolizumab, no specific safety signals were detected for reported CMs after exposure to other included non-TNFi biologics (abatacept, anakinra, belimumab, ixekizumab, rituximab, secukinumab, tocilizumab and ustekinumab). Regarding observed CCA cases for vedolizumab, further studies with a larger number of cases and pregnancy registries are suggested for external validation.

Currently, there is very scarce data available regarding exposure to non-TNFi biologics during pregnancy. Therefore, our study can be a starting point for further investigations, as the clinical need for information and decision making is crucial in this matter.

## COMPETING INTERESTS
R.J.E.M.D. received an unrestricted grant from Galapagos, UCB Pharma B.V. and Dutch Arthritis Association and speaking fees from UCB, Roche, AbbVie, Genzyme, Novartis and Lilly. The other authors have no competing interests to declare.

## CONTRIBUTORS
The idea for the study was conceived by J.M.W.H. and E.P.v.P., who also developed the methodology for the study together with N.G. N.G. was responsible for study validation, conducted the formal analysis and investigations, and also served as project administrator. H.J.M.J.C. was responsible for funding acquisition, and N.G. and J.E.H. B. curated the data. The study was supervised by J.M.W.H. and E.P.v. P. N.G. wrote the original draft of the manuscript, which was revised and edited by all the other authors.

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## DATA AVAILABILITY STATEMENT
For the purpose of this study, a protocol was submitted to and approved by the authorities in the European Medicines Agency (EMA). Stakeholders can access the EudraVigilance data in accordance with Regulation (EU) 2016/679, the General Data Protection Regulation (GDPR) and Regulation (EU) 2018/1725, the EU Data Protection legislation (EU DPR). As a member of the Dutch national medicines regulatory authority (CBG-MEB) and after approving the study protocol, N.G. gained access to the EudraVigilance database.

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