

# The Distribution of Congenital Anomalies Within the VACTERL Association Among Tumor Necrosis Factor Antagonist-exposed Pregnancies Is Similar to the General Population

HUBERTINA J.M.J. CRIJNS, JANNEKE JENTINK, ESTER GARNE, CHRISTINE C. GISPEN-de WIED, SABINE M.J.M. STRAUS, Lolkje T.W. de Jong-van den Berg, for the EUROCAT Working Group\*

**ABSTRACT.** *Objective.* To compare the distribution of congenital anomalies within the VACTERL association (vertebral defects, anal atresia, cardiac, tracheoesophageal, renal, and limb abnormalities) between patients exposed to tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) antagonist and the general population.

*Methods.* Analysis for comparison of proportional differences to a previous publication between anomaly subgroups, according to subgroup definitions of the European Surveillance of Congenital Anomalies (EUROCAT), a population-based database.

*Results.* Most EUROCAT subgroups belonging to the VACTERL association contained only one or 2 records of TNF- $\alpha$  antagonist exposure, so comparison of proportions was imprecise. Only the category "limb abnormalities" showed a significantly higher proportion in the general population.

*Conclusion.* The high number of congenital anomalies belonging to the VACTERL association from a report of pregnancies exposed to TNF- $\alpha$  antagonists could not be confirmed using a population-based congenital anomaly database. (J Rheumatol First Release July 1 2011; doi:10.3899/jrheum.101316)

## Key Indexing Terms:

VACTERL ASSOCIATION  
BIRTH DEFECT

EUROCAT

TUMOR NECROSIS FACTOR ANTAGONISTS  
SAFETY

Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) antagonists are indicated for treatment of autoimmune disorders, which have a higher incidence in women<sup>1</sup>. The teratogenic effect of TNF- $\alpha$  antagonists is unknown.

A case of VACTERL association (vertebral defects, anal atresia, cardiac, tracheoesophageal, renal, and limb abnormalities; Table 1) due to in-utero exposure to a TNF- $\alpha$  antagonist was identified by Carter, *et al*<sup>2</sup>. Based on this case, the US Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) database was searched for confir-

mation of this association of in-utero exposure to TNF- $\alpha$  antagonists<sup>3</sup>. Carter, *et al* concluded that their data suggest a possible causative effect of in-utero exposure to TNF- $\alpha$  antagonists and the VACTERL association.

A VACTERL association<sup>4</sup> is defined by at least 3 of the included congenital anomalies (Table 1) and is estimated to occur in 1.6–2.9/10,000 live births<sup>5,6</sup>. Carter, *et al*<sup>3</sup> also investigated the individual anomalies comprising the VACTERL association instead of the defined presence of at least 3 anomalies.

The FDA AERS database<sup>7</sup> is designed to identify signals of spontaneous reported adverse events in general, in contrast to the European Surveillance of Congenital Anomalies (EUROCAT), a population-based database specifically designed to identify and test signals of congenital anomalies<sup>7</sup>.

To assess whether in-utero exposure to TNF- $\alpha$  antagonists would provide a higher risk of one or more of the anomalies included in the VACTERL association, compared to the general population, we compared the distribution of congenital anomalies among the cases exposed to TNF- $\alpha$  antagonists as presented by Carter, *et al*<sup>3</sup> with the distribution of these anomalies in the EUROCAT database.

## MATERIALS AND METHODS

The EUROCAT central database, covering a large European population, contains individual standardized anonymous records of congenital anomalies since 1980 including live births, stillbirths, or fetal death from 20 weeks of

From the Medicines Evaluation Board, The Hague, The Netherlands; Department of PharmacoEpidemiology and PharmacoEconomics, University of Groningen, Groningen, The Netherlands; Paediatric Department, Lillebaelt Hospital, Kolding, Denmark; and Department of Medical Informatics, Erasmus Medical Center, Rotterdam, The Netherlands.

H.J.M.J. Crijns, MD, Medicines Evaluation Board; J. Jentink, MSc, Department of PharmacoEpidemiology and PharmacoEconomics, University of Groningen; E. Garne, MD, PhD, Paediatric Department, Lillebaelt Hospital; C.C. Gispén-de Wied, PhD; S.M.J.M. Straus, MD, PhD, Medicines Evaluation Board, Erasmus Medical Centre, Rotterdam; L.T.W. de Jong-van den Berg, RPh, PhD, Department of PharmacoEpidemiology and PharmacoEconomics, SHARE Graduate School, University of Groningen.

Address correspondence to Prof. L.T.W. de Jong-van den Berg, Department of PharmacoEpidemiology and PharmacoEconomics, University of Groningen, Ant Deusinglaan 1, 9713 AV Groningen, The Netherlands. E-mail: l.t.w.de.jong-van.den.berg@rug.nl

Accepted for publication April 28, 2011.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2011. All rights reserved.

Table 1. Congenital anomalies of the VACTERL association.

V	Vertebral defects
A	Anal atresia or imperforate anus
C	Cardiac abnormalities, most commonly atrial septal defect, ventricular septal defect, and tetralogy of Fallot
T	Tracheoesophageal fistula or tracheal atresia/stenosis
E	Esophageal atresia
R	Renal and/or radial abnormalities
L	Pre-axial limb abnormalities

gestational age, and terminations of pregnancy following prenatal diagnosis of congenital anomalies of any gestational age<sup>8</sup>. The EUROCAT antiepileptic study database is a validated part of the EUROCAT central database and can be regarded as representative with respect to the distribution of congenital anomalies in the general population based on several publications. For this reason this dataset was used. This dataset comprises 98,075 major congenital anomalies covering 3.8 million births. Medication use in this database is representative for the use of medication in pregnancy in the general population delivering a pregnancy outcome with congenital anomalies. We expect a low prevalence of use of TNF- $\alpha$  antagonists in pregnancy (less than 1/1000). The use of antiepileptic drugs noted in this database was 5.7/1000. That is very low and therefore it is expected that there is no influence on the general distribution of specific birth defects<sup>9</sup>.

We classified the anomalies listed in Table 1 of the Carter publication<sup>3</sup> according to EUROCAT anomaly subgroups. Only 31 of the 41 described cases could be classified to the EUROCAT classification. Ten cases were excluded because they contained unspecified congenital anomalies and minor anomalies according to the EUROCAT classification and/or were infants and fetuses with a chromosomal anomaly or single gene disorder (n = 3).

A working definition for VACTERL association was set up, as there are several definitions for VACTERL association<sup>4</sup>. For correct comparison we used the method used by Carter, *et al*<sup>3</sup> (one or more congenital anomalies that are part of VACTERL) as well as the agreed definition of at least 3 of the individual anomalies present<sup>4</sup>, as listed in Table 1.

Analysis was performed comparing the proportion of different anomaly subgroups as published by Carter, *et al* with proportions found in the EUROCAT database<sup>9</sup>, using the chi-square test to determine significance ( $p < 0.05$ ).

## RESULTS

The EUROCAT database contained 110 cases coded as VACTERL association, which might be an underestimation. Using the agreed VACTERL definition<sup>4</sup>, including at least 3 anomalies present, in the EUROCAT database, 619 (531 + 73 + 15, respectively) cases fulfilled these criteria (Table 2).

Counting all individual anomalies in the VACTERL association solely, according to Carter's definition, in the EUROCAT dataset, more than 50% of all cases of congenital anomaly would have a VACTERL association.

The congenital anomalies identified by Carter, *et al* included 9 minor anomalies that are excluded in the EUROCAT classification of malformations. These excluded anomalies belonged to the EUROCAT subgroups eye, genital, musculoskeletal, congenital heart disease, and respiratory.

Most cases from the Carter study had only one or 2 major anomalies, so comparison of proportions is imprecise (Table 3). In this context, one significant observation was seen for limb anomalies ( $p < 0.05$ ).

Table 2. Records of congenital anomalies included in the VACTERL definition in the EUROCAT database.

No. Congenital Included in Anomalies the VACTERL Definition	No. Records in EUROCAT Antiepileptic Study Database	Proportion per 1000	No. Cases Reported by Carter, <i>et al</i> <sup>3</sup>
0	40498	413	17
1	53896	550	14
2	3061	31	8
3	531*	5	1
4	73*	1	0
5	15*	0	0
6	0	0	0
7	0	0	1**

\* 619 (531 + 73 + 15) per 3.8 million = 1.6 per 10,000; see also Barnes and Smith<sup>5</sup>. \*\* Proband case.

## DISCUSSION

This study shows that the cases with congenital anomalies exposed to TNF- $\alpha$  antagonists as reported by Carter, *et al* have a distribution of specific congenital anomalies similar to those in a representation of the general population-based congenital anomaly database EUROCAT.

Based on currently known in-utero exposures to TNF- $\alpha$  antagonists, no specific embryopathy has been identified<sup>10,11,12</sup>.

A limitation for comparison of results between the Carter study and the EUROCAT data is the lack specificity of the congenital anomalies by Carter, *et al*, and because of this several anomalies could not be reclassified in detail according to the EUROCAT anomaly subgroups. Because cases with only minor anomalies are not included in the EUROCAT database, these cases in the publication of Carter, *et al* were excluded in our analysis.

Another possible limitation of our study is the difference between the FDA database and our database. The FDA AERS database is a spontaneous adverse reactions system and the EUROCAT database is a population-based congenital anomaly database.

In studies on VACTERL associations, a definition of the association should be included; for instance, the classic VATER association described by Quan, *et al*<sup>13</sup> does not include the cardiac and limb associations described by Carter, *et al*. Källén, *et al*<sup>4</sup> verified the original VATER association but not the extensions such as VACTERL.

Concluding protection by TNF- $\alpha$  antagonists for the congenital anomaly limb would be premature, because of the low number of cases (n = 2) in the population described by Carter, *et al*.

Our study was not designed to assess whether there is a generalized increased risk of congenital anomalies with use of TNF- $\alpha$  antagonists. In a postmarketing setting, 2 main approaches have been used to identify teratogenic effects of medicines, followup studies and case-control surveillance<sup>14</sup>. Carter, *et al* suggested a large followup study of pregnancies

Table 3. Proportions of VACTERL association in the EUROCAT database compared to those reported by Carter *et al*<sup>3</sup> (i.e., only anomalies within the spectrum reported by Carter, *et al* with at least one record in the EUROCAT antiepileptic dataset).

EUROCAT Subgroups*	Carter, <i>et al</i>		All VACTERL Records without Chromosomals	EUROCAT Database	
	Major Congenital Anomalies without Chromosomals	Proportion (%)		Proportion (%)	Prevalence per 10,000 births
Total number in group	31		86,290		
Nervous system	1	3.2	8172	9.5	21.0
Neural tube defects	1	3.2	3679	4.3	9.5
Anencephalus	1	3.2	1270	1.5	3.3
Eye	1	3.2	1427	1.7	3.7
Congenital cataract	1	3.2	339	0.4	0.9
Congenital heart disease <sup>†</sup>	7	22.6	26,650	30.9	68.7
Ventricular septal defect <sup>††</sup>	1	3.2	11,971	14.9	30.8
Atrial septal defect <sup>††</sup>	2	6.5	8509	9.9	22.0
Tetralogy of Fallot <sup>††</sup>	1	3.2	1003	1.2	2.6
Respiratory	2	6.5	1723	2.0	4.4
Orofacial cleft	1	3.2	6033	7.0	15.5
Cleft palate	1	3.2	2369	2.7	6.2
Digestive system	3	9.7	5501	6.4	14.2
Esophageal atresia <sup>†,††</sup>	1	3.2	907	1.1	2.3
Ano-rectal atresia and stenosis <sup>†,††</sup>	1	3.2	1086	1.3	2.8
Hirschsprung's disease <sup>††</sup>	1	3.2	337	0.4	0.9
Urinary	4	12.9	11,201	13	28.9
Genital	3	9.7	7022	8.1	18.1
Hypospadia	3	9.7	5490	6.4	14.1
Limb <sup>†</sup>	2	6.5	16,662	19.3	43.0
Clubfoot without spina bifida	1	3.2	3882	4.5	10.0
Musculoskeletal	1	3.2	3239	3.8	8.3

\* Only those subgroups in which Carter, *et al* had one or more congenital anomalies. <sup>†</sup> Anomaly belonging specifically to the VACTERL definition.

<sup>††</sup> Subgroups of the main group of anomalies.

exposed to TNF- $\alpha$  antagonists, especially etanercept, to further assess a possible increase in congenital anomalies. Indeed, for this purpose, large pregnancy registries can be useful; however, a case-control study might be more appropriate to identify such a very rare association<sup>14</sup>.

The seemingly high number of congenital anomalies belonging to the VACTERL spectrum within pregnancies exposed to TNF- $\alpha$  antagonists described by Carter, *et al* could not be confirmed. This neither reinforces nor excludes the possibility of an increased absolute risk associated with TNF- $\alpha$  antagonists. Evaluation of risks of specific major congenital malformations associated with use of TNF- $\alpha$  antagonists can be performed best in a case-control study database designed to test signals of congenital anomalies<sup>14</sup>.

## APPENDIX

List of study collaborators. Members of the European Surveillance of Congenital Anomalies Working Group: C. Verellen-Dumoulin (Centre de Génétique Humaine Institut de Pathologie et de Génétique), V. Nelen (Provinciaal Instituut voor Hygiene), Belgium; I. Barisic (Children's University Hospital Zagreb), Croatia; B. Khoshnood (Institut National de la Santé et de la Recherche Médicale), B. Doray (Registre des Malformations Congenitales d'Alsace), France; S. Poetzsch (Otto-von-Guericke Universität Magdeburg), A. Wiesel (Johannes Gutenberg Universität, Geburtenregister Mainzer Modell), Germany; M. O'Mahony (Health Service Executive), Ireland; A. Pierini (Istituto di Fisiologia Clinica del Consiglio Nazionale delle Ricerche), F. Rivieri (Azienda Ospedaliero Universitaria di Ferrara), Italy; M.

Gatt (Department of Health Information and Research), Malta; M. Bakker (University Medical Center Groningen, University of Groningen), The Netherlands; K. Melve (Norwegian Institute of Public Health, Medical Birth Registry of Norway), Norway; A. Latos-Bielenska, J.P. Mejnartowicz (Uniwersytet Medyczny im. Karola Marcinkowskiego w Poznaniu), Poland; I. Portillo (Dirección Salud Pública, Departamento Sanidad, Gobierno Vasco), Spain; M-C. Addor (Registre Vaudois des Malformations), Switzerland; D. Tucker (Swansea National Health Service Trust, Congenital Anomaly Register and Information Service for Wales), D. Wellesley (Southampton University Hospitals Trust), United Kingdom.

## REFERENCES

- Berthelot J-M, De Brandt M, Goupille P, Solau-Gervais E, Loité F, Goed V, et al. Exposition to anti-TNF drugs during pregnancy: Outcome of 15 cases and review of the literature. *Joint Bone Spine* 2009;76:28-34.
- Carter JD, Ladhani A, Vasey FB. Tumor necrosis factor inhibition and VATER association: a causal relationship? *J Rheumatol* 2006;33:1014-7.
- Carter JD, Ladhani A, Ricca LR, Valeriano J, Vasey FB. A safety assessment of TNF antagonists during pregnancy: a review of the FDA database. *J Rheumatol* 2009;36:635-41.
- Källén K, Mastroiacovo P, Castilla EE, Robert E, Källén B. VATER non-random association of congenital malformations: Study based on data from four malformation registers. *Am J Med Genet* 2001;101:23-32.
- Barnes JC, Smith WL. The VATER association. *Radiology* 1978;126:445-9.
- Botto LD, Khoury MJ, Mastroiacovo P, Castilla EE, Moore CA, Skjaerven R, et al. The spectrum of congenital anomalies of the

- VATER association: An international study. *Am J Med Genet* 1997;71:8-15.
7. US Food and Drug Administration. Adverse Event Reporting System. Silver Spring, MD. [Internet. Accessed May 11, 2011.] Available from: [www.fda.gov/drugs/GuidanceComplianceRegulatoryInformation/surveillance/adversedrugeffects](http://www.fda.gov/drugs/GuidanceComplianceRegulatoryInformation/surveillance/adversedrugeffects)
  8. EUROCAT. EUROCAT Guide 1.3 and reference documents, instructions for the registration and surveillance of congenital anomalies, September 2005. [Internet. Accessed May 11, 2011.] Available from: <http://www.eurocat.ulster.ac.uk/pdf/EUROCAT-Guide>
  9. Jentink J, Loane MA, Dolk H, Barisic I, Garne E, Morris JK, et al. Valproic acid monotherapy in pregnancy and major congenital malformations. *N Engl J Med* 2010;362:2185-93.
  10. European Medicines Agency. London. European public assessment reports: Enbrel. [Internet. Accessed May 11, 2011.] Available from: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000262/human\\_med\\_000764.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000262/human_med_000764.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125)
  11. European Medicines Agency. London. European public assessment reports: Humira. [Internet. Accessed May 11, 2011.] Available from: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000481/human\\_med\\_000822.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000481/human_med_000822.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125)
  12. European Medicines Agency. London. European public assessment reports: Remicade. [Internet. Accessed May 11, 2011.] Available from: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000240/human\\_med\\_001023.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000240/human_med_001023.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125)
  13. Quan L, Smith DW. The VATER association: Vertebral defects, anal atresia, T-E fistula with esophageal atresia, radial and renal dysplasia: A spectrum of associated defects. *J Pediatr* 1973;82:104-7.
  14. Mitchel AA. Systematic identification of drugs that cause birth defects — a new opportunity. *N Engl J Med* 2003;349:2556-9.