BIOLOGIC THERAPY AND PREGNANCY. A SYSTEMATIC LITERATURE REVIEW

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Abstract

Aim: To review available data regarding the safety of biological therapies during pregnancy, focusing on agents used in rheumatology.
Methods: A systematic literature search was carried out to identify all studies with human data on fetal and/or child outcomes following exposure to biologic agents during pregnancy.
Results: A total of 65 publications out of 745 identified references were included in the review.
Conclusions: Experience with pregnancy exposure to anti-TNF agents has been slowly accumulating. Although the numbers are small and with few controlled studies the reviewed data suggest that the overall risk of TNF antagonists is relatively low and benefits may outweigh the risks of drug exposure to the fetus. Information on other biologic agents is still very limited. Large controlled studies with longer follow-up periods will be necessary before firm conclusions about the safety of biologics during conception and pregnancy can be drawn.

Keywords: Biologics; anti-TNF; Pregnancy; Systematic literature review

Introduction

The use of medications during the conception period or throughout pregnancy is a cause of great concern and anxiety for patients and the physicians caring for them.

In the past 15 years, several biologic therapeutic agents have been approved for the treatment and have significantly improved outcomes among patients with various immune-mediated inflammatory disorders such as rheumatic and inflammatory bowel diseases which disproportionately affect females during reproductive years. Choosing appropriate treatment for pregnant patients may be challenging and important issues emerge addressing the risk of adverse fetal outcomes or adverse pregnancy.

All biological manufacturers recommend that these drugs should be avoided during pregnancy and lactation. Indeed, none of the biologic therapies are described as safe to use during human pregnancy either by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA)[1-3]. All approved anti-tumor necrosis factor (anti-TNF) agents and anakinra are classified as Pregnancy FDA Category B. This category indicates that although no risk is apparent from animal studies, there are no controlled studies of women receiving these agents during pregnancy, and therefore, it is not known if they can cause fetal harm. Rituximab, abatacept and tocilizumab are classified as Pregnancy FDA Category C, which means that no controlled studies in humans have been performed and that animal studies have either shown adverse events or are not available. For ethical reasons, randomized trials cannot be designed to evaluate the safety of these drugs during pregnancy. It is nearly inevitable though that there will be some patients exposed to these drugs during pregnancy, typically during the early stages of an unplanned or unknown pregnancy and that difficult decisions will have to be made in the individual clinical settings.

To provide further information on this topic and because biological agents may represent an important therapeutic alternative in pregnant women experiencing persistent or increased disease activity, we decided to perform a systematic literature review of the relevant data available focusing on agents used in rheumatology.

Methods

A systematic literature search for articles published

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up to October 20th of 2010 was carried out to identify all studies with human data on fetal and/or child outcomes following exposure to biologic agents during pregnancy. The search strategy for PubMed was restricted to articles published in English, French, German, Portuguese or Spanish and included the following medical subject headings (MeSH) terms: "infliximab", "adalimumab", "abatacept", "rituximab", "tocilizumab", "golimumab", "certolizumab", "pregnancy", and the non-MeSH terms "etanercept", "anakinra" and "teratogenicity". A hand-search of relevant references not captured by the electronic searches was also made looking for the reference lists of the retrieved articles. Other references, including the product monographs, data provided by the Organization of Teratology Information Specialists (OTIS) studies and the European League Against Rheumatism (EULAR), American College of Rheumatology (ACR) and the European Crohn's and Colitis Organisation (ECCO) congress abstracts were also reviewed.

Articles were selected in a systematic two-step approach. First, titles and abstracts of all identified references were screened, excluding articles that clearly did not address the topic of interest. Second, retrieved articles, including case reports, case series, letters, registries reports, and narrative reviews, were selected for full paper review, applying the following inclusion criteria: 1) data on women with any disease exposed to infliximab (INF), etanercept (ETA), adalimumab (ADA), rituximab (RTX), anakinra (ANAk), abatacept (ABAt), tocilizumab (TCZ), golimumab (GOL) and certolizumab (CTZ) during pregnancy; 2) reported outcome on pregnancy length, health condition of live births, neonatal complications, fetal development, congenital defects/malformations, miscarriages or elective terminations. Papers were included only if related to patients exposed to the biologic during pregnancy. Reports of patients exposed to treatment before conception were excluded, except for rituximab for which data will be presented separately.

Results

The systematic review search identified a total of 745 references, of which 65 met the inclusion criteria and were selected for detailed analysis. Data retrieved will be presented the most accurately possible avoiding duplication of reported cases. Nevertheless, it is difficult to be sure that individual cases were not reported in the registries. For studies with more than one publication describing results among overlapping groups of participants and with the same outcome measure, we considered only the dataset with the largest number of patients and the longest follow-up. In a first section, we will present the number of pregnancies and outcomes definitely known for each biologic. Afterwards and separately, we will show data describing the number of pregnancies and/or the number of live births and/or their outcomes for a whole group of patients where results cannot be individualized by anti-TNF agent or other biologic. As it is understandable, the exact number of pregnancies exposed to each biologic is therefore difficult to assess.

Additional information on reports of pregnancies exposed to biologic therapies may be seen in Table I.

TNF antagonists

Infliximab – FDA Pregnancy category B

Infliximab is a chimaeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNF. It's approved for the treatment of severe rheumatoid arthritis, ankylosing spondylitis, adult and paediatric Crohn's disease, ulcerative colitis, psoriatic arthritis and adult plaque psoriasis, when the response to conventional treatment has been inadequate.

Advised period of discontinuation of infliximab before conception based on the summary of the product characteristics (SPC) is 6 months[4]. However, according to other recommendations a pregnancy appears acceptable 2 months after interrupting infliximab, respecting a time interval of five half-lives and using the highest half-life values reported[5,6].

Experience with pregnancy exposure to infliximab has been slowly accumulating and this is reflected in the number of reports found in the literature search. Twenty-four references where the safety of infliximab during pregnancy was evaluated were selected for detailed analysis: data from four registries, three case series and individual case reports[7-30].

According to information from the selected articles, there were 156 patients treated with inflixi-

Table I. Summary of pregnancies exposed to anti-TNF therapies

Author, year	Study info	Biologic	Other drugs	Pregnancies, no.	Live births, no.	Exposition	Spont. Abortions, no.	Therap. Abortion, no.	Birth defects/ Complications	Comment	Other	Disease
Gracia, 2006	BIOBADASER	INF	yes	4	3	T1		1	0			RheumDis
Katz, 2004	INF Safety Database	INF	some: MTX 8%; AZA 33%, MTNZ 14%	96	64	32bC; 58T1; 6 ND	14	18	5 (all in patients exp. to INF during pregnancy)	1 premat with intracerebral and intrapulmonary bleeding died; 1IRDS; 1 intestinal malrotation (exp. LFN); 1 Tetralogy Fallot; delayed development and hypothyroidism		8RA, 82 CD, 2JIA, 1 UC; 3NR
Mahadevan, 2005	Intentional Tx	INF	some	10	10	2T1; 8T2-3	0	0	1	1 respiratory distress (ICU)	3 premat	CD
Schnitzler, 2007	Intentional Tx	INF		12	10	T1T2	1		0		2 premat	IBD
Berthelot, 2009	CRI	INF		3	3	1T1; 2T1-2	0	0	0			1JIA, 1RA, 1SpA
Chambers, 2004	OTIS	INF	no	4	3	T1	1		0		2 premat	RA
Tursi, 2006		INF	yes	1	1	T1-3	0	0	0			CD
Angelucci, 2008		INF	yes	1	1	T1	0	0	0			CD
Burt, 2003		INF	no	1	1	T1	0	0	0			CD
Kinder, 2004		INF	MTX	1	0	T1	1 (MTX)	0	0			RA
Vasiliauskas, 2006		INF	no	1	1	T1	0	0	0			CD
Stengel, 2008		INF	mesalazine	1	1	T1-3	0	0	0			CD
Chaparro, 2010		INF	ND	1	1	T1-3	0	0	0			CD
Akinci, 2008		INF	ND	1	1	T2-3	0	0	0			SpA
Palmer, 2008		INF	no	1	0	T1	1		1		delayed development	UC
Antoni, 2002		INF		1	1	T1			0			PsA
Srinivasan, 2001		INF		1	1	T1			0		death on day 3	CD
James, 2001		INF		1	1	T2 (single dose)			0			CD
Nerome, 2008		INF	MTX	1	1	T1-2			0		premat	JIA
Correia, 2010		INF		2	2	T3			0			IBD
Puig, 2009		INF		1	1	T1			0			Psoriasis
Ostensen, 2008		INF		5	1	T1			4			RA, PsA, Oligoart
Rosner, 2007		INF	AZA	3	3	T1-3	0	0	0		1 premat	1JIA and 2RA
Kane, 2009		INF		3	3	T1-2	0	0	0			CD

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Table I. Summary of pregnancies exposed to anti-TNF therapies *(continuation)*

Author, year	Study info	Biologic	Other drugs	Pregnancies, no.	Live births, no.	Exposition	Spont. Abortions, no.	Therap. Abortion, no.	Birth defects/ Complications	Comment	Other	Disease
Berthelot, 2009	CRI	ETA	1MTX	10	7	6T1; 2T1-2	2	1 (MTX)	0			2RA; 6SpA; 1PsA; 1JIA
García, 2006	BIOBADASER	ETA	NR	8	4	T1		2				RheumDis
Chakravarty, 2003		ETA	some	7	6	"during pregnancy"	1	0	0			RA
Kosvik, 2005		ETA	no	5	3	T1	2	0	0			IJA and RA
Roux, 2007		ETA	yes	3	2	T1	0	1	1	UTI + CAH		RA
Rump, 2004		ETA	no	1	1	T1	0	0	0			RA
Feyertag, 2004		ETA	no	1	1	T1-3	0	0	0			RA
Carter, 2006		ETA	no	1	1	T1-3 (high dose)	0	0	1	VACTERL assoc		PsA
Sinha, 2006		ETA	no	1	1		0	0	0			RA
Micheloud, 2006		ETA	no	1	1	T2-3	0	0	0			SLE (LN)
Otermin, 2007		ETA	no	1	1	T1-3	0	0	0			JIA
Rosner, 2007		ETA	MFM	1	1	T1-3	0	0	0			SLE
Umeda, 2010		ETA		1	1	T1, T2 and T3	0	0	0			RA
Murashima, 2009		ETA	PDN	1	1	T1-T3	0	0	0		premat	RA
Rump, 2010		ETA		8	6	C and "during pregnancy"	1		1	Megacolon congenitum		RA and AS
Borrego, 2010		ETA	NSAIDs	1	1	T1	0	0	0			PsA
Ostensen, 2008		ETA		9	5	6T1; 3T3		1	3 outcome unkown			RA and AS
Johnson, 2008	OTIS	ETA	yes	139	130	T1	6 (1 Trissomy 18)	2 (1 unspecified heart defect)	11	1 atrial septal defect + patent ductus arteriosus, esotropia, and inguinal hernia; 1 transverse stomach with epispadias + congenital eye defect in a twin whose co-twin had displaced stomach; 1 ventricular septal defect + patent foramen ovale + patent ductus arteriosus; 1 ventricular septal defect + pulmonic stenosis; 1 pyloric stenosis; 1 cystic adenomatoid malformation; 1 hypospadias + inguinal hernia; 1 volvulus; 1 microcephaly; 1 congenital hypothyroidism; 1 Trissomy 21	RheumDis	

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Table I. Summary of pregnancies exposed to anti-TNF therapies *(continuation)*

Author, year	Study info	Biologic	Other drugs	Pregnancies, no.	Live births, no.	Exposition	Spont. Abortions, no.	Therap. Abortion, no.	Birth defects/ Complications	Comment	Other	Disease
Johnson, 2009	OTIS	ADA		94	80	T1	13	1	7	1 undescended testicle, 1 microcephaly, 1 ventricular septal defect, 1 congenital hip dysplasia, 1 congenital hypothyroid, 1 bicuspid aortic valve and agenesis of the corpus callosum, 1 congenital hydronephrosis	CD and RA	
García, 2006	BIOBADASER	ADA		2	?	T1		1	0			RheumDis
Berthelot, 2009	CRI	ADA		2	2	1T1; 1 T1-3			0			1RA; 1 SpA
Vesga, 2005		ADA	no	1	1	T1-3	0	0	0			CD
Sanchez, 2005		ADA		1	1	T1		0	0			CD
Kraemer, 2008		ADA	LFN until W8	1	1	T1-3	0	0	0			Takayasu
Mishkin, 2006		ADA	no	1	1	T1-3	0	0	0			CD
Coburn, 2006		ADA	yes	1	1	T2T3	0	0	0			CD
Carter, 2007		ADA		1	1	T1	0	0	1	VACTERL assoc		?
Jurgens, 2009		ADA		1	1	T1	0	0	0			CD
Dessinioti, 2010		ADA		1	1	T1			0		low weight	Psoriasis
King, 2008	BSRBR	7INF+ 40ETA+ 11ADA	29MTX	58	30	55T1; 3T1-3 (3ETA:T1-T3 "all healthy")	18	6	4 + 2	3 intrauterine death and 1 neonatal death; 1 congenital hip dysplasia and 1 pyloric stenosis		RheumDis (mostly RA)
Strangfeld, 2007	RABBIT	INF+ETA +ADA	2 MTX/LFN	22	20	mostly T1; 3T2 /T3	2	0	0			RheumDis
Cush, 2005	On-line query (USA)	INF+ETA +ADA		454	378	"during pregnancy"	25	5	0		9 premat	RA
Oussalah, 2009		CTZ		1	1	T1 and T3				0		CD

mab during pregnancy. Of these women, about 70% were exposed in the first trimester, around 5 to 10% throughout pregnancy and the remaining on the first two trimesters or punctually to control flares.

Congenital malformations and other complications occurred in 8 infants one intestinal malrotation (concomitant leflunomide), one tetralogy of Fallot, one child experienced intracerebral and intrapulmonary hemorrhage and died at 24 weeks, another died on day 3 (reason not known), 2 had respiratory distress (1 in an infant with seizures) and 2 delayed development (1 with hypothyroidism)[9,10,20,22].

Etanercept – FDA Pregnancy category B

Etanercept is a TNF receptor-IgG fusion protein that binds TNF molecules preventing these from binding TNF receptors on the cell surface. It is approved for the treatment of severe rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult and paediatric plaque psoriasis, in patients who failed to respond to conventional therapies.

In the SPC, the safety interval between the last treatment and conception is not referred[31]. Recommendations vary advocating different safety intervals from 3 weeks to 2 months[5,6].

Eighteen papers were selected for their report of etanercept exposure in pregnant women: data from three registries, five small case series and individual case reports[7,8,27,28,32-45]. Overall, taking into account the included studies, exposure to etanercept was reported in 199 pregnancies. Exposure occurred in the first trimester in about 70% of the patients and in other trimesters or throughout pregnancy in the remainder.

Congenital malformations or other complications in confirmed pregnancies exposed to etanercept were noticed in 14 cases: 1 VACTERL syndrome (Vertebral defects [V], Anal atresia [A], Cardiac abnormalities [C], Tracheoesophageal fistula or tracheal atresia/stenosis [T], Esophageal atresia [E], Renal and/or Radial abnormalities [R], and pre-axial Limb abnormalities [L]), 1 megacolon congenitum, 1 atrial septal defect with patent ductus arteriosus, esotropia and inguinal hernia, 1 transverse stomach with epispadias and congenital eye defect in a twin whose co-twin had displaced stomach, 1 ventricular septal defect with patent foramen ovale and patent ductus arteriosus, 1 ventricular septal defect with pulmonary stenosis, 1 pyloric stenosis, 1 cystic adenomatoid malformation, 1 hypospadias with inguinal hernia, 1 volvulus, 1 microcephaly, 1 congenital hypothyroidism and 1 Trissomy 21. Another case with trissomy 18 resulted in abortion[37,38,44]. There was another case described as a congenital abnormality but that might be interpreted as hereditary adrenal hyperplasia with 21 hydroxilase inheritated from the father [34].

Adalimumab – FDA Pregnancy category B

Adalimumab is a fully human monoclonal antibody that binds to TNF±, preventing it from activating TNF receptors. It is approved for the treatment of severe rheumatoid arthritis, ankylosing spondylitis, idiopathic juvenile arthritis, adult and paediatric Crohn's disease, ulcerative colitis, psoriatic arthritis and adult plaque psoriasis, when the response to conventional treatment has been inadequate.

The SPC advises a safety interval between the last treatment of adalimumab and the conception of 5 months[46]. Again, other recommendations exist based on half-lives of the product, stating shorter periods of 8 weeks and 3 months as possibly safe[5,6].

Existing data on adalimumab use during pregnancy is more limited than for the previous agents and based on the information from three registries and individual case reports. Overall, eleven papers were selected for the information on adalimumab exposure during pregnancy[7,27,47-55]. According to information from the selected articles, exposure to adalimumab during pregnancy occurred in 106 patients. Exposure occurred in the first trimester in approximately 90% and throughout pregnancy in just about 10% of patients.

Overall there were 8 reported malformations: 1 VACTERL syndrome, 1 undescended testicle, 1 microcephaly, 1 ventricular septal defect, 1 congenital hip dysplasia with inguinal hernia, 1 congenital hypothyroidism, 1 bicuspid aortic valve and agenesis of the corpus callosum (twin pregnancy in which 2nd twin had patent ductus arteriosus) and 1 congenital hydronephrosis (twin pregnancy in which 2nd twin was spontaneously aborted)[51,52].

Other data on pregnancy exposure to anti-TNF

As referred before, further data come from studies describing the number of pregnancies and/or the number of live births and/or their outcomes for a whole group of patients that cannot be individualized by anti-TNF or other biologic. These data is discussed here, separately.

One of the largest descriptions on anti-TNF ex-

posure during pregnancy comes from an internet survey based on practicing US rheumatologists recall on the use of biological agents published by Cush in 2005[56]. This study describes 454 pregnancies exposed to anti-TNF agents (81% to etanercept) with 378 normal deliveries, 9 premature babies, 5 therapeutic abortions, and 25 miscarriages in this group. TNF antagonists were used throughout the pregnancy in 31.3% of the patients. There were no birth defects, fetal malformations, or neonatal deaths reported. However, detailed information could only be retrieved on part of the patients and therefore, there is some uncertainty as to the exactitude of the data[57].

In 2006, Hyrich et al published the outcomes of 23 pregnant patients exposed to anti-TNF treatment (ETA, n=17; INF, n=3; ADA, n=3) at the time of conception and/or during pregnancy identified from the British Society for Rheumatology Biologics Registry (BSRBR) database[58]. In 2008, the BSRBR updated the previous publication and reported 58 women directly exposed (DE) to an anti-TNF drug (INF, n=7; ETA, n=40; ADA, n=11; and MTX, n=29), during pregnancy[59]. Data from the BSRBR were described in patients receiving anti-TNF therapy for rheumatic diseases alongside a parallel DMARD control group: 41 women previously exposed (PE) to anti-TNF therapy (INF, n=14; ETA, n=21; ADA, n=6; MTX, n=1 at conception) and 6 pregnancies in the DMARD only control group. Anti-TNF therapy was discontinued in all but 2 pregnancies in the DE group (3 babies - 1 twin pregnancy). A trend towards a higher miscarriage rate was seen in the DE group compared to the PE group and DMARD group: 18/58 (31%) versus 7/41(17%) and 1/6 (16%). There were 30/58, 32/41, and 5/6 live births in the DE group, PE group, and DMARD control group, respectively. Two congenital abnormalities were reported in each DE (1 congenital hip dysplasia and 1 pyloric stenosis) and PE (1 strawberry naevus and 1 "winking jaw syndrome") groups. Additionally, 3 intrauterine deaths, 1 neonatal death, and 6 elective terminations were reported in the DE group. One intrauterine death and one elective termination were reported in the PE group.

Strangfeld et al collected data from the German biologics register (RABBIT), a study evaluating patients with Rheumatoid Arthritis (RA) who initiated therapy with a biologic agent[60]. Analysis was performed of 37 pregnancies in 29 women who were exposed to anti-TNF agents during conception or at least the first trimester of pregnancy: INF (n=2), ADA (n=5), ETA (n=20), DMARDs (n=8). Comparison was made to those who stopped either biologic and/or other DMARDs before conception. Mean birth weight was similar in infants exposed to biologic therapy (3.1 kg) compared to infants exposed to non-biologic therapy (3.1 kg). There were no congenital malformations reported. Three patients re-initiated treatment with the biologic after week 20 and continued the therapy until delivery. Mothers and newborns were reported to be well post-partum (ETA, n=2; INF, n=1).

See additional information on Table I.

Golimumab and Certolizumab – FDA Pregnancy category B

Golimumab (a human monoclonal anti-TNF-α antibody) and certolizumab (a PEGylated Fab fragment of humanized monoclonal TNF-α antibody) are the two latest anti-TNF biologics. Golimumab is indicated for the treatment of severe rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis and certolizumab is indicated for rheumatoid arthritis, in both cases, in patients who have responded inadequately to conventional therapy.

According to the SPC, women of childbearing potential should use adequate contraception to prevent pregnancy and continue its use for at least 5 and 6 months after the last certolizumab and golimumab administration, respectively[61,62].

As both of these therapies are relatively new, there are no published data regarding their use in human pregnancy apart from a report in abstract form of a woman treated with certolizumab during the first and third trimesters delivering a normal baby[63].

Rituximab – FDA Pregnancy category C

Rituximab is a monoclonal chimaeric human-mouse antibody that binding specifically to a transmembrane antigen, CD20, located on pre-B and mature B lymphocytes, mediates B cell death. This drug is indicated for the treatment of non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukaemia (CLL) in combination with chemotherapy, and for severe, refractory rheumatoid arthritis.

Since rituximab is an IgG-based antibody, it is likely to cross the placental barrier and interfere with fetal and neonatal B-cell development and given its pharmacokinetic properties and its long-term effects it may cause some concern even when

the mother is exposed to treatment before conception[64,65]. Due to the long retention time of rituximab in B-cell-depleted patients, the SPC mentions that women of child-bearing potential should use effective contraceptive methods for 12 months following the last infusion before conception[65]. However, the elimination half-life of rituximab suggests that a 6-month wait may be adequate, as stated by some published recommendations[5,6].

Published experiences on the use of rituximab during pregnancy consist of a limited number of case reports. Our literature search found 16 women exposed to rituximab at least 6 months before conception, at conception or during pregnancy[28,64,66-76]. Some of them were also exposed to other treatments, potentially harmful, for life threatening situations as lymphomas[69,71,74-76]. Treatment with rituximab was administered in the first trimester in three, in the second and/or third in eight pregnancies. There were 15 live healthy neonates and 1 elective termination. There were no serious infectious complications documented. Additional information on reports of pregnancies exposed to rituximab may be seen in Table II.

Anakinra – FDA Pregnancy category B

Anakinra is a human interleukin-1 receptor antagonist approved for the treatment of severe rheumatoid arthritis in patients who have not responded adequately to convencional therapy. Although without a formal indication it has also been used to treat the systemic form of juvenile idiopathic arthritis.

The safety interval between the last administered dose and conception is not referred in the SPC[77].

Information regarding ANAk during pregnancy is limited to data from the German Register[60]. Two pregnancies exposed to ANAk during the conception/first trimester have had good outcome with no malformations described.

Abatacept – FDA Pregnancy category C

Abatacept is a fusion protein that selectively modulates a key costimulatory signal required for full activation of T lymphocytes. It is approved for the treatment of refractory rheumatoid arthritis and polyarticular juvenile idiopathic arthritis.

The elimination half-life of abatacept suggests that an 18 week wait between the last abatacept infusion and conception may be adequate[5]. The SPC advises effective contraceptive methods for at least 14 weeks following the last infusion until attempts to conceive[78].

In the double blind and open-label periods of the 5 core studies and in another phase II trial, 10 pregnancies that involved women treated with abatacept were reported[79].

Of these 8 women, 7 received MTX and 1 leflunomide as concomitant medication. Three subjects experienced a spontaneous abortion during the first trimester (two had a history of previous spontaneous abortions). Two subjects had their pregnancy terminated. Three pregnancies were ongoing at the time of the report.

In a phase II trial of abatacept for multiple sclerosis (IM101200), 2 women became pregnant. One subject delivered a healthy baby 10 months after discontinuation from the study (was not exposed during pregnancy) and the other subject had an elective abortion at 4 weeks gestation[79].

Tocilizumab – FDA Pregnancy category C

Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors. It is indicated for the treatment of refractory rheumatoid arthritis. According to SPC, pregnancy appears acceptable 3 months after stopping tocilizumab[80].

No data on exposure to tocilizumab during human pregnancy have been published.

Discussion

Although currently available data are sparse and limited in number, experience with pregnancy exposure to biological therapies is slowly accumulating. Interpretation of the results must be cautious and some important issues need to be considered:

Many women had active disease and were concomitantly exposed to potential teratogenic drugs such as MTX, leflunomide and metronidazole.

Exposure may be divided into two groups: a) unplanned pregnancies – exposure occurred at the time of conception and 1st trimester; b) pregnant women who were treated intentionally because of active refractory disease. The duration and time of exposure during pregnancy to these agents may lead to different outcomes; in most of the reports, women have suspended the biologic treatment as soon as the pregnancy was confirmed, usually in the first trimester.

Doses of anti-TNF vary depending on the di-

Table II. Summary of pregnancies exposed to other biologics (non-anti-TNF)

Author, year	Study info	Biologic	Other drugs	Pregnancies, no.	Live births, no.	Exposition	Spont. Abortions, no.	Therap. Abortion, no.	Birth defects/ Complications	Comment	Other	Disease
Ng, 2009		RTX	AAS+Igs+ PDN	1	1	>=6months befC	0	0	0			APPS
Ponte, 2010		RTX		2	2	T1	0	0				Atopic Dermatitis
Pellkofer, 2009		RTX		1	1	C	0		0			Optic Neuromyelitis
Ostensen, 2008		RTX		3	2	3 mo bC e T1-T2	0	1	0			SLE
Herold, 2001		RTX	HOP	1	1	T2 e T3	0	0	0		premat	Lymphoma
Kimby, 2004		RTX		1	1	T1	0		0			Lymphoma
Friedrichs, 2006		RTX	CHOP	1	1	T2 e T3	0	0	0			Lymphoma
Scully, 2006		RTX		1	1	T2 e T3	0	0	0		premat	TTP
Ojeda-Uribe, 2006		RTX		1	1	T1	0		0			AI HemolAn
Maglorie, 2006		RTX	CHOP	1	1	T2	0	0	0			Lymphoma
Decker, 2006		RTX	CHOP	1	1	T2	0	0	0		premat	Lymphoma
Klink, 2008		RTX	Igs	1	1	T3	0	0	0			ITP
Rey, 2009		RTX	CHOP	1	1	T2 e T3	0	0	0		premat	Lymphoma
Strengfeld, 2007	RABBIT	ANAk		2	2	>T1; 2 T2-3			0			RheumDis
Abatacept_EMA 2007		ABAt	MTX or LFN	8	3?		T1 (3 ongoing pregnancies when reported)	3	2 (MTX or LFN)	?	RA	
Abatacept_EMA 2007		ABAt		1	0	T1		1				Multiple Sclerosis

sease being treated; in some reports a high dose was used to obtain disease control (ex. the patient who delivered a baby diagnosed with a VACTERL association was being treated with 100 mg weekly of etanercept for severe psoriatic arthritis).

The outcome of each pregnancy may be dependent on several other factors including the individual women herself, the disease, the activity state and the presence of other co-morbidities[81]. This information is lacking in most of the reports.

Congenital anomalies are seen in 3 to 5% of live births and some are relatively more common like those that involve the nervous system, the heart, the limbs and the urinary system (with a prevalence of more than 20 cases per 10,000 births)[82]. VACTERL is a nonrandom association of birth defects that occurs in 1.6/10,000 live births[83]. The frequency of preterm births varies from 5 to 13% in most of developed countries[84]. The risk for congenital anomalies or prematurity is described to be higher in RA when compared to women without RA[81]. It is obvious that the lack of a nontreated control group in most of the reports included in this systematic review may lead to some bias but, importantly, no specific pattern of congenital defects has been noted in infants prenatally exposed to biologics.

The Otis (Organization of Teratology Information Specialists) Collaborative Research Group, a not-for-profit organization in United States and Canada, has been prospectively following pregnant women exposed to anti-TNF during pregnancy. They provide the some of the few controlled information included in this systematic review based on data from pregnancy outcomes in exposed group compared with those in a disease-matched non-treated control and healthy control groups[29,37,52]. The preliminary data of the information published suggest that the rate of major structural defects in the TNF treated group is similar to the general population rates[52]. Preterm delivery and poor growth are increased in the exposed group and diseased non exposed group suggesting that it might be attributable to the underlying maternal disease[37,52].

Aside from the current systematic review, three other publications have to be mentioned and introduced in the discussion. A recently published paper raised concerns of a possible causative effect of the TNF antagonists in some congenital anomalies that are part of the VACTERL spectrum[51]. This study based on a voluntary post-marketing adverse event database of FDA was not included in the systematic review because it is not possible to know the total number of pregnant women exposed to TNF-antagonists and it reports only those with bad pregnancy outcomes. The information provided may still, nevertheless, be important. The review reported 41 children with 61 congenital anomalies born to 40 mothers receiving a TNF antagonist. The TNF antagonist was considered the "primary suspect" as the cause of the birth defect in all cases (22 ETA and 19 INF). The most commonly reported anomaly was a form of heart defect. A total of 24 children (59%) had ≥1 congenital anomaly considered part of VACTERL association.

Conversely, Snoeckx et al conducted a search of the Benefit Risk Management Worldwide Safety Database (SCEPTRE) of Johnson & Johnson for all medically confirmed cases of pregnancy reported in patients who have ever received INF (before or after conception) in order to identify any cases of VACTERL association[85]. Pregnancy outcome data were available for 627 cases. The number of patients directly exposed to INF during pregnancy is not specified and the report included women that had been treated with INF years before conception. There were 14 cases with ≥1 congenital anomalies/malformations but none of the reported cases met the criteria for VACTERL association.

Also the TREAT registry was designed to assess the long-term safety of infliximab in patients with Crohn's disease. A total of 114 pregnancy known outcome reports in patients treated with infliximab have been collected as of June 2008[86]. Again, the number of patients directly exposed to INF during pregnancy is not known and many women treated with INF years before conception were included. A total of 9 neonatal problems were reported (5 premature infants, 1 jaundice, 1 hypoxia, 1 ventricular defect and 1 with congenital ectrodactyly). None of the reports with neonatal problems met the criteria for VACTERL association.

As it is the predominant route of communication between the mother and the fetus, understanding the process of placental transfer of some drugs would help us to better evaluate the risk of their exposure during pregnancy. Theoretically, the structure of several of the molecules, which contain a human immunoglobulin G1 (IgG1) constant region, allows little placental transfer of the molecule during the first trimester[87]. However, IgG subclasses are readily passed into the foetus during the second and third trimesters, which specifical-

ly raises questions regarding safety of administration of these drugs beyond the 2nd trimester of pregnancy. There are studies that prospectively analyzed INF serum levels in newborns exposed in utero to INF during 2nd and/or 3rd trimesters[15,30,88]. Data is somewhat contradictory. In one study, levels of INF were not detectable in the newborn, suggesting that INF was not transferred from mother to child[30]. In the other studies, the authors found detectable levels of INF in the newborn and until 2 to 6 months of age[15,88].

Rituximab was also evaluated in similar studies describing women treated with the drug during the 2nd and 3rd trimester of pregnancy. Serum levels of the drug and B lymphocytes in the neonate and in the mother were measured[64,71,75]. At birth, RTX serum levels were detectable and neonates had very low or no detectable B-cells. Time of rituximab administration during gestation did not appear to influence this outcome. A decline in RTX levels seemed consistent with the known half-life of rituximab and at the age of 6 months, the number of B-cells was in the normal range. In addition, normal immunoglobulin levels and normal vaccination responses could be demonstrated.

Despite the persistence of some doubts and the insufficient data on the safety of these agents, some important organizations have already stated their position on the use of biologics during pregnancy. The official recommendations of the American Society of Gastroenterology published in 2006 declared that "there is growing body of evidence suggesting low risk of infliximab during pregnancy"[89]. The reference centre for teratogenicity of France (CRAT) has implied that infliximab might be used for the treatment of a refractory disease if this is the only way for controlling active disease, warning however to avoid the final weeks of the third trimester[5].

We may conclude that the true implications of biologic exposure during pregnancy are yet unknown. The existing evidence suggests that the overall risk of TNF antagonists is relatively low and benefits may outweigh the risks of drug exposure to the fetus. At least we may say that although the numbers are small and there is little information from controlled studies the reviewed data suggest that women who inadvertently become pregnant while taking anti-TNF agents may be reassured that stopping the treatment and continuation of pregnancy does not appear to hold a real increased risk of congenital malformations. Information on other biologic agents (not TNF blockers) is still very limited. The decision to treat with a biologic agent in pregnancy should be made on a case-by-case basis. What remains for the patient, the rheumatologist and the obstetrician to do is to balance the risk between the importance of remaining in remission or with partial control of the disease with the potential risk of these drugs to cause any harm.

Patients with inflammatory rheumatic disorders and the physicians caring for them should keep in mind that disease activity at the time of conception or during the course of pregnancy may be associated with a risk of low birth weight, premature births and spontaneous abortions. In women with a severe, refractory disease course, in whom biological therapies have been the only agents to induce and maintain remission, therapy may probably be continued at least until conception.

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