Research Review™
EDUCATIONAL SERIES
Biologics and pregnancy

Making Education Easy 2021

Independent commentary by Professor Paul Bird & Dr Diana Rubel

Professor Paul Bird
FRACP, PhD, Grad Dip MRI

Professor Paul Bird is a Rheumatologist in private practice and Conjoint Professor at the University of New South Wales. In addition to his clinical duties, he is the Director of Optimus Clinical Research, a clinical research center undertaking Phase 2, 3, and 4 trials of novel agents for the treatment of rheumatic diseases. He has completed a Post Graduate Diploma in Magnetic Resonance Imaging (RMIT University) and his PhD thesis (University of NSW) examined the feasibility, reliability, and validity of MRI as an outcome measure in patients with rheumatoid arthritis. He maintains ongoing participation in research projects examining the application of Magnetic Resonance Imaging (MRI) in inflammatory arthritis and is co-chair of the OMERACT international MRI imaging group.

Independent commentary by Dr Diana Rubel
MBBS, FACD, MMed, DipPaeds

Dr Diana Rubel is a consultant dermatologist in private practice at Woden Dermatology, Canberra, and a visiting medical officer and Senior Lecturer at The Canberra Hospital and Australian National University. She completed her undergraduate medical degree (1988) and postgraduate Diploma in Paediatrics (1992) at University of NSW, her Masters of Medicine (specialising in cutaneous immunology) at Sydney University (1995) and Australasian College of Dermatologists' fellowship in 1998. She has over 15 years' experience at the Skin and Cancer Foundation, Darlinghurst, Sydney, and has been a Staff Specialist at the Sydney Childrens Hospital for 10 years.She runs a multidisciplinary Clinical Practice in Canberra and conducts clinical research in association with Probity Medical Research and the Australian National University. Her subspecialty interests include acne, psoriasis and atopic dermatitis, skin cancer management, clinical trials, and cosmetic dermatology.

This education review aims to raise awareness of the potential benefits and risks associated with the use of biologics during pregnancy in patients with autoimmune inflammatory diseases. Since pregnant women are rarely studied in randomised, controlled trials, data relating to the use of biologics during pregnancy have come largely from case studies, population-based observational studies, or registry/databases. This review will briefly outline outcomes from these studies. Data relating to the *in utero* use of biologics, and during lactation, on the outcomes of the neonate will also be briefly reviewed.

Introduction

Chronic inflammatory autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), ankylosing spondylitis (AS), psoriatic arthritis (PsA), psoriasis (Ps), and inflammatory bowel disease (IBD; ulcerative colitis [UC] and Crohn's disease [CD]) are common in women of child-bearing age.[1] Population-based studies indicate that women with autoimmune diseases are generally at higher risk of complications during pregnancy (such as pre-eclampsia, gestational diabetes, infection, preterm birth, and intra-uterine growth delay).[2-7] For example, population-based studies in women with IBD,[4, 5] PsA,[3] AS,[3] RA,[2, 6, 7] or Ps[8] indicate an increased risk for selected adverse pregnancy outcomes.

It is therefore crucial that medications used to treat these diseases are used effectively in women who are, or who are likely to become pregnant, especially since the withdrawal of efficacious therapies can result in suboptimal care and unfavourable outcomes, including disease flares[9] and adverse pregnancy outcomes.[2-7] For women with autoimmune diseases, there is increasing recognition that with well-controlled disease before pregnancy, and continuation of appropriate therapies alongside close monitoring during gestation, pregnancy may not be contraindicated.[10, 11]

It is important that women with chronic inflammatory or autoimmune disease consider pre-pregnancy counselling.[10, 12-14] Women of childbearing age with autoimmune inflammatory diseases commonly have concerns pertaining to pregnancy and lactation.[15] It is essential that these concerns are addressed and advice is given that relates to the possible risks and complications associated with the mothers' disease process during pregnancy.[15, 16] The natural history for many autoimmune disease involves a relapsing-remitting course, with improved maternal and foetal outcomes associated with entering pregnancy during periods of quiescent/low activity disease.[10] Counselling should also involve the likely impact of current (or alternative medication) on the mother's health during pregnancy, on the developing foetus, and on the infant during lactation.[12, 13]

Pregnancy and drugs

A significant proportion of pregnant women take medication at some point during their pregnancy.[12, 17] To this end, Australian Drug Evaluation Committee's (ADEC) categorisation system provides guidance on the risk of drugs used in pregnancy (**Table 1**).[13, 18] However, this system has limitations — the categories should not be interpreted as representing a gradation of risk (e.g. Category B3 may not necessarily be safer than Category C) and this system does not provide guidance on the risks during the different stages of pregnancy.[18] The ADEC categories are often assigned on the basis of animal studies and may be slow to change despite new evidence.[13, 18] In addition, ADEC categories do not provide guidance on drug safety during breastfeeding.[13, 18]

Table 1. **Australian Drug Evaluation Committee's (ADEC) categorisation system for drugs used in pregnancy**

Category A	Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.
Category B1	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.
Category B2	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.
Category B3	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.
Category C	Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible.
Category D	Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
Category X	Drugs which have such a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

A similar risk categorisation system which was previously used by the FDA has been replaced by a new labelling system.[12] This labelling system has been designed to improve the risk versus benefit assessment of drugs used in pregnant and nursing mothers.[12] It hoped that this new system will provide information for both patients and healthcare providers pertaining to the use of drugs during pregnancy and lactation, and the effect of drugs on the reproductive potential of both females and males.

Biologics and pregnancy

Biologic therapy has revolutionised the treatment of autoimmune diseases, including RA, SLE, AS, PsA, Ps, and IBD, with new targets for therapy emerging as the understanding of inflammation and the autoimmune process improves.[19, 20]

Biologics are genetically engineered proteins derived from human genes (**Table 2**).[20] Biologics target key components of the immune system that play pivotal roles in inflammation such as cytokines (including tumour necrosis factor [TNF] and interleukins [ILs]) or immune cells such as T and B cells.[20] Biologics are largely composed of immunoglobulin (Ig)G with modified Fc receptors or Fab fragments that bind and neutralise their target molecule.[21, 22]

Placental transfer of antibodies

Biologics are large molecular structures that are not easily transported across the placenta, especially during the first trimester when foetal Fc receptors have yet to develop. Any biologics that reach the foetus prior to 14 weeks' gestation, do so by passive diffusion, and consequently only limited amounts reach the foetus during the period of embryogenesis (up to 12 weeks).[21]

After 17-22 weeks of pregnancy, IgG is actively transported across the placenta, with most antibodies being transferred during the third trimester.[23-25] IgG crosses the placenta by receptor-mediated binding of the Fcγ portion of the IgG molecule to its receptor, FcRn (Fc receptor neonatal) [**Figure 1**].[25] This complex is then transported within coated vesicles to the foetal circulation allowing the release of intact IgG into the foetal bloodstream.[25] The main concern about the transfer of biologics to the foetus regards their potential to disrupt the infant's growth and immunity, and response to infections and vaccinations.[22]

Not all biologics have the same affinity for binding to the neonatal Fc receptor. IgG1 (adalimumab, infliximab, secukinumab, ustekinumab, guselkumab) and IgG4 (ixekizumab) inhibitors probably cross the placenta in a similar manner.[26, 27] Certolizumab does not have an Fc portion and has very low levels of passive placental transfer, and is thus less likely to impact the foetus.[26-29]

The potential risk for biologics include teratogenicity and malformations with early exposure (up to week 14 of gestation), increased maternal immunosuppression, or foetal and neonatal immunosuppression.[21, 22] At the time of the first introduction of biologics (anti-TNF drugs) more than 20 years ago, they were not permitted for use during preconception, pregnancy, or breastfeeding.[25] However, women with autoimmune diseases are increasingly continuing treatment with biologics during pregnancy, or at least up to the third trimester.[30, 31]

Table 2. **Biologics, half-lives, and rate of transplacental transfer**

	Biologic		ADEC	Half-life (days)	Transplacental transfer
Anti-TNF	Infliximab[27, 32, 33]	IgG1	C	8-10	+++
	Adalimumab[27, 34]	IgG1	C	10-20	+++
	Golimumab[35]	IgG1	C	12	+++
	Etanercept[36, 37]	Fusion protein	D	≈3	++
	Certolizumab[27, 29]	Pegylated IgG1	C	14	+
Anti-IL12/23	Ustekinumab[38, 39]	IgG1	B1	15 to 32	+++
	Guselkumab[40]	IgG1	B1	15 to 18	+++
	Tildrakizumab[41]	IgG1	B1	23	+++
Anti-IL17	Secukinumab[42]	IgG1	C	17 to 41	+++
	Ixekizumab[43]	IgG4	C	13	++
Anti-IL-23	Rizankizumab[44]	IgG1	B1	28	+++
Anti-IgE	Omalizumab[45]	IgG1	B1	22	+++
Anti-IL4/13	Dupilumab[46]	IgG4	B1	*	++
Anti IL5	Mepolizumab[47]	IgG1	B1	16-22	+++
	Benralizumab[48]	IgG1	B1	3.5	+++
Anti-IL-6	Tocilizumab[49]	IgG1	C	11-32	+++
Anti-CTLA 4	Abatacept[50]	Fusion protein	C	13-17	+++
Anti-IL-1	Anakinra[51]	Protein	B1	4-6 hours	+++
Anti-integrin $\alpha_4\beta_7$	Vedolizumab[52]	IgG1	B2	24	+++

*Elimination is mediated by parallel linear and nonlinear pathways. + limited transplacental transfer; ++ moderate transplacental transfer; +++ easily transfered across placenta.

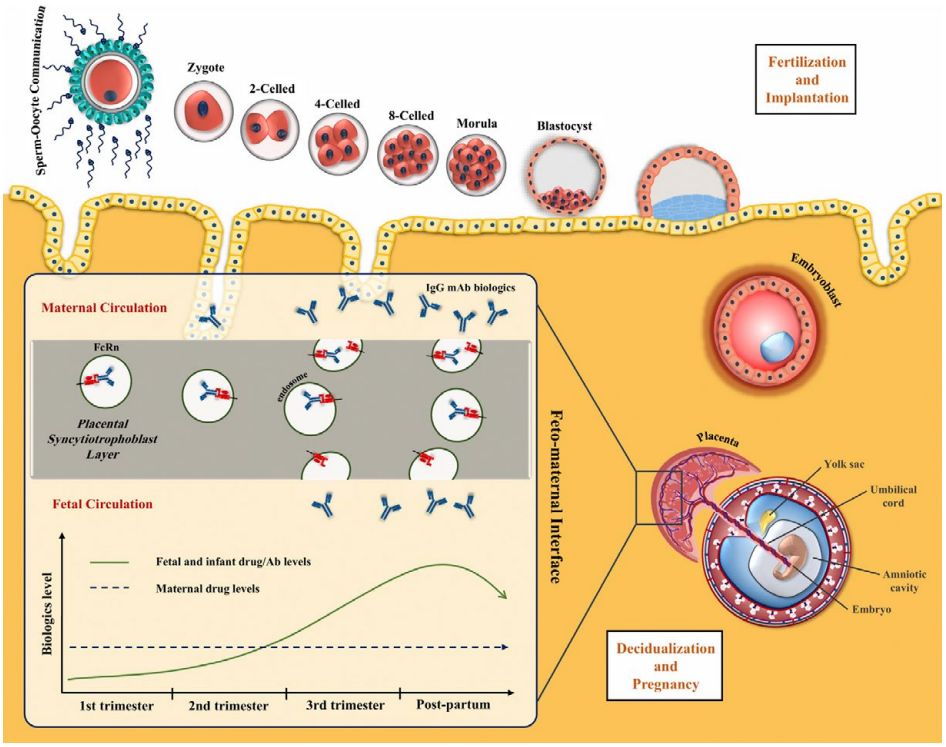

Figure 1. Neonatal transfer of immunoglobulins[22] (Image obtained from Beltagy et al. Front Pharmacol. 2021;12:621247)

Expert comments: Diana Rubel

In women of child-bearing age with chronic autoinflammatory diseases, it is important to consider the impact of treated versus untreated disease and biologic agents on the outcomes of pregnancy. Frustratingly, there is a paucity of knowledge and experience in treating pregnant women with biologics due to the exclusion of pregnant women from clinical trials. However, extensive knowledge of placental transfer of immunoglobulins allows us to calculate the extent of exposure of the developing baby at various time points during gestation, to optimise maternal treatment and minimize foetal exposure.

RESEARCH REVIEW™
Australia's Leader in Specialist Publications

Expert comments: Paul Bird

Many women in their childbearing years are prescribed biologic therapy, and it is important that clinicians assist them in understanding the benefit/risk information pertaining to therapy cessation versus continuing therapy throughout pregnancy so that patients and their partners can make an informed choice. Medical providers caring for this patient population must be well informed and feel comfortable counselling and working with their patients for the best pregnancy outcome possible.

The data for TNF inhibitors is very reassuring, with the science and epidemiological data providing reassurance for clinicians and their patients. Published guidelines regarding the use of biologics in pregnancy are an important guide for clinicians, and these continue to evolve as new data become available.[30, 53-55]

As further data emerge, clinicians will have increasing confidence in prescribing biologics for patients in their childbearing years and be confident in continuing patients on biologics throughout the pregnancy and postpartum period. It is vital, however, that we continue to gather *and interpret* data, particularly for new and emerging agents.

Biologics during lactation

IgA (not IgG1) is the predominant immunoglobulin found in breastmilk, and the large structure of most biologic molecules means that they are less likely to be excreted in breastmilk.[56] In addition, orally administered immunoglobulins undergo intestinal proteolysis and have low bioavailability.[21] Case studies indicate that the transfer of biologics from the serum to the mother's milk is minimal.[57-60] Researchers of a multicentre, prospective study collected breastmilk samples from women with IBD treated with biologics (n=72),[61] and reported low concentrations of the biologics in the breastmilk samples. Breastfed infants of these mothers had similar risks of infection and rates of milestone achievements compared with non-breastfed infants or infants unexposed to these drugs.[61] Further details relating to the use of specific biologics in breastfeeding mothers are given below.

Biologics and the neonate

Limited data are available regarding the outcomes of children exposed to biological drugs *in utero* or during breastfeeding. Data available from drug registries and observational studies generally report minimal or no side effects in infants exposed to biologics, with no negative impact on infectious complications, allergies, growth, or psychomotor development compared with unexposed children.[62-65] However, there was an early report of a serious disarray in the immune response of an infant exposed *in utero* to infliximab, with fatal consequences when given a Bacille Calmette–Guérin (BCG) vaccine.[66] A more recent study has shown no adverse effects in infants (whose mothers received TNF inhibitors during pregnancy) when the BCG vaccination was given at a median age of 6 months.[67] International guidelines recommend avoiding the administration of live or live-attenuated vaccines (e.g. BCG, rotavirus) in the first 6-12 months of life if the infant was exposed to TNF inhibitors *in utero*, particularly in the late second or third trimester.[52, 54, 67-69]

Biologics and fathers

Limited data are available to address concerns regarding infertility, and pregnancy outcomes after paternal exposure to biological drugs. Nevertheless, available cohort studies have not indicated any increased risk of undesirable pregnancy outcomes or congenital malformations in infants whose fathers were exposed to biologics around the time of conception.[70-74]

A few studies have reported decreased spermatozoa number or questionable abnormality of motility and morphology in men treated with infliximab.[75, 76] However, most other studies have indicated no impact of biologics on sperm quality or male fertility.[72, 77-82] In general, international guidelines indicate that there is no need to discontinue anti-TNF-α treatment in men who plan to have children.[54, 83]

Expert comments: Diana Rubel

It is generally considered safe to breastfeed whilst a mother is being treated with biologics, as there is limited transfer to breastmilk from maternal serum, and low bioavailability to the infant from ingested biologic proteins. Live or live-attenuated vaccines need to be avoided in the first 6-12 months of life in infants whose mothers received biologics during pregnancy, particularly during the third trimester. Limited data suggests that biologics have no impact on sperm quality or male fertility.

Expert comments: Paul Bird

Biologics, particularly TNF inhibitors, have not shown any major adverse effects in multicentre, international databases. In a study of women receiving treatment for IBD and their infants, low concentrations of infliximab, adalimumab, certolizumab, natalizumab, and ustekinumab were found in breastmilk samples.[61] In this study, breastfed infants of mothers on biologics, immunomodulators, or combination therapies had similar risks of infection and rates of milestone achievement compared with non-breastfed infants or infants unexposed to these drugs.[61] The most important information regarding neonates is avoiding the administration of live or live-attenuated vaccines (e.g. BCG, rotavirus) in the first 6-12 months of life if the infant was exposed to TNF inhibitors *in utero*, particularly in the late second or third trimester.[52, 54, 67-69] Paternal exposure to biologic agents at the time of conception does not appear to lead to undesirable pregnancy outcomes or congenital malformations in infants. In a large cohort study of 7453 expectant fathers with immune mediated inflammatory diseases (IMIDs), exposure to immunosuppressive or biologic agents around conception was not associated with increased risk of adverse birth outcomes.[71]

Clinical evidence for the use of biologics

Since pregnant women, neonates, and infants are rarely studied in randomised, controlled trials, studies involving the risk/benefits of biologics in pregnant women and their foetus/neonates have largely involved population-based observational studies (individual case reports, case series, or cohort observations) or registry/database analyses to characterise the safety of biologics in these special populations.[1, 30]

Large population-based studies have been conducted,[62, 63] such as that involving 6218 women (8607 pregnancies) who had an autoimmune disease diagnosis; 90 women were exposed to biologics during pregnancy, with 100 babies born to these women.[62] Most of these women had RA (44%) or IBD (50%). Data from this study suggested that the use of biologics during pregnancy was not associated with an increased risk of serious infections in mothers postpartum or in infants during the first year of life.[62] Data from similar large population-based studies in women with autoimmune diseases suggested that the use of biologics before and during pregnancy was not associated with an increased risk of preterm delivery or small for gestational age births,[84] or an increased risk of congenital anomalies.[63]

Data from PSOLAR, a multicentre, disease-based, observational registry was used to evaluate the long-term safety and clinical outcomes for patients receiving or eligible to receive treatment for Ps with biologics and/or conventional systemic therapies.[85] For the 220 women with 298 pregnancies evaluated, 81.9% resulted in live births.[85] Rates of spontaneous abortion, neonatal problems, and congenital anomalies were similar to rates in the general US population, and pregnancy outcomes for women exposed to biologics were similar to those for women with exposure to non-biologics.[85]

Data involving individual biologics will be reviewed in the following sections.

TNF-α inhibitors

Various population-based studies and meta-analyses indicate that anti-TNFα therapies generally appear to be safe if used during pregnancy in patients with autoimmune disease.[86-89] Given the overall safety findings, a number of international guidelines support the use of anti-TNF agents when used earlier in pregnancy in patients with autoimmune disease, but suggest that anti-TNF agents (with the exception of certolizumab) may not be advised later in pregnancy (generally beyond the third trimester).[30, 54, 68, 69, 90-92] However, the differences in placental transfer related to molecule structure and half-life need to be taken into account when selecting a TNF inhibitor for women of fertile age (**Table 1**).[1]

Infliximab

Infliximab is a chimeric IgG1, anti-TNF-α antibody **(Figure 2)**, which is not recommended for use during pregnancy (category C) or during lactation, according to the Australian product information.[32] Infliximab is indicated for use in patients with RA, AS, PsA, Ps, CD, and UC.[32]

Data from a global safety database in 8170 reports of innovator infliximab-exposed pregnancies indicated that the prevalence of adverse pregnancy outcomes was similar to that in the general population.[93]

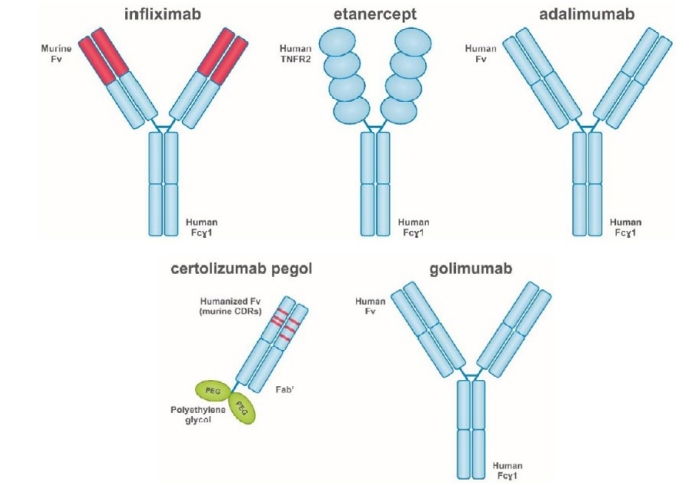

Figure 2. Structure of tumour necrosis factor-alpha (TNF-α) inhibitors
(Image obtained from Romanowska-Prochnicka, et al. Int J Mol Sci. 2021)

Spontaneous abortion, preterm births, and low birth weight infant rates were 12.1, 9.2, and 3.6%, respectively.[93] Trimester of exposure did not appear to affect the prevalence of congenital anomalies or other adverse outcomes.[93]
Infliximab can be detected in the serum of infants up to six months following birth.[32] Studies have indicated no clinical consequences in neonates (including an increased rate of infection) who experienced *in utero* exposure to infliximab.[65, 89, 93]

A fatal case of disseminated Bacillus Calmette-Guérin (BCG) infection was reported in an infant born to a mother taking infliximab for Crohn's disease.[66] A waiting period of at least six months is recommended following birth before the administration of live or live-attenuated vaccines to infants exposed *in utero* to infliximab.[32]

Adalimumab

Adalimumab is a monoclonal IgG1, anti-TNF-α antibody (**Figure 2**).[34] Adalimumab binds to TNF and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.[34] Additionally, adalimumab modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration.[34]
Adalimumab is indicated for use in patients with RA, AS, PsA, CD, UC, and Ps.[34] The product information states that adalimumab should only be used during pregnancy if clearly needed (Category C). Women of child-bearing potential should consider the use of adequate contraception to prevent pregnancy and continue contraception for at least 5 months after the last adalimumab injection.[34]

Data from a prospective cohort pregnancy exposure registry involving 257 women with RA or CD treated with adalimumab at least during the first trimester and 120 women with RA or CD not treated with adalimumab indicated no significant differences in the overall rates of major birth defects in the adalimumab-exposed group (adjusted odds ratio [OR] 0.84, 95% confidence interval [CI] 0.34, 2.05).[34, 94] There were no significant differences between the two groups for rates of minor birth defects, spontaneous abortion, preterm delivery, low birth weight, and serious or opportunistic infections.[34, 94] No stillbirths or malignancies were reported.[34, 94] Data from the North American Adalimumab Pregnancy Exposure Registry (72 pregnancies) found that the relative risk of major birth defects in adalimumab-exposed women was similar to those of unexposed women with RA and healthy women.[95] Similarly, a study involving the Japanese adalimumab safety registry (74 pregnancies) did not report any additional risk to pregnancy outcomes with adalimumab exposure.[96]

Administration of live or live-attenuated vaccines to infants exposed to adalimumab *in utero* is not recommended for 5 months following the mother's last adalimumab injection during pregnancy.[34]

Golimumab

Golimumab is a human IgG1κ monoclonal antibody (**Figure 2**) which forms high affinity, stable complexes with TNF and prevents the binding of TNF to its receptors.[35] Golimumab is indicated for use in patients with RA, PsA, AS, non-radiographic axial spondyloarthritis (axSpA), and UC.[35] Golimumab crosses the placenta,[25,35] and so the use of golimumab in pregnant women is not recommended (Category C).[35] Golimumab should be given to a pregnant woman only if clearly needed.[35] The use of golimumab while breastfeeding is not recommended.[35]

Etanercept

Etanercept is a dimer of a genetically engineered protein resulting from the fusion of the extracellular ligand-binding domain of human tumour necrosis factor receptor-2 (TNFR2/p75) to the Fc domain of human IgG1 (**Figure 2**).[37] It binds to TNF and blocks its interaction with cell surface TNF receptors.[37] Etanercept is indicated for use in patients with RA, AS, PsA, Ps, non-radiographic axSpA, juvenile idiopathic arthritis, and paediatric Ps.[37]

According to the prescribing information, the safe use of etanercept during pregnancy has not been established (Category D).[37] Case series, cohort, case-control, claims-database, and registry studies have addressed the safety profile of etanercept during pregnancy and lactation.[37, 97-99] Data from registry studies (included pregnant women exposed to etanercept during the first trimester in the Organization of Teratology Information Specialists [OTIS] study) indicate that there was no increased risk of major birth defects or pregnancy outcomes in women exposed to etanercept during pregnancy.[37, 100] There was no increase in rates of intrauterine or postnatal growth deficits or delayed postnatal development, or increased rate of infections in the first year of life in infants exposed to etanercept during pregnancy.

Studies in breastfeeding women treated with etanercept indicated very low levels of etanercept in breastmilk and no detected absorption by the child.[101, 102]

Certolizumab

Certolizumab pegol is a recombinant, pegylated humanised Fab' fragment of an IgG1 monoclonal antibody, and has high affinity for TNF-α (**Figure 2**).[29] According to the prescribing information, certolizumab is ascribed a category C rating. It is indicated for use in patients with RA, AS, non-radiographic axSpA, PsA, and plaque Ps.[29]

A study of a drug company pharmacovigilance safety database analysed 1137 prospectively reported pregnancies with maternal exposure to certolizumab (most exposures occurred during the first trimester).[103] Most mothers had RA or CD.[103] Outcomes were known for 528 pregnancies.[103] Analysis did not indicate a teratogenic effect of certolizumab, compared with the general population, nor an increased risk of foetal death.[103] Although the study had limitations (such as unknown outcomes for a third of the pregnancies, no untreated control group), the researchers concluded that the data are reassuring for women of childbearing age wanting to use certolizumab to control their chronic inflammatory diseases.[103]

Because certolizumab lacks an IgG Fc region, it does not bind to FcRn and is not expected to undergo FcRn-mediated transfer across the placenta, as confirmed in preclinical[104] and clinical[27, 28, 105, 106] studies. An *in vitro* study found no binding affinity between certolizumab and placental FcRn, ascribed to the lack of the Fc portion and in an *ex vivo* model placental transfer of certolizumab was minimal.[104] Studies involving women treated with certolizumab throughout pregnancy, have detected no or very low levels of the drug in the cord blood.[27, 28, 105, 106] The prospective, postmarketing, pharmacokinetic CRIB study reported a lack of transfer of certolizumab from sixteen women (who were ≥30 weeks pregnant) to their children.[28] Given the low placental transfer, international guidelines consider certolizumab a pregnancy-compatible medication that may be used if needed during pregnancy.[30, 53, 55, 68, 69, 90-92]

The pharmacokinetic CRADLE study in 17 lactating women indicated minimal to no transfer of certolizumab to breastmilk.[107] The median relative infant dose (RID) was 0.15%; an RID <10% is considered safe by lactation specialists.

Interleukin and interleukin receptor inhibitors

Ustekinumab

Ustekinumab is a human IgG1kappa, monoclonal antibody that specifically binds to the shared p40 protein subunit of the IL-12 and IL-23.[38] It is indicated for the treatment of Ps, PsA, CD, UC, and it should be given to a pregnant woman only if the benefit clearly outweighs the risk (Category B1).[38] Case reports and case series involving pregnant women treated with ustekinumab have been published, with most reporting uneventful pregnancies.[39, 108-115]

In pregnant women with IBD (n=39)[116] or Ps (n=24)[117] enrolled in the ustekinumab clinical trial programme, no congenital anomalies were reported and rate of observed spontaneous abortions was generally comparable to the rate in the general US population. Ustekinumab treatment was discontinued upon the report of pregnancy in all cases.

Outcomes in pregnant women exposed to ustekinumab are being collected in the OTIS study registry.[118]

According to the prescribing information, women of childbearing potential should use effective methods of contraception during treatment with ustekinumab and for at least 15 weeks after treatment.[38]

Case reports suggest that low levels of ustekinumab can be found in the infants of breastfeeding mothers, but with no effect on the newborn's subsequent physical or mental development.[61, 115]

Guselkumab

Guselkumab is a human IgG1 monoclonal antibody that binds selectively to the IL-23 protein with picomolar affinity.[40] It is indicated for the treatment of Ps and PsA, and should only be used during pregnancy under the advice of a physician if the potential benefit outweighs the potential risk (Category B1).[40] Limited data are available from 24 pregnancies treated with guselkumab in company-sponsored clinical trials.[119] No congenital anomalies were reported and no other safety signals were identified. Outcomes in pregnant women exposed to guselkumab are being collected in the OTIS study registry.[118]

Tildrakizumab

Tildrakizumab is a humanized IgG1/κ monoclonal antibody that specifically binds to the p19 protein subunit of IL-23 and inhibits its interaction with the IL-23 receptor.[41] It is indicated for the treatment of moderate-to-severe plaque Ps.[41] The product information notes that it is preferable to avoid the use of tildrakizumab during pregnancy (Category B1). Women of childbearing potential should use an effective method of contraception during treatment and for at least 17 weeks after treatment.[41] Only limited data are available from 14 pregnancies involving women enrolled in the phase I-III clinical trials. The outcomes from these pregnancies were not associated with any new safety signals and there were no reports of birth defects.[120]

Secukinumab

Secukinumab is a fully human IgG1 antibody that selectively binds to and neutralises the IL-17A.[42] It is indicated for the treatment of Ps, PsA, non-radiographic axSpA, and AS.[42] The product information states that secukinumab should be used in pregnancy only if the benefits clearly outweigh the potential risks (Category C).[42] Data from a global safety database involving 292 pregnancies did not identify any safety signals with regard to spontaneous abortions or congenital malformations.[74] Most women discontinued secukinumab during the first trimester.[74] Data on the effects of secukinumab on the immune system of neonates born after *in utero* exposure were not available.[74] If secukinumab has been used during pregnancy, administration of live or live-attenuated vaccines to new-borns/infants for 16 weeks after the mother's last dose of secukinumab is generally not recommended.[42]

Risankizumab

Risankizumab is a humanised IgG1 monoclonal antibody that selectively binds with high affinity to the p19 subunit of human IL-23 and inhibits its interaction with the IL-23 receptor complex.[44] It is indicated for the treatment of Ps.[44] Limited data are available regarding the use of risankizumab in pregnant women and are insufficient to inform any drug-associated risks.[44] Whether risankizumab is excreted in human milk is unknown.[44] It should be used during pregnancy and in breastfeeding women only if the benefits outweigh the potential risks (Category B1).[44]

Ixekizumab

Ixekizumab is a recombinant human monoclonal anti-human IL-17A antibody of the IgG1/kappa isotype.[43] Ixekizumab is indicated for Ps, PsA, AS, and non-radiographic axSpA.[43] The product information notes that ixekizumab should be used in pregnancy only if the benefits clearly outweigh the potential risks (Category C).[43] Data regarding the use of ixekizumab during pregnancy are limited.[121]

Dupilumab

Dupilumab is a fully human monoclonal antibody that inhibits IL-4 and IL-13 signalling by specifically binding to the IL-4Rα subunit of the IL-4 and IL-13 receptor complexes.[46] It is indicated for the treatment of moderate-to-severe atopic dermatitis.[46] It should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus (Category B1).[46] Data regarding its use during pregnancy are limited to case studies/series, which do not indicate any safety signals when used in pregnant women. A retrospective cohort study using administrative healthcare databases is being conducted to evaluate safety issues associated with the use of dupilumab during pregnancy.[122]

Mepolizumab

Mepolizumab is a humanised monoclonal antibody (IgG1, kappa) directed against IL-5.[47] It is indicated for the treatment of severe eosinophilic asthma, and as an add-on treatment for relapsing or refractory eosinophilic granulomatosis with polyangiitis.[47] It should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the foetus (Category B1).[47] Data regarding its use during pregnancy are limited to a case study.[123] A pregnancy registry has been established to monitor the outcomes of pregnant women exposed to this drug.[124]

Benralizumab

Benralizumab is an antibody that binds to the alpha subunit of the human IL-5 receptor with high affinity and specificity.[48] It is indicated as add-on therapy for patients with severe eosinophilic asthma.[48] Its administration should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus (Category B1).[48] Data regarding its use during pregnancy are limited to a case study involving a successful pregnancy in a woman with hyper-eosinophilic syndrome.[125] A prospective, observational, exposure cohort study of pregnancy and infant outcomes in women with asthma exposed to benralizumab anytime during pregnancy is currently being conducted.[126]

Tocilizumab

Tocilizumab is a recombinant, humanised monoclonal antibody (IgG1) that binds to soluble and membrane-bound IL-6 receptors.[49] Tocilizumab is indicated for RA, giant cell arteritis, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, and cytokine release syndrome.[49] The product information states that tocilizumab should not be used during pregnancy unless clearly necessary (Category C).[49] Data relating to tocilizumab is available from case studies/series,[60, 127-134] and an analysis of a global safety database.[73] The analysis of the global safety database did not indicate any substantially increased malformation risk with tocilizumab treatment in during 180 prospectively followed pregnancies.[73]

Very low levels of tocilizumab have been detected in cord blood and breastmilk (1/500 to 1/1000 of those in the mother's serum).[60]

Anakinra

Anakinra, a recombinant protein, blocks the biological activity of IL-1 by competitively inhibiting IL-1 binding to the IL-1 type I receptor.[51] Anakinra is indicated for RA, cryopyrin-associated periodic syndromes, and systemic juvenile idiopathic arthritis.[51] The product information notes that it should be used during pregnancy only if clearly needed (Category B1).[51] There are limited data on the efficacy and safety of anakinra during pregnancy, with case studies generally reporting successful pregnancies in women treated with anakinra.[135-137] It is not known whether anakinra is secreted in human breastmilk.[51]

IgE inhibitor

Omalizumab

Omalizumab is a recombinant DNA-derived humanised monoclonal antibody (IgG1/kappa) that selectively binds to human IgE.[45] It is indicated in chronic spontaneous urticaria, chronic rhinosinusitis with nasal polyps, and allergic asthma.

According to the prescribing information, treatment with omalizumab may be considered during pregnancy if clinically needed (Category B1).[45] However, there are no well-controlled clinical studies of omalizumab in pregnant women. A prospective pregnancy registry study (EXPECT) in 250 pregnant women with asthma treated with omalizumab indicated that the prevalence of major congenital anomalies was similar (8.1% vs 8.9%) between the EXPECT data and disease-matched (moderate and severe asthma) patients.[138] The EXPECT study did not indicate any adverse effects in 54 infants who had been exposed to omalizumab during pregnancy and through breastfeeding.[45]

T-cell co-stimulation modulator

Abatacept

Abatacept is a fusion protein produced by recombinant DNA technology that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to the modified Fc portion of human IgG1.[50] It inhibits the co-stimulation of T cells by binding to CD80 and CD86 molecules on the surface of antigen presenting cells.[50] It is indicated for use in patients with RA, polyarticular juvenile idiopathic arthritis, or PsA.[50] The product information notes that its use during pregnancy is not recommended (Category C).[50]

Data from case studies of women exposed to abatacept in the first trimester of pregnancy have reported positive pregnancy outcomes.[59, 139] An analysis of the manufacturer's clinical trial and post-marketing data involving 151 pregnancies with maternal exposure to abatacept suggest that incidence of congenital abnormalities (8.1%) was slightly greater than that seen in the general population (3–5%), although the study was subject to a number of limitations.[72] No immunodeficiencies was observed in the 16 infants followed for up to 1 year after birth.[72] A manufacturer's registry is currently collecting safety data regarding the use of abatacept during pregnancy.[140] A case study reported that abatacept was secreted into breastmilk at levels 1/200 to 1/300 of those in maternal serum, with no adverse effects on the infant.[59]

Anti-$\alpha_4\beta_7$-integrin

Vedolizumab

Vedolizumab is a humanised monoclonal antibody that binds to the $\alpha_4\beta_7$ integrin.[52] Vedolizumab inhibits adhesion of cells expressing $\alpha_4\beta_7$ to mucosal addressin cell adhesion molecule-1 (MAdCAM-1), but not vascular cell adhesion molecule-1 (VCAM-1).[52] Vedolizumab is indicated for the treatment of UC and CD.[52] Vedolizumab is to be used during pregnancy only if the benefits to the mother clearly outweigh any potential risk to the foetus (Category B2).[52] Vedolizumab has been detected in human breastmilk and a risk to the infant cannot be excluded.[52] The use or discontinuation of vedolizumab during breastfeeding should take into account the benefit of breastfeeding for the child and the benefit of therapy for the women.[52]

Expert comments: Diana Rubel

Large population studies and registries of patients receiving biologics in the real world have collected data on pregnancy outcomes in women on biologic therapies. TNF-α inhibitors can exacerbate tuberculosis infections and the use of infliximab throughout pregnancy in a patient resulted in fatal dissemination of TB in her infant who received BCG vaccination.[66] Certolizumab, a TNF inhibitor which lacks the Fc component and hence is not actively transported across the placenta, is considered the safest option in this biologic group for use in pregnant women.

No other significant signals in terms of teratogenicity, immune suppression, infection, or growth retardation have been seen in observational studies of pregnant women receiving biologics including TNFα inhibitors, IL-17 inhibitors, IL-12/-23 inhibitors, or IL-23 inhibitors.

Expert comments: Paul Bird

Active inflammation prior to conception and during pregnancy has been associated with unfavourable maternal and neonatal outcomes.[141] Poorly controlled inflammatory diseases in rheumatology patients and increased prednisone use have been shown to increase the risk of delivering a low birthweight infant.[142] It has also been suggested that elevated TNF-α, IL-10, and IL-6 can decrease the level of the enzyme that deactivates maternal cortisol and may lead to lower birthweights in a similar mechanism.[143]

Decisions regarding cessation of therapy prior to conception or during pregnancy should include this information to facilitate a shared patient-doctor decision. This needs to be balanced against the probability of rheumatic disease remission during pregnancy versus the risk of postpartum flare.[144, 145]

Moreover, the safety data for TNF inhibitors as a class, recognising the unique safety data for certolizumab in pregnancy and lactation, provides reassuring information for clinicians and patients to guide decisions regarding therapy.

As databases mature and more detailed information is available on newer agents, this will assist the clinician in framing a personalised, shared-decision treatment schedule for each patient.

Conclusions

For women with chronic inflammatory autoimmune diseases, the optimisation of outcomes during pregnancy and for the neonate requires involvement of both the healthcare professionals and the women even before pregnancy is considered. Family planning is essential in these diseases so that pregnancy can be timed for a period when symptoms are stable. Medications (including biologics) compatible with pregnancy should be maintained, if possible, to control the underlying disease activity, which requires knowledge and evidence of the impact of the medication on both the women and foetus. Since infants and pregnant women are generally excluded from randomised, controlled trials, much of the evidence for the use of biologics during pregnancy has been derived from case studies and smaller observational cohort studies. In general, sufficient data are available to suggest that TNF inhibitors are safe and effective without significant maternal or foetal risk, especially if used earlier in pregnancy. Most available anti-TNF-α drugs cross the placenta and can be detected in foetal blood later during pregnancy, except for certolizumab whose minimal transfer across the placenta increases its potential to be used safely throughout pregnancy. Analyses of post-marketing registries/databases and larger epidemiological studies are essential for fully characterising the safety and effectiveness of biologics for both the pregnant woman and the developing foetus.

Expert conclusions: Diana Rubel

Allowing our pregnant patients to continue with effective disease–controlling therapies is best for both mothers and babies. A lack of controlled data and heritage for these modern biologics presents challenges to the treating physician, but a thorough understanding of their mode of action and metabolism in pregnancy and lactation, coupled with extensive observational data in numerous specialties, has indicated that in the vast majority of cases, continuing biologic therapy throughout pregnancy and lactation is associated with no greater morbidity than that seen in the general population (with the important caveat that live or live-attenuated vaccinations must be avoided in the first 6-12 months' of infant age). Certolizumab, by virtue of its pegylated structure, is not actively transported across the placenta, and is an optimal choice for pregnant women with TNF-α– responsive disease.

Expert conclusions: Paul Bird

This review provides a comprehensive analysis of the science and epidemiology informing shared patient-doctor decisions when prescribing therapy to patients during pregnancy and lactation. Ongoing data collection and analysis are critical to the ongoing research agenda if the best outcomes possible are to be delivered.

References

1. Ghalandari N, Dolhain R, Hazes JMW, et al. Intrauterine exposure to biologics in inflammatory autoimmune diseases: A systematic review. Drugs. 2020;80(16):1699-722.
2. Smith CJF, Förger F, Bandoli G, et al. Factors associated with preterm delivery among women with rheumatoid arthritis and women with juvenile idiopathic arthritis. Arthritis Care Res (Hoboken). 2019;71(8):1019-27.
3. Smith CJF, Bandoli G, Kavanaugh A, et al. Birth outcomes and disease activity during pregnancy in a prospective cohort of women with psoriatic arthritis and ankylosing spondylitis. Arthritis Care Res (Hoboken). 2020;72(7):1029-37.
4. Stephansson O, Larsson H, Pedersen L, et al. Congenital abnormalities and other birth outcomes in children born to women with ulcerative colitis in Denmark and Sweden. Inflamm Bowel Dis. 2011;17(3):795-801.
5. Shand AW, Chen JS, Selby W, et al. Inflammatory bowel disease in pregnancy: a population-based study of prevalence and pregnancy outcomes. BJOG. 2016;123(11):1862-70.
6. Bharti B, Lee SJ, Lindsay SP, et al. Disease severity and pregnancy outcomes in women with rheumatoid arthritis: Results from the organization of teratology information specialists autoimmune diseases in pregnancy project. J Rheumatol. 2015;42(8):1376-82.
7. Lin HC, Chen SF, Lin HC, et al. Increased risk of adverse pregnancy outcomes in women with rheumatoid arthritis: a nationwide population-based study. Ann Rheum Dis. 2010;69(4):715-7.
8. Yang YW, Chen CS, Chen YH, et al. Psoriasis and pregnancy outcomes: a nationwide population-based study. J Am Acad Dermatol. 2011;64(1):71-7.
9. Förger F, Villiger PM. Immunological adaptations in pregnancy that modulate rheumatoid arthritis disease activity. Nat Rev Rheumatol. 2020;16(2):113-22.
10. Somers EC. Pregnancy and autoimmune diseases. Best Pract Res Clin Obstet Gynaecol. 2020;64:3-10.
11. Nielsen OH, Gubatan JM, Juhl CB, et al. Biologics for inflammatory bowel disease and their safety in pregnancy: A systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2020.
12. Mosley JF, 2nd, Smith LL, Dezan MD. An overview of upcoming changes in pregnancy and lactation labeling information. Pharm Pract (Granada). 2015;13(2):605.
13. Rademaker M, Agnew K, Andrews M, et al. Psoriasis in those planning a family, pregnant or breast-feeding. The Australasian Psoriasis Collaboration. Australas J Dermatol. 2018;59(2):86-100.
14. de Lima A, Zelinkova Z, Mulders AG, et al. Preconception care reduces relapse of inflammatory bowel disease during pregnancy. Clin Gastroenterol Hepatol. 2016;14(9):1285-92.e1.
15. Mills BS, Dao KH, Tecson KM, et al. Perceptions of pregnancy and lactation from the pregnancy and lactation autoimmune network registry. J Rheumatol. 2020;47(1):149-54.
16. Lassi ZS, Imam AM, Dean SV, et al. Preconception care: screening and management of chronic disease and promoting psychological health. Reprod Health. 2014;11 Suppl 3(Suppl 3):S5.
17. Mitchell AA, Gilboa SM, Werler MM, et al. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am J Obstet Gynecol. 2011;205(1):51.e1-8.
18. Therapeutic Goods Administration. Australian categorisation system for prescribing medicines in pregnancy. 2011.
19. Wolfe RM, Ang DC. Biologic therapies for autoimmune and connective tissue diseases. Immunol Allergy Clin North Am. 2017;37(2):283-99.
20. Scott DL. Biologics-based therapy for the treatment of rheumatoid arthritis. Clin Pharmacol Ther. 2012;91(1):30-43.
21. Soh MC, Moretto M. The use of biologics for autoimmune rheumatic diseases in fertility and pregnancy. Obstet Med. 2020;13(1):5-13.
22. Beltagy A, Aghamajidi A, Trespidi L, et al. Biologics during pregnancy and breastfeeding among women with rheumatic diseases: Safety clinical evidence on the road. Front Pharmacol. 2021;12:621247.
23. Kane SV, Acquah LA. Placental transport of immunoglobulins: a clinical review for gastroenterologists who prescribe therapeutic monoclonal antibodies to women during conception and pregnancy. Am J Gastroenterol. 2009;104(1):228-33.
24. Simister NE. Placental transport of immunoglobulin G. Vaccine. 2003;21(24):3365-9.
25. Romanowska-Prochnicka K, Felis-Giemza A, Olesinska M, et al. The role of TNF-alpha and anti-TNF-alpha agents during preconception, pregnancy, and breastfeeding. Int J Mol Sci. 2021;22(6).
26. Irani V, Guy AJ, Andrew D, et al. Molecular properties of human IgG subclasses and their implications for designing therapeutic monoclonal antibodies against infectious diseases. Molecular Immunology. 2015;67(2, Part A):171-82.
27. Mahadevan U, Wolf DC, Dubinsky M, et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2013;11(3):286-92; quiz e24.

28. Mariette X, Förger F, Abraham B, et al. Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study. Ann Rheum Dis. 2018;77(2):228-33.
29. UCB Pharma. Certolizumab pegol - Cimzia®- Australian product information 2021. Available from: 'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-02405-3'.
30. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. Arthritis Rheumatol. 2020;72(4):529-56.
31. Tsao NW, Lynd LD, Sadatsafavi M, et al. Patterns of biologics utilization and discontinuation before and during pregnancy in women with autoimmune diseases: A population-based cohort study. Arthritis Care Res (Hoboken). 2018;70(7):979-86.
32. Janssen Cilag Pty Ltd. Infliximab - Remicade® powder for injection 2021. Available from: 'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2011-PI-03023-3'.
33. Zelinkova Z, de Haar C, de Ridder L, et al. High intra-uterine exposure to infliximab following maternal anti-TNF treatment during pregnancy. Aliment Pharmacol Ther. 2011;33(9):1053-8.
34. AbbVie Pty Ltd. Adalimumab - Humira® – solution for subcutaneous injection 2021. Available from:'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-03779-3&d=202106151016933'.
35. Janssen-Cilag Pty Ltd. Golimumab (Simponi®) - Australian product information 2021. Available from:'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2011-PI-03025-3&d=202106271016933'.
36. Berthelsen BG, Fjeldsøe-Nielsen H, Nielsen CT, et al. Etanercept concentrations in maternal serum, umbilical cord serum, breast milk and child serum during breastfeeding. Rheumatology (Oxford). 2010;49(11):2225-7.
37. Pfizer Australia Pty Ltd. Etanercept - EnbreL® - Australian product information 2021. Available from: 'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-05235-3&d=202106291016933'.
38. Janssen-Cilag Pty Ltd. Ustekinumab - Stelara® - Australian product information 2020. Available from: 'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2020-PI-02581-1&d=202106151016933'.
39. Rowan CR, Cullen G, Mulcahy HE, et al. Ustekinumab drug levels in maternal and cord blood in a woman with Crohn's disease treated until 33 weeks of gestation. J Crohns Colitis. 2018;12(3):376-8.
40. Janssen-Cilag Pty Ltd. Guselkumab - Tremfya® - Australian product information 2021. Available from: 'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2018-PI-01506-1'.
41. Sun Pharma ANZ Pty Ltd. Tildrakizumab - IlumyaTM -Australian product information 2018. Available from: 'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2018-PI-02292-1'.
42. Novartis Pharmaceuticals Australia Pty Ltd. Secukinumab - Cosentyx® - Australian Product Information 2020. Available from: 'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2015-PI-01060-1'.
43. Eli Lilly Australia Pty Ltd. Ixekizumab - Taltz - Australian Product information 2020. Available from: 'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2016-PI-02453-1'.
44. AbbVie Pty Ltd. Risankizumab (Skyrizi®) Australian product information. 2019. https://www.tga.gov.au/sites/default/files/auspar-risankizumab-200122-pi.pdf.
45. Novartis Pharmaceuticals Australia Pty Ltd. Omalizumab - Xolair® - Australian product information 2021. Available from: 'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2009-PI-00304-3'.
46. Sanofi-aventis Australia Pty Ltd. Dupilimab - Dupixent®- Australian product information 2021. Available from: 'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2018-PI-01199-1'.
47. GlaxoSmithKline Australia Pty Ltd. Mepolizumab - Nucala - Australian product information 2019. Available from: 'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2016-PI-01215-1&d=202106161016933'.
48. AstraZeneca Pty Ltd. Benralizumab - Fasenra® - Australian product information 2020. Available from: 'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2018-PI-01520-1'.
49. Roche Products Pty Ltd. Tocalizumab - Actemra® - Australian product information. 2021. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2011-PI-01333-3&d=20210826172310101.
50. Bristol-Myers Squibb Australia Pty Ltd. Abatacept - Orencia®- Australian product information 2019. Available from: 'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-03513-3&d=20210'.
51. A Menarini Australia Pty Ltd. Anankinra - Kineret® - Australian product information 2021. Available from: 'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-02912-3'.
52. Takeda Pharmaceuticals Australia Pty Ltd. Vedolizumab (entyvio®) - Australian product information 2020. Available from: 'https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2014-PI-02140-1'.
53. Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016;75(5):795-810.
54. Australian Rheumatology Association. Notes on prescribing medications for rheumatic diseases in pregnancy 2017. Available from: 'https://rheumatology.org.au/gps/documents/ARAPregnancyPrescribingnotes29Aug17_000.pdf'.
55. Flint J, Panchal S, Hurrell A, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford). 2016;55(9):1693-7.
56. Ben-Horin S, Yavzori M, Katz L, et al. Adalimumab level in breast milk of a nursing mother. Clin Gastroenterol Hepatol. 2010;8(5):475-6.
57. Ben-Horin S, Yavzori M, Kopylov U, et al. Detection of infliximab in breast milk of nursing mothers with inflammatory bowel disease. J Crohns Colitis. 2011;5(6):555-8.
58. Saito J, Yakuwa N, Sandaiji N, et al. Omalizumab concentrations in pregnancy and lactation: A case study. J Allergy Clin Immunol Pract. 2020;8(10):3603-4.
59. Saito J, Yakuwa N, Takai C, et al. Abatacept concentrations in maternal serum and breast milk during breastfeeding and an infant safety assessment: a case study. Rheumatology (Oxford). 2019;58(9):1692-4.
60. Saito J, Yakuwa N, Takai C, et al. Tocilizumab concentrations in maternal serum and breast milk during breastfeeding and a safety assessment in infants: a case study. Rheumatology (Oxford). 2018;57(8):1499-501.
61. Matro R, Martin CF, Wolf D, et al. Exposure concentrations of infants breastfed by women receiving biologic therapies for inflammatory bowel diseases and effects of breastfeeding on infections and development. Gastroenterology. 2018;155(3):696-704.
62. Tsao NW, Lynd LD, Sayre EC, et al. Use of biologics during pregnancy and risk of serious infections in the mother and baby: a Canadian population-based cohort study. BMJ Open. 2019;9(2):e023714.
63. Tsao NW, Hanley GE, Lynd LD, et al. Risk of congenital anomalies in infants born to women with autoimmune disease using biologics before or during pregnancy: a population-based cohort study. Clin Exp Rheumatol. 2019;37(6):976-82.
64. Duricova D, Dvorakova E, Hradsky O, et al. Safety of anti-TNF-alpha therapy during pregnancy on long-term outcome of exposed children: A controlled, multicenter observation. Inflamm Bowel Dis. 2019;25(4):789-96.
65. Chaparro M, Verreth A, Lobaton T, et al. Long-term safety of in utero exposure to anti-TNFα drugs for the treatment of inflammatory bowel disease: Results from the multicenter European TEDDY study. Am J Gastroenterol. 2018;113(3):396-403.
66. Cheent K, Nolan J, Shariq S, et al. Case report: Fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. J Crohns Colitis. 2010;4(5):603-5.
67. Park SH, Kim HJ, Lee CK, et al. Safety and optimal timing of BCG vaccination in infants born to mothers receiving anti-TNF therapy for inflammatory bowel disease. J Crohns Colitis. 2020;14(12):1780-4.
68. Nguyen GC, Seow CH, Maxwell C, et al. The Toronto Consensus Statements for the management of inflammatory bowel disease in pregnancy. Gastroenterology. 2016;150(3):734-57.e1.
69. Smith CH, Yiu ZZN, Bale T, et al. British Association of Dermatologists guidelines for biologic therapy for psoriasis 2020: a rapid update. Br J Dermatol. 2020;183(4):628-37.
70. Wallenius M, Lie E, Daltveit AK, et al. No excess risks in offspring with paternal preconception exposure to disease-modifying antirheumatic drugs. Arthritis Rheumatol. 2015;67(1):296-301.
71. Meserve J, Luo J, Zhu W, et al. Paternal exposure to immunosuppressive and/or biologic agents and birth outcomes in patients with immune-mediated inflammatory diseases. Gastroenterology. 2021;161(1):107-15.
72. Kumar M, Ray L, Vemuri S, et al. Pregnancy outcomes following exposure to abatacept during pregnancy. Semin Arthritis Rheum. 2015;45(3):351-6.
73. Hoeltzenbein M, Beck E, Rajwanshi R, et al. Tocilizumab use in pregnancy: Analysis of a global safety database including data from clinical trials and post-marketing data. Semin Arthritis Rheum. 2016;46(2):238-45.
74. Warren RB, Reich K, Langley RG, et al. Secukinumab in pregnancy: outcomes in psoriasis, psoriatic arthritis and ankylosing spondylitis from the global safety database. Br J Dermatol. 2018;179(5):1205-7.
75. Mahadevan U, Terdiman JP, Aron J, et al. Infliximab and semen quality in men with inflammatory bowel disease. Inflamm Bowel Dis. 2005;11(4):395-9.
76. Montagna GL, Malesci D, Buono R, et al. Asthenoazoospermia in patients receiving anti-tumour necrosis factor {alpha} agents. Ann Rheum Dis. 2005;64(11):1667.
77. Perrier d'Hauterive S, Kesseler S, Ruggeri P, et al. FRI0160 Certolizumab PEGOL did not result in a decrease in semen quality in healthy volunteers: Results from a phase 1 study. Ann Rheum Dis. 2013;71(Suppl 3):365-6.
78. Micu MC, Micu R, Surd S, et al. TNF-α inhibitors do not impair sperm quality in males with ankylosing spondylitis after short-term or long-term treatment. Rheumatology (Oxford). 2014;53(7):1250-5.
79. Grosen A, Bungum M, Christensen LA, et al. Semen quality and sperm DNA integrity in patients with severe active inflammatory bowel disease and effects of tumour necrosis factor-alpha inhibitors. J Crohns Colitis. 2019;13(5):564-71.
80. Heppt F, Colsman A, Maronna A, et al. Influence of TNF-alpha inhibitors and fumaric acid esters on male fertility in psoriasis patients. J Eur Acad Dermatol Venereol. 2017;31(11):1860-6.
81. Mouyis M, Flint JD, Giles IP. Safety of anti-rheumatic drugs in men trying to conceive: A systematic review and analysis of published evidence. Semin Arthritis Rheum. 2019;48(5):911-20.
82. Saougou I, Markatseli TE, Papagoras C, et al. Fertility in male patients with seronegative spondyloarthropathies treated with infliximab. Joint Bone Spine. 2013;80(1):34-7.
83. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. Arthritis Care Res (Hoboken). 2020;72(4):461-88.
84. Tsao NW, Sayre EC, Hanley G, et al. Risk of preterm delivery and small-for-gestational-age births in women with autoimmune disease using biologics before or during pregnancy: a population-based cohort study. Ann Rheum Dis. 2018;77(6):869-74.
85. Kimball AB, Guenther L, Kalia S, et al. Pregnancy outcomes in women with moderate-to-severe psoriasis from the psoriasis longitudinal assessment and registry (psolar). JAMA Dermatol. 2021;157(3):301-6.
86. Bortlik M, Machkova N, Duricova D, et al. Pregnancy and newborn outcome of mothers with inflammatory bowel diseases exposed to anti-TNF-α therapy during pregnancy: three-center study. Scand J Gastroenterol. 2013;48(8):951-8.
87. Narula N, Al-Dabbagh R, Dhillon A, et al. Anti-TNFα therapies are safe during pregnancy in women with inflammatory bowel disease: a systematic review and meta-analysis. Inflamm Bowel Dis. 2014;20(10):1862-9.
88. Shihab Z, Yeomans ND, De Cruz P. Anti-tumour necrosis factor α therapies and inflammatory bowel disease pregnancy outcomes: A meta-analysis. J Crohns Colitis. 2016;10(8):979-88.
89. Julsgaard M, Christensen LA, Gibson PR, et al. Concentrations of adalimumab and infliximab in mothers and newborns, and effects on infection. Gastroenterology. 2016;151(1):110-9.
90. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. J Am Acad Dermatol. 2019;80(4):1029-72.
91. Lau CS, Chia F, Dans L, et al. 2018 update of the APLAR recommendations for treatment of rheumatoid arthritis. Int J Rheum Dis. 2019;22(3):357-75.
92. van der Woude CJ, Ardizzone S, Bengtson MB, et al. The second European evidenced-based consensus on reproduction and pregnancy in inflammatory bowel disease. J Crohns Colitis. 2015;9(2):107-24.
93. Geldhof A, Slater J, Clark M, et al. Exposure to infliximab during pregnancy: Post-marketing experience. Drug Saf. 2020;43(2):147-61.
94. Chambers CD, Johnson DL, Xu R, et al. Birth outcomes in women who have taken adalimumab in pregnancy: A prospective cohort study. PLoS One. 2019;14(10):e0223603.
95. Burmester GR, Landewé R, Genovese MC, et al. Adalimumab long-term safety: infections, vaccination response and pregnancy outcomes in patients with rheumatoid arthritis. Ann Rheum Dis. 2017;76(2):414-7.
96. Kawai Y, Tsuchiya T, Aoki S. Pregnancy outcomes of patients exposed to adalimumab in Japan. Dig Dis. 2019;37(2):123-30.
97. Echeverría-García B, Nuño-González A, Dauden E, et al. A case series of patients with psoriasis exposed to biologic therapy during pregnancy: The BIOBADADERM register and a review of the literature. Actas Dermosifiliogr. 2017;108(2):168-70.
98. Carman WJ, Accortt NA, Anthony MS, et al. Pregnancy and infant outcomes including major congenital malformations among women with chronic inflammatory arthritis or psoriasis, with and without etanercept use. Pharmacoepidemiol Drug Saf. 2017;26(9):1109-18.
99. Önalan G, Tohma YA, Zeyneloğlu HB. Effect of etanercept on the success of assisted reproductive technology in patients with endometrioma. Gynecol Obstet Invest. 2018;83(4):358-64.
100. ClinicalTrials.gov. Organization of Teratology Information Services (OTIS) autoimmune diseases in pregnancy project 2021. Available from: 'https://www.clinicaltrials.gov/ct2/show/NCT00116272'.
101. Berthelsen BG, Fjeldsoe-Nielsen H, Nielsen CT, et al. Etanercept concentrations in maternal serum, umbilical cord serum, breast milk and child serum during breastfeeding. Rheumatology (Oxford). 2010;49(11):2225-7.
102. Murashima A, Watanabe N, Ozawa N, et al. Etanercept during pregnancy and lactation in a patient with rheumatoid arthritis: drug levels in maternal serum, cord blood, breast milk and the infant's serum. Ann Rheum Dis. 2009;68(11):1793-4.
103. Clowse MEB, Scheuerle AE, Chambers C, et al. Pregnancy outcomes after exposure to certolizumab pegol: Updated results from a pharmacovigilance safety database. Arthritis Rheumatol. 2018;70(9):1399-407.
104. Porter C, Armstrong-Fisher S, Kopotsha T, et al. Certolizumab pegol does not bind the neonatal Fc receptor (FcRn): Consequences for FcRn-mediated in vitro transcytosis and ex vivo human placental transfer. J Reprod Immunol. 2016;116:7-12.
105. Morita T, Fujimoto K, Shima Y, et al. Minimal neonatal transfer of certolizumab pegol in a Japanese patient with rheumatoid arthritis. Ann Rheum Dis. 2018;77(9):e56.
106. Förger F, Zbinden A, Villiger PM. Certolizumab treatment during late pregnancy in patients with rheumatic diseases: Low drug levels in cord blood but possible risk for maternal infections. A case series of 13 patients. Joint Bone Spine. 2016;83(3):341-3.
107. Clowse ME, Förger F, Hwang C, et al. Minimal to no transfer of certolizumab pegol into breast milk: results from CRADLE, a prospective, postmarketing, multicentre, pharmacokinetic study. Ann Rheum Dis. 2017;76(11):1890-6.

108. Galluzzo M, D'Adamio S, Bianchi L, et al. Psoriasis in pregnancy: case series and literature review of data concerning exposure during pregnancy to ustekinumab. J Drugs Dermatol. 2019;30(1):40-4.
109. Gisbert JP, Chaparro M. Safety of new biologics (vedolizumab and ustekinumab) and small molecules (tofacitinib) during pregnancy: A review. Drugs. 2020;80(11):1085-100.
110. Cortes X, Borrás-Blasco J, Antequera B, et al. Ustekinumab therapy for Crohn's disease during pregnancy: a case report and review of the literature. J Clin Pharm Ther. 2017;42(2):234-6.
111. Rocha K, Piccinin MC, Kalache LF, et al. Pregnancy during ustekinumab treatment for severe psoriasis. Dermatology. 2015;231(2):103-4.
112. Sheeran C, Nicolopoulos J. Pregnancy outcomes of two patients exposed to ustekinumab in the first trimester. Australas J Dermatol. 2014;55(3):235-6.
113. Andrulonis R, Ferris LK. Treatment of severe psoriasis with ustekinumab during pregnancy. J Drugs Dermatol. 2012;11(10):1240.
114. Galli-Novak E, Mook SC, Büning J, et al. Successful pregnancy outcome under prolonged ustekinumab treatment in a patient with Crohn's disease and paradoxical psoriasis. J Eur Acad Dermatol Venereol. 2016;30(12):e191-e2.
115. Klenske E, Osaba L, Nagore D, et al. Drug levels in the maternal serum, cord blood and breast milk of a ustekinumab-treated patient with Crohn's disease. J Crohns Colitis. 2018;13(2):267-9.
116. Abraham BP, Ott E, Busse C, et al. 178 Pregnancy outcomes in women exposed to ustekinumab in the Crohn's disease and ulcerative colitis clinical trials. Gastroenterology. 2021;160(6):S-43.
117. Scherl E, Jacobstein D, Murphy C, et al. A109 Pregnancy outcomes in women exposed to ustekinumab in the Crohn's disease clinical development program. J Can Assoc Gastroenterol. 2018;1(Suppl 2):166-.
118. ClinicalTrials.gov. Stelara and Tremfya Pregnancy Exposure Registry OTIS Autoimmune Diseases in Pregnancy Project 2021. Available from: 'https://clinicaltrials.gov/ct2/show/NCT02103361'.
119. Allison C, Huilgol S, Ramachandran P, et al. Pregnancy outcomes in women exposed to guselkumab: experience from the clinical development program: Abstract 52. 2021 Dermcoll; 2020; Virtual.
120. Haycraft K, DiRuggiero D, Rozzo SJ, et al. Outcomes of pregnancies from the tildrakizumab phase I-III clinical development programme. Br J Dermatol. 2020;183(1):184-6.
121. Feldman S, Pangallo B, Xu W. Ixekizumab and pregnancy outcome. J Am Acad Dermatol. 2017;76(6 (Suppl.1)):AB419.
122. ClinicalTrials.gov. Dupilumab and pregnancy outcomes: A retrospective cohort study using administrative healthcare databases (Dupi PODS) 2021. Available from: 'https://clinicaltrials.gov/ct2/show/NCT03936335'.
123. Kasuya A, Kitano S, Hoshino T, et al. Successful control of severe eosinophilic granulomatosis with polyangiitis in a pregnancy and perinatal period: A use of mepolizumab. J Dermatol. 2019;46(9):e309-e11.
124. GlaxoSmithKline. The Mepolizumab Pregnancy Exposure Study 2021. Available from: 'https://pregnancyregistry.gsk.com/mepolizumab.html'.
125. Manetz S, Maric I, Brown T, et al. Successful pregnancy in the setting of eosinophil depletion by benralizumab. J Allergy Clin Immunol Pract. 2021;9(3):1405-7.e3.
126. ClinicalTrials.gov. Benralizumab pregnancy exposure study 2021. Available from: 'https://clinicaltrials.gov/ct2/show/NCT03794999'.
127. Saito J, Yakuwa N, Kaneko K, et al. Tocilizumab during pregnancy and lactation: drug levels in maternal serum, cord blood, breast milk and infant serum. Rheumatology (Oxford). 2019;58(8):1505-7.
128. Dalkilic E, Coskun BN, Yağız B, et al. A successful pregnancy in a patient with Takayasu's arteritis under tocilizumab treatment: A longitudinal case study. Int J Rheum Dis. 2019;22(10):1941-4.
129. Naqvi M, Zakowski P, Glucksman L, et al. Tocilizumab and remdesivir in a pregnant patient with coronavirus disease 2019 (COVID-19). Obstet Gynecol. 2020;136(5):1025-9.
130. Nakajima K, Watanabe O, Mochizuki M, et al. Pregnancy outcomes after exposure to tocilizumab: A retrospective analysis of 61 patients in Japan. Mod Rheumatol. 2016;26(5):667-71.
131. Tada Y, Sakai M, Nakao Y, et al. Placental transfer of tocilizumab in a patient with rheumatoid arthritis. Rheumatology (Oxford). 2019;58(9):1694-5.
132. Weber-Schoendorfer C, Schaefer C. Pregnancy outcome after tocilizumab therapy in early pregnancy-a case series from the German Embryotox Pharmacovigilance Center. Reprod Toxicol. 2016;60:29-32.
133. Kaneko K, Sugitani M, Goto M, et al. Tocilizumab and pregnancy: Four cases of pregnancy in young women with rheumatoid arthritis refractory to anti-TNF biologics with exposure to tocilizumab. Mod Rheumatol. 2016;26(5):672-5.
134. Jiménez-Lozano I, Caro-Teller JM, Fernández-Hidalgo N, et al. Safety of tocilizumab in COVID-19 pregnant women and their newborn: A retrospective study. J Clin Pharm Ther. 2021;46(4):1062-70.
135. Chang Z, Spong CY, Jesus AA, et al. Anakinra use during pregnancy in patients with cryopyrin-associated periodic syndromes (CAPS). Arthritis Rheumatol. 2014;66(11):3227-32.
136. Smith CJF, Chambers CD. Five successful pregnancies with antenatal anakinra exposure. Rheumatology (Oxford). 2018;57(7):1271-5.
137. Fischer-Betz R, Specker C, Schneider M. Successful outcome of two pregnancies in patients with adult-onset Still's disease treated with IL-1 receptor antagonist (anakinra). Clin Exp Rheumatol. 2011;29(6):1021-3.
138. Namazy JA, Blais L, Andrews EB, et al. Pregnancy outcomes in the omalizumab pregnancy registry and a disease-matched comparator cohort. J Allergy Clin Immunol. 2020;145(2):528-36.e1.
139. Ojeda-Uribe M, Afif N, Dahan E, et al. Exposure to abatacept or rituximab in the first trimester of pregnancy in three women with autoimmune diseases. Clin Rheumatol. 2013;32(5):695-700.
140. Clinicaltrials.gov. Abatacept Pregnancy Exposure Registry 2021. Available from: 'https://clinicaltrials.gov/ct2/show/NCT01087125'.
141. Sugawara E, Kato M, Fujieda Y, et al. Pregnancy outcomes in women with rheumatic diseases: a real-world observational study in Japan. Lupus. 2019;28(12):1407-16.
142. Bandoli G, Palmsten K, Forbess Smith CJ, et al. A review of systemic corticosteroid use in pregnancy and the risk of select pregnancy and birth outcomes. Rheum Dis Clin North Am. 2017;43(3):489-502.
143. Žák P, Souček M. Correlation of tumor necrosis factor alpha, interleukin 6 and interleukin 10 with blood pressure, risk of preeclampsia and low birth weight in gestational diabetes. Physiol Res. 2019;68(3):395-408.
144. Polachek A, Li S, Polachek IS, et al. Psoriatic arthritis disease activity during pregnancy and the first-year postpartum. Semin Arthritis Rheum. 2017;46(6):740-5.
145. McHugh J. RA remission attainable during pregnancy. Nat Rev Rheumatol. 2021;17(4):188.

Company Commissioned Article

This article has been commissioned by UCB Australia Pty Ltd. The content is entirely independent and based on studies and the author's opinion. The views expressed do not necessarily reflect the views of UCB. Treatment decisions based on these data are the full responsibility of the prescribing physician. Please review the relevant full Product Information before prescribing. The Cimzia® Product Information can be found here. Cimzia® is listed on the PBS for RA, PsA, AS, and non-radiographic-axSpA; but it is not listed for Ps. Please visit www.pbs.gov.au for further details.

