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Review Article

Biological agents in pregnancy and lactation – A rational approach

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ABSTRACT

Biologicals are a rapidly evolving group of drugs derived from biological agents which target specific immune mediators. The use of biologicals in dermatology is on the rise, especially for inflammatory and immunological conditions. As pregnancy and lactation are associated with exacerbation of various inflammatory conditions necessitating administration of biologicals in certain cases, their use in these physiologically altered states has to be evaluated. This article aims at reviewing the common biologicals used in dermatology and their feasibility in pregnancy and lactation. Tumor necrosis factor-alpha inhibitors are the most experienced group of biologicals in pregnancy and lactation, the newer biologicals have only animal studies and isolated case reports to back up their use. The commonly used biologicals are tabulated and discussed herewith. The guidelines and recommendations are derived from the data of use in other conditions such as inflammatory bowel disease and rheumatoid arthritis as there is no sufficient literature evidence for the use of biologicals in pregnancy for dermatological conditions. It was extrapolated that biologicals, being large molecular weight immunoglobulins or recombinant proteins, may be used with judicious care in the first two trimesters of pregnancy and after the 1st week of lactation, if benefits to the mother outweigh the theoretical risk to the infant.

Keywords: Biological agents, Pregnancy, Lactation

INTRODUCTION

The term "biologicals" refer to a group of drugs derived from biological agents, which target specific immune mediators. The use of biologicals in dermatology is on the rise, especially in conditions such as psoriasis, atopic dermatitis, autoimmune collagen vascular disorders, immunobullous disorders, hidradenitis suppurativa, and urticaria, due to relatively better efficacy and ease of administration, with less frequent intervals.

Biologicals in pregnancy

There is a shift from T helper (Th) 1 response to Th2 response in pregnancy. If pregnancy is associated with autoimmune or other inflammatory diseases, there is increased ratio of Th17 to T regulatory (Treg) cells, whereas reverse is true in normal healthy pregnancy.[1] Pregnancy outcomes are generally poor in patients with severe psoriasis and other immunological diseases, thus justifying the use of biologicals in pregnancy in severe conditions. Most biologicals pass minimally through the placental barrier in the first two trimesters until active transport of immunoglobulins starts at the beginning of the third trimester, with the development of fetal Fc receptor on the placenta.[2]

Biologicals in lactation

Overall, there is a limited information regarding their use; though few published case reports do not indicate any adverse effects on the lactating infant. Due to high molecular weights, they are secreted in breast milk to a very minuscule extent. However, during the first 3 days, the breast alveolar cells have wide gaps to allow immunoglobulins to pass through, and hence, it is prudent to avoid biologics in this interval. As these are protein molecules, these are likely to be destroyed by the acid and proteolytic enzymes in the infantile gut and even the minuscule amount secreted in breast milk may not be absorbed.[3] Pharmaceutical industry with concerns of future liability issues aims at caution and excludes the use of biologics in pregnancy and lactation.

This article aims at dissecting the feasibility of biologicals in pregnancy and lactation for dermatological indications. The guidelines and recommendations are extrapolated from the data of use in other conditions such as inflammatory bowel disease and rheumatoid arthritis (RA) as there is no sufficient literature evidence for the use of biologicals in pregnancy for dermatological conditions. It is essential to remember that while treating a pregnant woman, the chief objective should be to control the disease while taking care to minimize maternal and fetal risk to side effects of medication. Benefit of treatment should always outweigh the risk.

Biologicals used in dermatology and their use in pregnancy and lactation has been tabulated in Table 1. (Biologicals such as alefacept and efalizumab which have been withdrawn are not being discussed here).

Tumor necrosis factor-alpha (TNF-α inhibitors)

Infliximab

This is a chimeric human – murine monoclonal antibody, which irreversibly binds to soluble as well as transmembrane forms of TNF–α, thereby blocking its action. It also depletes TNF-α producing cells by apoptosis induced by complement lysis and antibody-dependent cellular cytotoxicity.

Indications in dermatology include moderate-to-severe plaque psoriasis, psoriatic arthritis, pustular psoriasis, and erythrodermic psoriasis. Off-label uses include hidradenitis suppurativa, pyoderma gangrenosum, Behcet's syndrome, vasculitis, graft versus host disease, systemic lupus erythematosus (SLE), sarcoidosis, and Sjogren's syndrome.[4] Mode of administration: 3, 5, or 10 mg/kg body weight intravenous infusion in 500 ml normal saline at 0, 2, and 6 weeks and thereafter, every 8 weeks.

Etanercept

Etanercept is a soluble TNF receptor, a dimeric fusion protein composed of extracellular ligand-binding portion of human p75 tumor necrosis receptor linked to Fc portion of human IgG1. It modulates all the biological responses of TNF. Chief indications are rheumatoid, juvenile idiopathic, and psoriatic arthritis, though it is also used in other conditions, similar to infliximab. Dosage is 50 mg subcutaneous (s/c) once or twice a week for 3 months.

Adalimumab

This is a fully human IgG1 monoclonal antibody against soluble as well as membrane bound TNF –α administered as initial 80 mg dose subcutaneously, thereafter 40 mg subcutaneously every 2 weeks. Indications in dermatology are similar to those of infliximab and are also used in alopecia areata, pemphigus, and multicentric reticulohistiocytosis.[5]

TNF-α inhibitors in pregnancy and lactation

Pregnancy or breastfeeding is an exclusion criterion to use of infliximab according to manufacturer excerpts. However, there are studies and reports on the use of infliximab in pregnancy. Both infliximab and adalimumab are IgG1 proteins which are transferred through the placenta only at the beginning of the third trimester, facilitated by the neonatal Fc receptor. Etanercept, a fusion protein, also has IgGFc portion but is less readily transported than the above two.

A study on 495 women exposed to a TNF inhibitor in early pregnancy for autoimmune diseases, with nearly one-third each on infliximab, etanercept, and adalimumab did not reveal any increased risk for abortion, though there was slightly increased risk of low birth weight and preterm birth as compared to normal cohort.[6] Whether this is due to medication or underlying autoimmunity was debatable. Infants have not shown high risk to acquire infections and can be immunized with killed vaccines, though live vaccines have to be postponed to after 6 months of age or when the serum levels of biologicals become undetectable. Discontinuing TNF inhibitors in the third trimester of pregnancy should minimize fetal risk.[45]

In addition to the above study, evidence from case reports and studies of more than 300 pregnancy outcomes show that infliximab carries low risk to the fetus and is compatible with use till the first two trimesters and is pregnancy category B.

Etanercept and adalimumab are also pregnancy category B, similar to infliximab. There are no fertility problems or increased risk of miscarriage or birth defects in newborns of pregnant adalimumab users.[6]

In lactation, all above three biologicals, due to their high molecular weight, are minimally secreted in breast milk, and minimally absorbed from the infant's gut.[7] Hence, a pregnant woman may be administered these, if benefits outweigh risks, though these have to be avoided according

Table 1: Biologicals in pregnancy and lactation.

Biological	Mechanism	Chief indications	Unique side effects	Use in pregnancy. US FDA category*	Use in lactation**
Infliximab	TNF-alpha inhibitors	Psoriasis and psoriatic arthritis	Infections	1st and 2nd trimester. (if benefits outweigh) Pregnancy category B	+May be used with caution
Adalimumab					+May be used with caution
Etanercept					+May be used with caution
Golimumab and certolizumab					Probably safe
Ustekinumab	IL-12 and 23 antibody	Chronic plaque psoriasis, psoriatic arthritis		Pregnancy category B	+May be used with caution
Secukinumab Ixekizumab	IL-17 inhibitor	Chronic plaque psoriasis, psoriatic arthritis		Pregnancy category not assigned	+May be used with caution
Rituximab	CD 20 antibody	Pemphigus and variants MMP, EBA SLE, Dermatomyositis, Scleroderma GVHD AD, Vitiligo	First trimester abortions Premature birth >30 weeks	Pregnancy category C	+May be used with caution
Omalizumab	FcE IgE receptor blocker	Urticaria		Pregnancy category B	+May be used with caution
Anakinra	IL-1 receptor antagonist	Urticarial syndromes, psoriasis, hidradenitis suppurativa	Hypersensitivity infections	Pregnancy category B	+May be used with caution
Dupilumab	IL-4 receptor antagonist	Atopic dermatitis		Pregnancy category not assigned	+May be used with caution

IL: Interleukin, MMP: Mucous membrane pemphigoid, EBA: Epidermolysis bullosa acquisita, SLE: Systemic lupus erythematosus, GVHD: Graft versus host disease, AD: Atopic dermatitis, US FDA: United States Food and Drug Administration. + According to the US FDA and manufacturers, women should not breastfeed for at least 6 months after treatment is discontinued as immunoglobulins are secreted in breast milk. If absolutely essential for the lactating mother, biologicals may be used except in mothers of preterm infants and neonates. *Data from "US FDA database," **data from "Drugs and lactation database[45]

to the United States Food and Drug Administration (US FDA) guidelines. Premature babies with GI tract that is not fully formed may absorb more drug. There are isolated case reports which demonstrate the efficacy and safety of infliximab,[8,9] etanercept,[10] and adalimumab[11] in lactating mothers and infants. According to latest studies, though it is advisable to stop TNF inhibitors at 22–24 weeks of pregnancy, in cases of severe disease and if really indicated, these may be continued up to week 30.[12] In comparison to adalimumab, infliximab is absorbed more and persists for a longer time in the fetal blood. Although recommendations are same for both, adalimumab thus scores over infliximab.

Caution

There are a couple of case reports of vertebral, anal, tracheal, esophageal, and radial or renal association to mothers treated with etanercept.[13] However, further evaluation of large registries did not confirm the association.[14,15]

Golimumab

Although it is available in India and is indicated in psoriasis and psoriatic arthritis, it has only limited use. It is given 50 mg s/c once a month.

Pregnancy

There are no good clinical trials in pregnancy. Analysis of data in 40 pregnant women, which was presented to the American College of Rheumatology Meeting, reported 19 live births, 13 spontaneous abortions (32.5%), and one intrauterine death with congenital abnormality. Methotrexate was coadministered in four patients with abortion, and there were no conclusive statements.[16] At present, it is classified as the US FDA pregnancy

category B if used intravenously, and pregnancy category is not assigned for subcutaneous administration. It could affect normal immune response in newborn due to TNF inhibition. Women with childbearing potential are advised contraception for at least 6 months after the last dose. Administration of live vaccine to infants exposed *in utero* is not recommended for up to 6 months after the last dose.

Lactation

As it is a large molecule, it is unlikely to be excreted in human milk in significant amounts. Current recommendations suggest withholding lactation for at least 6 months after the last dose as effect in the nursing infant is unknown.[17]

Certolizumab

It is used in rheumatoid and psoriatic arthritis at a dose of 400 mg s/c initially, followed by 200 mg every 2 weeks, has been recently approved by FDA in pregnant and lactating mothers with pregnancy category B. In the CRIB study, certolizumab levels were below the lower limit of quantification in 13 of 15 infant blood samples at birth and in all samples at weeks 4 and 8. No anti-certolizumab antibodies were detected in mothers, umbilical cords, or infants.[18] It was not detected in 134 of 137 breast milk samples from 19 lactating mothers, and all infants were normal.[19] Although it is minimally excreted in breast milk, it is destroyed by the infant's gut and absorption is unlikely. Although manufacturers recommend cessation of breastfeeding, most experts consider this to be probably safe in lactation.

Other biologicals

As pregnancy is commonly an exclusion criterion for clinical trials, there are no large properly conducted studies on newer biologicals. Data are usually extrapolated from animal studies, or from case reports, series, or retrospective studies. There are surveillance registries in some countries, but bias of preferentially reporting only adverse effects cannot be excluded.

Ustekinumab

This is a monoclonal antibody against interleukin (IL) 12 and 23, indicated in the treatment of resistant moderate to severe plaque psoriasis, active psoriatic arthritis, and Crohn's disease. Dose is 45 mg s/c on day 0, at 4 weeks, subsequently every 12 weeks.

There are no adequate human studies for its use in pregnancy, though animal studies do not indicate any risk. It is preferable to avoid using in pregnancy as a precautionary measure.[20]

There is limited published information on its use in lactation. It is only minimally detectable in breast milk, and absorption is unlikely as it is destroyed by the infant's gastrointestinal tract. In the PIANO registry multicentric study, there were six women who breastfed infants while on ustekinumab. Among these six as well as others on different biologicals in mothers who were pregnant or lactating, there was no difference in infant growth, development, or infection rate as compared to infants of mothers who did not receive treatment.[21] If ustekinumab is essential to the mother, it is not a reason to discontinue lactation but may be used with caution while nursing newborn or preterm infants.[22]

Secukinumab

It is a recombinant high-affinity fully human monoclonal antibody of the IgG1/kappa isotype that selectively targets IL-17A, used in resistant moderate-to-severe plaque psoriasis and psoriatic arthritis at initial dose of 300 mg s/c weekly.[23] As an IgG1 molecule, secukinumab could cross the placenta, but antibody transfer mostly occurs in the third trimester. Animal studies do not indicate harmful effects in pregnancy. It is pregnancy category B and may be used if benefits outweigh risks.

Of 292 pregnancies studied from the global safety database, there was no overall pattern of abnormality and secukinumab was not connected to any of the abortions or congenital malformations that occurred, which was in concordance with the normal rates of attrition.[24] There is no clinical information on use in breastfeeding, though isolated cases report no side effects[25] Being a large molecule, the amount in milk is likely to be very low and absorption is unlikely because it is probably destroyed in the infant's gastrointestinal tract. Secukinumab may be used with caution during breastfeeding, especially while nursing a newborn or preterm infant.[26]

Ixekizumab

This is also a humanized monoclonal IgG antibody which binds to IL-17a receptor, thus inhibiting IL-17 activities, and is used in the treatment of moderate-to-severe chronic plaque psoriasis. It is administered as 160 mg s/c at the first visit, thereafter 80 mg s/c at fixed intervals.

Pregnancy

Embryofetal developmental study in cynomolgus monkeys detected no malformation or toxicity even at 19 times the maximum recommended human dose.[27] However, human IgG can cross placental barrier and may affect neonatal immunity. Hence, contraception in susceptible women is advised during and for 10-week post-therapy. The US FDA has not assigned any pregnancy category to this molecule yet.

Lactation

Ixekizumab was detected in the milk of lactating cynomolgus monkeys. It is secreted in breast milk in animals,[27] and caution is advised during breastfeeding, especially in preterms and neonates, although it is a large molecule and absorption by the infant gut is unlikely.

Rituximab

Rituximab is a chimeric human monoclonal antibody against CD20 cell marker present on B-cells and causes depletion of B-cells *in vivo*; indications include large B-cell non-Hodgkin's lymphoma (NHL), rheumatoid arthritis (RA), chronic lymphocytic leukemia (CLL), granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).[28] The off-label use in dermatology includes autoimmune blistering disorders (pemphigus and its variants, mucous membrane pemphigoid, and epidermolysis bullosa acquisita), systemic lupus erythematosus (SLE), atopic dermatitis, vitiligo, graft versus host disease, dermatomyositis, and scleroderma.[29]

There are two conventional protocols for the drug in adults – the RA protocol(the drug is given as an infusion of 1 gm every two weeks for two doses) and the lymphoma protocol(the drug is given at 375mg/m^2 body surface area doses every week for 4 weeks).

Pregnancy

Rituximab is a category C drug as it crosses the placenta and can be detected in the newborn. B-cell lymphocytopenia lasting <6 months may occur in exposed infants. Reports on outcomes of inadvertent pregnancy during rituximab treatment describe premature births and infant hematologic abnormalities and infections; however, no specific pattern of birth defects has been observed. In case of inadvertent exposure to rituximab, the pregnancy should be constantly monitored and defects ruled out by appropriate screening investigations. In a review of literature, it was noted that of 231 pregnancies with preconceptional or antepartum exposure to rituximab, most resulted in uncomplicated live births. However, the first-trimester pregnancy loss occurred in 21%, whereas it is 10%–15% in the general population. Premature birth was seen in 24%; however, all were >30 weeks of gestation.[30] Significant reduction in B-cell counts in neonates may lead to opportunistic infections. Recovery of B-cell population takes 6 months. The children born without any anomalies had a normal growth.[31]

It has been suggested that effective contraception be used in women of reproductive potential during therapy and for 12 months following treatment with rituximab.

Rituximab is also secreted in breast milk and manufacturers recommend abstaining from lactation for at least up to 6 months after its last dose. However, there are case reports of successful and non-deleterious use of rituximab in lactation.[32]

Omalizumab

Omalizumab is a recombinant, humanized, monoclonal antibody against immunoglobulin IgE which neutralizes IgE by binding to the same site on FcεR I. Initially used for the treatment of severe allergic asthma, it got FDA approval for treatment of chronic spontaneous urticaria in 2014.[33] Off-label uses include atopic dermatitis, bullous and systemic mastocytosis, and bullous urticaria.[34] Recommended dose and best response is seen with 300 mg subcutaneous injection once in 4 weeks. Some patients may respond to 150 mg once in 4 weeks.[35]

Pregnancy

Omalizumab has been recently assigned to pregnancy category B by the FDA based mainly on the Xolair Pregnancy Registry (EXPECT) trial in pregnant asthmatic women who were exposed to one or more doses of omalizumab within 8 weeks before conception or at any time during pregnancy. Of 169 pregnancies with known outcomes, there were 156 live births of 160 infants (4 twin pairs), 1 fetal death/stillbirth, 11 spontaneous abortions, and 1 elective termination. No pattern of anomalies was observed. However, these figures are consistent with the rates reported for women with severe asthma.[36]

There have been few case reports where omalizumab has been continued throughout conception and pregnancy after thorough counseling regarding risks and benefits were explained. All pregnancies progressed till term and healthy neonates were delivered without any complications or congenital abnormalities.[37-39] A clinical trial is underway to measure the fertility rates and pregnancy outcomes of women who are using omalizumab.[40] However, it is considered a relatively safe drug to use in pregnancy in case of severe asthma or chronic urticaria.

There are no data on the excretion of omalizumab into human milk. Animal studies with cynomolgus monkeys have demonstrated milk levels that were 1.5% of maternal blood levels. IgE is excreted into human milk, and it is expected that omalizumab is also excreted, though being a large molecule, the amount in milk is likely to be very low. The effects in the nursing infant are unknown.[41]

Anakinra

This is a recombinant human IL-1 receptor antagonist (IL-1Ra) used in diverse dermatological conditions such as

psoriasis, atopic dermatitis, Schnitzler syndrome, pyoderma gangrenosum, pyogenic arthritis, pyoderma gangrenosum and acne syndrome, hidradenitis suppurativa, familial Mediterranean fever, and synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome. Dosage is 100 mg s/c daily, drawbacks being the expense and increased propensity to allergies and infections. It is not widely used in India.

It is pregnancy category B, and excretion in breast milk is not determined. Natural IL-1Ra is present in human milk as an anti-inflammatory agent, but excretion of exogenous administration is not studied. Infants who have been breastfed by mothers on anakinra have not experienced any side effects. Hence, if maternal benefits outweigh risks, anakinra may be used in pregnancy as well as lactation.[42]

Dupilumab

Dupilumab, a fully humanized monoclonal IgG4 antibody, acts as IL-4Ra, blocks IL-4/IL-13 signaling and thereby inhibits the Janus Kinase-Signal Transducer and Activation of Transcription pathway which leads to increased eosinophil recruitment and IgE production,[43] and has got FDA approval for the treatment of atopic dermatitis. The recommended initial dose is 600 mg (two 300-mg injections in different injection sites) followed by 300 mg every other week, subcutaneously.[44]

Pregnancy and lactation

There are no formal studies or case reports on the role of dupilumab in pregnancy and lactation. Dupilumab can cross the placenta and is most likely to be transmitted to the fetus. Animal studies show no adverse fetal effects in up to 10 times the recommended maximum human dosage.[44]

There are also no available data on the presence of dupilumab in human milk, the effects on the breastfed infant, or the effects on milk production. However, human immunoglobulin G is known to be present in human milk.

Clinical trials and studies are underway, discerning the safety profile, and efficacy of dupilumab in pregnancy.

CONCLUSION

Based on available data, biologicals appear to be safe in pregnancy, especially if benefits outweigh risks, at least in the first two trimesters. Most are the US FDA pregnancy category B, except for rituximab which is category C and ixekizumab and dupilumab, for which category has not been assigned.[37] However, biologicals have not been assigned lactation category and though most are safe, as these are larger molecules and only minuscule amounts are secreted in breast milk and whatever ingested by the infant is destroyed by the infant's gut, caution should be exerted and biologicals administered to the mother only if benefits outweigh risks.

It is better to avoid the use of biologicals after the late second trimester of pregnancy and in a mother who is lactating a neonate or a preterm infant.

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Conflicts of interest

There are no conflicts of interest.

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