

An Oral Physicians Perspective of the Usage of Biologics in Pregnancy, Lactation and Pediatrics

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Abstract

Biologics are newer drugs in the arsenal of therapeutics. These are agents which counteract the natural inflammatory process of several diseases and help us in counteracting the disease process. There are three broad classes of biologics viz: tumor necrosis factor -alpha inhibitors, lymphocyte modulators and interleukin inhibitors. With increasing incidence of auto immune diseases there is a widespread application of these biologics in the management of these disorders. This article aims to highlight the usage of biologics in the management of oral mucosal diseases affecting during pregnancy and lactation of mothers, and the usage of biologics in the pediatric population for the treatment of oral mucosal diseases. The literature has a good account of the usage of these group of pharmaceuticals in the above states.

Keywords-Biologics, Tumor necrosis factor alpha inhibitors, lymphocyte modulators, interleukin inhibitors

INTRODUCTION

Medications known as “biologics” or “biopharmaceuticals” are large protein molecules synthesised in living cells. The use of biologics are innovative treatments aimed at modulating lymphocytes or cytokines. There are three broad classes of biologic therapies, tumour necrosis factor-alpha inhibitors, lymphocyte modulators and interleukin inhibitors; all are increasingly used in the treatment of inflammatory immune mediated conditions, and several have applications in oral medicine.[1] Addition of selective adhesion molecule (SAM) inhibitor has expanded the therapeutic efficacy.[2]

The biologics have been used to treat the autoimmune diseases such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, and also malignancy. All these above mentioned conditions are prevalent among the women of reproductive age. This is a review article on the safety of use of biologics in pregnancy, lactating mothers and in pediatric population.

BIOLOGICS USED IN PREGNANCY

The examples of the biologics used include abatacept (T-cell costimulation inhibitor), tocilizumab (interleukin 6 inhibitor), anakinra (interleukin 1 inhibitor), rituximab (B-cell depletor), and also a number of tumour necrosis factor-alpha inhibitors like adalimumab, certolizumab, golimumab, infliximab, and etanercept.[2,3]

ABATACEPT (ORENCIA®)

Abatacept is a selective costimulation modulator that modulates a key costimulatory signal required for full activation of T lymphocytes expressing CD28. It is used for the treatment of adult and juvenile rheumatoid arthritis, and juvenile idiopathic arthritis. There are 7 reported cases of fetal exposure to abatacept. Four were during the double-blind period of the drug's rheumatoid arthritis

trials, where methotrexate has been added to abatacept[4] Of these, three women suffered spontaneous abortions and one woman had an elective termination. There was case report of a 33-year-old woman with rheumatoid arthritis who was treated with abatacept (10 mg/kg every 4 weeks) and methotrexate (15 mg per week). Both the drugs were stopped when the pregnancy was established. At 40 weeks, a healthy infant was delivered and follow-up after 3.5 years showed that the child was doing well.[4]

TUMOUR NECROSIS FACTOR-ALPHA (TNFA) INHIBITORS

Tumour necrosis factor-alpha is a key pro inflammatory cytokine and recognised to play a central role in the pathogenesis of immunologically driven disease acting in a number of pathways to promote increased leucocyte activation and recruitment to sites of tissue inflammation.[2,3]

ADALIMUMAB (HUMIRA®)

Adalimumab is a recombinant human IgG1 monoclonal antibody binds to soluble TNF α with high affinity and specificity, thus interfering with its interaction with cell surface receptors. Indications are rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, and also psoriasis. The drug has also been used off-label for treatment for infertility.[5] There was no evidence of an association between adalimumab exposure and major birth defects, or any kind of specific pattern of malformation. The World Congress of Gastroenterology on Biological Therapy (WCOG) suggests that adalimumab be considered as low risk and compatible with use during

conception and pregnancy in at least the 1st and 2nd trimesters.[6]

ETANERCEPT (ENBREL®)

Etanercept is a fusion protein consisting of the extracellular ligand-binding portion of the human TNF receptor linked to the Fc portion of human IgG1. It binds specifically to soluble and cell surface tumour TNF, blocking interaction with cell surface TNF receptors. Indications are rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, and also plaque psoriasis.[7]

Etanercept does not increase the risk for major congenital malformations above the baseline risk in general population. Benefits of treatment for the mother should be weighed against the unknown risks to the fetus when considering if etanercept is used during pregnancy.[8]

ADVERSE EFFECTS OF BIOLOGICS IN PREGNANCY VACTERL SPECTRUM

When the patients were exposed to anti- TNF agents , one child with the VACTERL syndrome was born, which is a syndrome seen in the embryo and foetus characterized by the abnormalities of the vertebrae (V), anus(A), cardiovascular tree(C), trachea (T), oesophagus(E), renal spectrum (R) and the limb buds.[9]

VERTEBRAL DEFECTS

Defects of the spinal column usually consists of vertebrae or hemevertebrae where only one half of the bone was formed, later in life these spinal column abnormalities may put the child at the risk of developing scoliosis or curvature of the spine.[9]

ANAL DEFECTS

Anal atresia or imperforate anus is seen in about 85% of the patients with the VACTERL syndrome. The babies born with Anal defects because the pregnant women have been exposed to antiTNF-agents which will require several surgeries to fully reconstruct the intestine and anal canal.[9]

CARDIAC DEFECTS

The kids associated with the VACTERL syndrome have been reported to have congenital heart disease . The main defect is the ventricular septal defect, atrial septal defect.[10]

TRACHEA-OESOPHAGEAL FISTULA DEFECT

Tracheo-esophageal fistula is seen in about 70% of the patients with VACTERL syndrome.[10]

RENAL /KIDNEY DEFECTS

They are seen to have single umbilical artery which is associated with additional kidney or urologic problems . It leads to incomplete formation of the one or both kidneys or urologic abnormalities such as obstruction or outflow of urine.[10]

LIMB DEFECTS

Limb defects include a displaced or hypo plastic thumb, extra digits (polydactyl, fusion of digits and fore arm defects).[10]

Anti-TNF therapies have been available for the management of arthritis. Anti-TNF agents has been reassuring and there are few adverse pregnancy outcomes. There has been many studies conducted by Carter et al, who listed 61 congenital anomalies affected children when the pregnant women were exposed to anti-TNF agents . The pregnant women were exposed to the biological therapies and the various studies were conduct.[10] As result there were many adverse effects seen in the patient when they were exposed to biological therapies during pregnancy, highest rate of spontaneous abortion was seen at the time of conception. The children that were born , were born prematurely and with low birth weight , and few died in utero. The cause of death was perinatal hypoxia.[11]

BIOLOGICS IN LACTATION

The usage of biologics in lactating mothers is not well supported with their clinical data. [11] In the case of the medications that lack any human lactation data, their pharmacokinetic properties must be assessed in order to estimate their safety. Because biologics have high molecular weights, they likely transfer into breastmilk only in small amounts, if at all.However, during the first 3 days postpartum the breast alveolar cells have wide gaps between them, allowing larger molecules such as immunoglobulins to pass through into the milk.Thus, the timing of the first postpartum dose of a biologic medication should be considered, as it may impact the extent of transfer into breastmilk. Because biologics are protein molecules, they would likely be destroyed by the acids and proteolytic enzymes in the infant's gastrointestinal tract and therefore not be absorbed.[12]

BIOLOGICS WITH LACTATION DATA:

Adalimumab is a monoclonal antibody that acts as a TNF inhibitor. It transfers into breastmilk in small amounts but is not likely absorbed by the infant. Most experts state that adalimumab is likely compatible with breastfeeding. Infant serum levels measured in two cases (at 8 weeks in one infant and 3 months in the other) were undetectable. No adverse effects or developmental abnormalities have been reported in infants exposed to adalimumab mono therapy during breastfeeding.[12]

Anakinra is a recombinant human interleukin-1 receptor antagonist. There is one case report of a woman breastfeeding her infant while using anakinra without any apparent adverse outcomes. Because interleukin-1 receptor antagonist naturally occurs in breastmilk, the risk of exposing a nursing infant to this medication is likely low.[13]

Certolizumab is a monoclonal antigen-binding fragment that acts as a TNF inhibitor. One infant was exposed both in utero and via breastmilk, with a serum certolizumab

concentration of 1.02 mg/L at birth and 0.84 mg/L at 1 month postpartum. These decreasing levels imply that the infant received the medication while in utero only, rather than through breastmilk. Certolizumab was undetectable in breastmilk samples from the mother, and infant oral absorption would be unlikely even if it were present. No adverse effects or developmental abnormalities have been reported in infants exposed to certolizumab mono therapy during breastfeeding.[14]

Etanercept is a fusion protein that acts as a TNF inhibitor. Even though etanercept is excreted in breastmilk (the relative infant dose is 0.07–0.2%), it is not orally absorbed by the infant. Note that in infants exposed to this medication in utero as well as via breastmilk, the serum levels decline as the postpartum period progresses. In one infant, the serum level was 21 µg/L at 1 week postpartum and undetectable at 12 weeks postpartum despite continued breastfeeding, indicating that the 1-week serum value was measurable because of in utero exposure. As is to be expected, given the lack of absorption, no adverse events or developmental abnormalities have been reported in infants exposed to etanercept in breastmilk.[15]

Infliximab is a monoclonal antibody that acts as a TNF inhibitor. Most experts state that infliximab is compatible with breastfeeding. As with etanercept, absorption by the infant is unlikely despite some transfer into breastmilk (the relative infant dose is 0.3%). Serum levels in infants are either low or undetectable. In one infant exposed to infliximab during both pregnancy and lactation, maternal and infant serum levels were equal at 6 weeks postpartum, but the infant level declined over the next 7 weeks despite continued breastfeeding and maternal therapy. This suggests that the high infant serum level at 6 weeks was due to in utero exposure. No adverse effects or developmental abnormalities have been reported in infants exposed to infliximab mono therapy during breastfeeding.[16]

BIOLOGIC AGENTS WITHOUT LACTATION DATA:

Abatacept is an immunomodulating fusion protein that inhibits T cell activation.[17]

Golimumab is a monoclonal antibody that acts as a TNF inhibitor.[18]

Rituximab is a monoclonal antibody that induces B-cell destruction.[19]

Tocilizumab is an anti-interleukin-6 receptor antibody.[20]

Ustekinumab is an anti-interleukin 12/23 monoclonal antibody.[21]

There are no published human data on the use of the above medications in lactation. However, transfer into breastmilk would likely be low, and infant absorption unlikely, because they are high-molecular-weight proteins. There is greater caution with rituximab compared with other biologics, probably because of its antineoplastic uses. It is advised that women should not breastfeed if they are less than 2 weeks postpartum or after receiving a dose, despite the unlikelihood of rituximab entering breastmilk in clinically relevant amounts.

BIOLOGICAL IN PAEDIATRICS:

Tumour necrosis factor alpha inhibitors are considered safe and effective for its use in psoriasis, Crohn's disease, juvenile idiopathic arthritis, aphthous like ulcers in Behcet disease etc.[22-25] Aim of the therapy is to relieve symptoms, optimise growth and improve the quality of life at the same time minimising drug toxicity. Anti-TNF alpha therapy is indicated as a second line drug therapy following a failure of conventional therapy.[26] Those patients with diseases in undesirable location should be considered for earlier use of biological therapy. Patients with duodenal involvement, small bowel disease and anorectal involvement should be considered as a strong patients for early biological therapy because surgery has high likelihood of postoperative lifelong morbidity. In paediatric population, children's with growth retardation and delayed pubertal development should be considered for early biological therapy.[27]

GUIDELINES :

Guidelines for their use in licensed indications (e.g. rheumatoid arthritis, psoriasis, inflammatory bowel disease) include recommendations and guidance for patient selection and subsequent monitoring with discussion of potential adverse effects.[28]

The European Cystic Fibrosis Society best practice guidelines have recommended that ivacaftor be part of standard of care for patients with the G551D mutation and

the US CF Foundation pulmonary clinical practice guidelines committee has assigned it a grade A recommendation (high certainty of substantial net benefit) for patients 6 years and older with at least one G551D mutation using the US Preventive Services Task Force Scheme.[29]

Nikolay Tzaribachev et al (2009), Children with refractory autoimmune disorders often require treatment with various combinations of immunosuppressants including high doses of steroids and cyclophosphamide. These drugs may have significant side effects and toxicity, especially when given over longer periods of time. Representing a new therapeutic option with a potentially lower rate of adverse events, rituximab may be an important alternative and should be considered alone or in combination treatment.

CONDITIONS :

In children, TNF-a inhibitors are generally considered safe and effective for use in appropriate indications, including CD, juvenile idiopathic arthritis and psoriasis / psoriatic arthritis

Pemphigus:

Pemphigus is a rare group of blistering autoimmune diseases that affect the skin and mucous membranes. *Mabrouk and Ahmed (2011)*, Rituximab has been used with some reported benefit in two children with pemphigus and has also shown a limited response in infant with oral and cutaneous bullous pemphigoid, although treatment was associated with significant adverse effects – with hypogammaglobulinaemia, parainfluenza pneumonia and disseminated varicella zoster virus sepsis.

Crohn's disease:

Crohn's disease is a type of inflammatory bowel disease which may affect any part of the gastrointestinal tract from mouth to anus. In 2009, corticosteroids are frequently used as the treatment of choice for induction of remission in patients with a flare-up of CD. Episodic dosing with any monoclonal antibody for the treatment of CD is not recommended due to the potential of developing anti-drug antibodies. For IFX, the induction dosing is 5mg/kg intravenously (IV) given at weeks 0, 2, and 6. Infusions are carried out in a hospital or outpatient setting. Most patients will respond within the first 4 weeks or the first two doses.[30]

PSORIASIS:

It is an autoimmune disease which is characterized by patches of abnormal skin with typical red colour, itchy, and scaly. The prevalence of psoriasis is estimated to be 2.2% in the United States, and 6–39% of patients with psoriasis also develop psoriatic arthritis. New advances have been made in developing treatment options. New biologic therapies also include antibodies to interleukin-12 and interleukin-23. Phase II studies suggest that ustekinumab is effective in alleviating symptoms of psoriasis and psoriatic arthritis. There are three biologics approved in the United States for the treatment of psoriasis including alefacept, efalizumab, and etanercept, with several others currently under clinical investigation.[31]

ADVERSE EFFECTS OF BIOLOGICS:

A variety of adverse effects has been reported with administration of TNF- α blockers, which includes hypersensitivity, drug eruption and haematological reaction.[32] Type I hypersensitivity reactions, are the most common significant adverse event and incidence is higher with patients who develop antibodies. Local reactions only are more common with injectable subcutaneous agents.[33] Infusion reactions are also the most common adverse effect with rituximab therapy, in particular following first administration, and also in those patients with HCV infection. Haematological complications of biologics are uncommon, neutropaenia and pancytopenia can occur with all such agents, so frequent full blood counts assessment is mandatory.[34]

SAFETY CONCERN OF BIOLOGICS:

Safety is the first and foremost concern in treating a paediatric patient with biological therapy as it has many adverse side effects. Children with haemophilia and immune deficiency disorders are commonly treated with plasma derived proteins like coagulation factor and IGIV which has a risk of blood borne infection. To overcome this risk, now a days donor screening, improved testing methods and viral inactivation procedures are performed by the manufacturer.[35] Paediatric patients with haemophilia develop an inhibitor which may block the success of the treatment. Inhibitor is a type of antibody, which gets attached to the factor VII or IX and reduces its ability to cease bleeding.[35] Haemophilic patients who develop inhibitor against the factors

experiences orthopaedic and other life threatening bleeding disorder which makes the treatment difficult.[36] Administration of IGIV causes infusion related reactions with various severities that manifest with head ache, myalgia, fever, chills and backache. [37] Other serious adverse effects occur with IGIV administration include renal failure, aseptic meningitis, hemolysis, thrombotic events and transfusion related lung disorder.[38] Long term administration of TNF inhibitors is quite serious because it may lead to occurrence of malignancy and development of autoimmune phenomena such as demyelinating disease, uveitis, lupus like syndrome, inflammatory bowel disease and psoriasis. [39] Reports of such infections in children administered with TNF have subsequently decreased since 2000, with only very few case reports with development of tuberculosis and histoplasmosis.[39]

CONCLUSION :

Biologics represents the most advanced therapeutic approach for many disease states for chronic conditions like rheumatoid arthritis, psoriasis in adults. These agents have improved the quality of life of adult patients with these similar autoimmune mediated disease and induce a remission of symptoms for certain diseases. The usage of biologics in pregnant mothers and lactating mothers have a good clinical evidence for most scenarios. But the role of biologics in paediatric patient is not yet clear. Some biological therapy have approved for children with type 1 diabetes, atopic dermatitis, childhood cancers. They have increased the quality of life, but in which many cases extended to adulthood. Betterment of biologics in paediatrics with proper investigation of the long term effects of biologics.

REFERENCES:

- O'Neill C, Scully C. Centre d'Affaires Poincaré, Rue Poincaré, Nice, France. Biologics in oral medicine: principles of use and practical considerations ID. WHO Collaborating Centre for Oral Health-General Health, Oral Medicine, Bristol. 2012; 18:525–36.
- Anna Pupco. The new biologics in pregnancy. J Popul Ther Clin Pharmacol. 2014; 21(3):e548-e54.
- Smith CH, Anstey AV, Barker JN et al. British Association of Dermatologists's Guidelines for biologic interventions for psoriasis. British Journal of Dermatology. 2009; 161:987–1019.
- 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.
- Winger EE, Reed JL, Ashoush S, et al. Birth defect rates in women using adalimumab (Humira®) to treat immunologic-based infertility in IVF patients. Am J Reprod Immunol 2011; 66(3):237-241.
- Mahadevan U, Kane SV, Church JA, et al. The effect of maternal peripartum infliximab use on neonatal immune response Gastroenterology 2008; 134(4 Suppl 1):A-69.
- Johnson TL, Jones KL, Chambers CD, The OTIS Collaborative Research Group. Pregnancy outcomes in women exposed to etanercept: the OTIS Autoimmune Diseases in Pregnancy Project; (ClinicalTrials.gov Identifier NCT01797224.)
- Carter JD, Ladhani A, Ricca LR, Valeriano J, Vasey FB. A safety assessment of tumor necrosis factor antagonists during pregnancy: a review of the Food and Drug Administration database. J Rheumatol; (2009). 36: 635–641.
- Furst DE, Keystone EC, So AK, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2012. Annals of Rheumatic Disease. 2013; 72(Suppl 2):ii2–ii34.

10. Sarah J Witzel. Lactation and the Use of Biologic Immunosuppressive Medications. *Breastfeed Med.* 2014;9(10):543-6.
11. U.S. National Library of Medicine. Drugs and Lactation Database (LactMed). Adalimumab. 2014.
12. U.S. National Library of Medicine. Drugs and Lactation Database (LactMed). Anakinra. 2014.
13. U.S. National Library of Medicine. Drugs and Lactation Database (LactMed). Certolizumab. 2014.
14. Vinet E., Pineau C., Gordon C, et al. Anti-TNF therapy and pregnancy outcomes in women with inflammatory arthritis. *Expert Rev Clin Immunol.* 2009;5:27-34.
15. U.S. National Library of Medicine. Drugs and Lactation Database (LactMed). Infliximab. -2014.
16. Revers L., Furczon E. An introduction to biologics and biosimilars. Part II: Subsequent entry biologics: Biosame or biodifferent? *Can Pharm J* 2010;143:84-191.
17. U.S. National Library of Medicine. Drugs and Lactation Database (LactMed). Golimumab. 2014.
18. U.S. National Library of Medicine. Drugs and Lactation Database (LactMed). Rituximab. 2013.
19. U.S. National Library of Medicine. Drugs and Lactation Database (LactMed). Tocilizumab. 2014.
20. U.S. National Library of Medicine. Drugs and Lactation Database (LactMed). Ustekinumab. 2013.
21. Chong BF, Wong HK. Immunobiologics in the treatment of psoriasis. *Clin Immunol.* 2007;123:129-38.
22. Shirota Y, Illei GG, Nikolov NP. Biologic treatments for systemic rheumatic diseases. *Oral Dis.* 2008;14:206-16.
23. Remo Panaccione. Optimal use of biologics in the management of Crohn's disease. *Therap Adv Gastroenterol.* 2010;3:179-89.
24. Allez, M., Lemann, M., Bonnet, J., et al. Long-term outcome of patients with active Crohn's disease exhibiting extensive and deep ulcerations at colonoscopy. *Am J Gastroenterol.* 2002. 97: 947-53.
25. ID O'Neill, C Scully. Biologics in oral medicine: principles of use and practical considerations. *Oral Diseases.* 2012;18:525-36.
26. D Haens, G, Baert F, Van Assche G et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* 2008;371(9613):660-7.
27. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. *Gut.* 2012;61:1619-35.
28. Mogayzel PJ Jr, Naureckas ET, Robinson KA, et al. Cystic Fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *Am J Respir Crit Care Med.* 2013;187:680-9.
29. Sukhatme SV, Gottlieb AB. Pediatric psoriasis: updates in biologic therapies. *Dermatol Ther.* 2009;22:34-9.
30. Hanauer, S.B., Wagner, C.L., Bala, M., et al. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. *Clin Gastroenterol Hepatol.* 2004;2:542-53.
31. Marji JS, Marcus R, Moennich J et al, Use of biologic agents in pediatric psoriasis. *J Drugs Dermatol.* 2010;9:975-86.
32. Lecluse LL, Piskin G, Mekkes JR, et al. Review and expert opinion on prevention and treatment of infliximab-related infusion reactions. *Br J Dermatol.* 2008;159: 527-36.
33. Cheifetz A, Smedley M, Martin S et al. The incidence and management of infusion reactions to infliximab: a large center experience. *Am J Gastroenterol.* 2003;98:1315-24.
34. Tarantino M, Ma A, Aledort L. Safety of human plasma-derived clotting factor products and their role in hemostasis in patients with hemophilia: meeting report. *Haemophilia.* 2007;13(5):663-69.
35. Duhem C, Dicato MA, Ries F. Side-effects of intravenous immune globulins. *Clin Exp Immunol.* 1994;97:79-83.
36. Nydegger UE, Sturzenegger M. Adverse effects of intravenous immunoglobulin therapy. *Drug Saf.* 1999;21:171-85.
37. Hashkes PJ, Shajrawi I. Sarcoid-related uveitis occurring during etanercept therapy. *Clin Exp Rheumatol.* 2003;21:645-646.
38. Diak P, Siegel J, La Grenade L, Choi L, Lemery S, McMahon A. Tumor necrosis factor α blockers and malignancy in children. *Arthritis Rheum.* 2010;62(8):2517-24.
39. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor α -neutralizing agent. *N Engl J Med.* 2001;345:1098-04.