Live vaccinations for infants exposed to maternal infliximab in utero and via breast milk – the need for nuanced decision making

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Infant health outcomes are a key consideration in decisions regarding therapy for pregnant and breast-feeding women with inflammatory bowel disease (IBD). A recent study by Kanis *et al* reported outcomes from 1000 children born to mothers with IBD (196 exposed to anti-TNFs) with no increased risk of adverse outcomes associated with anti-TNF exposure.[1] Anti-TNF therapy should be continued through all trimesters to avoid maternal flares and consequent adverse fetal outcomes.[2 3] Discontinuation in the third trimester is not associated with a decrease in infant infection risks.[2] As the infant will be exposed to anti-TNF by active placental transfer, live vaccinations for the infant should be delayed to avoid potentially fatal infant outcomes.[3]

The Medicines and Healthcare products Regulatory Agency (MHRA) and European Medicines Agency (EMA) have recently issued guidance for infants exposed to Infliximab in utero and by breast feeding.[4] They recommend that infants exposed to Infliximab in utero should not receive live vaccinations until 12 months of age.[4] As clearance of Infliximab from the infant's blood stream occurs after a mean of 7 months and may take 12 months, this is logical and is reflected in the new European Crohns and Colitis Organisation (ECCO) guidelines.[3 5] The second recommendation is that live vaccinations should be avoided in infant exposed to Infliximab through breast milk.[4] While Infliximab has been detected in breast milk in small amounts, there is no credible evidence that this leads to clinically significant serum levels in infants.[6] In the few cases where levels were reported in infants, most had in utero exposure. Additionally, even when these drugs are ingested by the baby, they are inactivated by digestive enzymes and poorly absorbed, making exposure less relevant.[7] In light of the very limited but mainly reassuring evidence we take issue with this blanket recommendation.

Breast feeding has significant benefits from excellent nutrition to potential reductions in childhood infections, and (in women without IBD), a reduced risk of the infant developing IBD.[1 8] Despite this, breastfeeding rates are low in anti-TNF exposed mothers.[1] For most women on Infliximab breast feeding their infant, the impact of the new MHRA and EMA guidance should be limited. Although previous guidance advocated delaying live vaccinations for at least 6 months[9] and a meta-analysis showed that adverse events from vaccination only occurred when these were given during first 6 months of life,[10] the MHRA recommendation to delay live vaccinations to 12 months aims to maintain safety. This is now supported by the newest ECCO guidelines on reproduction and lactation.[3] The main vaccines affected by this are rotavirus (at 8 and 12 weeks) and BCG (4 weeks in high-risk groups) vaccines. However, the first dose of the Measle Mumps Rubella vaccine is given at 12 months.

There are two important scenarios that we feel need careful consideration. First, in cases of in utero exposure and breast feeding for longer than 12 months, should we continue to avoid BCG vaccine in high risk groups? The risk of the infant developing tuberculosis post BCG vaccination associated with breast milk infliximab exposure is probably extremely low. Second, in women without Infliximab exposure during pregnancy, and when Infliximab is started post-partum while breast feeding, the risk would seem similarly low.

In the absence of credible evidence supporting infection risk and adverse events in breast-fed infants of mothers treated with infliximab, the consequences of breast-fed infants not receiving scheduled live vaccines beyond 12 months, or indeed mothers choosing not to breast feed as a result, mandates careful consideration and a nuanced approach. Especially for infants at high-risk of developing tuberculosis if not vaccinated a balanced approach is required as earlier vaccination protect better from acquiring TB through community exposure.

We are surprised that the MHRA and EMA have issued guidance only on Infliximab when similar considerations may be applied to Adalimumab and Golimumab therapy.

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While Adalimumab may clear earlier from the infant's blood stream after in utero exposure than Infliximab, we feel that the principal safety issues are very similar and clear guidance should be applied to the class of anti-TNF medications used.[5] The new ECCO guidelines therefore have a simple unified message for all anti-TNF medications and recommend a delay of all live vaccinations for 1 year.[3] We caution against a "one size fits all" approach and suggest that, IBD and obstetric teams continue to provide well-considered and evidence based advice on effects of maternal IBD medication on suitability of childhood vaccinations. Clinicians need to weight the risk of vaccination against the risk of acquiring TB through community exposure without discouraging women from breast feeding.

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