A systematic review of live vaccine outcomes in infants exposed to biologic disease modifying anti-rheumatic medications (DMARDs) in-utero

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Word count: 1615 excluding abstract and table, 2147 with table included

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ABSTRACT:

Objectives: Transplacental passage of certain biologic- and targeted synthetic DMARDs lead to detectable levels in the neonate which may impact on the safety of live vaccines. Guidelines advise delaying live vaccine administration in biologic exposed infants until they are 7 months old.

Methods: A systematic review of Embase, Medline and Cochrane identified live vaccine outcomes in infants exposed to biologic or targeted synthetic DMARDs in-utero.

Results: Studies included 276 in-utero exposures to adalimumab, certolizumab, etanercept, infliximab, golimumab, tocilizumab and ustekinumab. Live vaccine exposures <12 months of age included BCG (n=215), rotavirus (n=46) and MMR (n=12). We identified no reactions following MMR, 7 mild reactions to rotavirus vaccination, and 8 reactions to BCG including one death. All infants with an adverse reaction to BCG had been exposed to infliximab in-utero, and 6 had received BCG in the first month of life. A freedom of information request to the Medicines and Healthcare products Regulatory Agency revealed 4 fatal disseminated BCG infections in infants exposed to TNF inhibitors in-utero, including infliximab, adalimumab and one unspecified TNF inhibitor.

Conclusion: Most evidence for clinically harmful effect was for early administration of the BCG vaccine to infants exposed in-utero to TNF inhibitors with high transplacental transfer rates.

Key words: Pregnancy and rheumatic disease, biological therapies, rheumatoid arthritis, DMARDs, immunosuppressants

Key messages:

1. In-utero bDMARD exposure can cause detectable newborn drug levels and make live vaccination unsafe
2. BCG vaccination should be delayed following exposure in 2nd/3rd trimester to TNFis with significant transplacental transfer
3. No adverse events following rotavirus vaccination in bDMARD exposed infants have been reported

Introduction:

There is a concern for the safety of live vaccine administration in infants exposed to biologic disease modifying anti-rheumatic drugs (bDMARDs) in-utero. British Society for Rheumatology (BSR) guidance states that live vaccines should be avoided until 7 months of age in these infants [1].

Vaccination schedules in the United Kingdom (UK) are dictated by The Green Book – a document produced and updated by the Department of Health and Public Health England [2]. Restricting live vaccines until 7 months of age primarily impacts on the rotavirus vaccine, which is given at 8 and 12 weeks of age and cannot be started after 15 weeks of age due to an association between rotavirus vaccination and intussusception in older infants [3]. In the UK, Bacille Calmette Guérin (BCG) is only offered to high-risk populations (e.g. those born in or with parents born in a place with a high incidence of mycobacterium tuberculosis). BCG can be given at any time but is preferably given in early life to protect against the most severe forms of the disease (e.g. tuberculous meningitis). The measles, mumps and rubella (MMR) vaccine, usually given first at 12 months, may be given earlier in local outbreaks or travel to an endemic area.

Advice to avoid live vaccines in infants after in-utero bDMARD exposure is heavily influenced by the known placental transfer of many bDMARDs and a fatal case of disseminated BCG in a 4-month-old infant who received BCG at 3 months following in-utero exposure to infliximab throughout pregnancy [4]. Currently, the only way to avoid these restrictions is to discontinue bDMARD in the 2nd or early 3rd trimester, several half-lives prior to delivery to limit transplacental passage. This approach has been validated in a study demonstrating that adherence to European League Against Rheumatism (EULAR) recommendations for timing of Tumor Necrosis Factor inhibitor (TNFi) discontinuation in pregnancy results in absent or low cord blood levels of TNFi [5].

Whilst there is limited information on breastfeeding on bDMARDs, a permissive approach is taken by most guidelines given that minimal transfer to the infant is expected due to their large molecular size and predominantly IgG rather than IgA structure [6]. Oral intake via breastmilk is also likely to be ineffective due to destruction of the bDMARD protein in the acidic environment of the infant stomach. Consequently, no restrictions on live vaccination are advised based on breastfeeding exposure alone in The Green Book [7].

It is not known whether all bDMARDs that cross the placenta pose equal risks for all live vaccines. Therefore, we completed the first systematic review of live vaccine outcomes in infants exposed to bDMARDs and targeted-synthetic (ts)DMARDs in-utero – with a focus on those biologic agents routinely used in rheumatological practice.

Methods:

In June 2021 we searched Embase, Medline and Cochrane databases for English language papers meeting our search criteria using a combination of pregnancy, vaccination and medication related terms (see supplementary data S1). We excluded reviews containing no original data or conference abstracts. Additional studies were identified through searching the reference lists of other articles and where necessary, original authors were contacted for further information. Papers identified by the searches were evenly allocated to 3 independent reviewers, then each cross-checked by a second reviewer. Studies were assessed according to Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. Data was extracted using an Excel proforma.

We also made a Freedom of Information request to the UK's Medicines and Healthcare products Regulatory Agency (MHRA) for reported fatal reactions to BCG vaccination after in-utero exposure to TNFi.

Results:

Initially 266 unique papers were identified, 43 full text papers were reviewed and 10 studies [4,8–16] included in the final analysis of 276 infant exposures to live vaccines after in-utero bDMARD use. No tsDMARD exposures were identified. Findings are summarised in Table 1.

A total of 215 infants received the BCG vaccine. One death was recorded alongside 7 adverse reactions - 2 cases of injection site swelling with axillary lymphadenopathy, 4 cases of injection site swelling and 1 case of axillary lymphadenopathy alone. The death occurred in an infant exposed to infliximab in the 3rd trimester (exact date unspecified) who received the BCG vaccine at 3 months of age. In those who experienced adverse reactions, 6/7 had received BCG vaccination <1 month of age and 7/7 were exposed to infliximab in-utero. The last in-utero exposure to infliximab was at 27 weeks, 28 weeks and 31 weeks of gestation in 3 cases and in the remainder, it was not possible to ascertain the date. All of the adverse reactions resolved without the need for anti-tuberculous therapy. The Freedom of Information request to the MHRA identified a further 4 fatal reports of BCG infection in neonates after in-utero exposure to TNFi – 2 had been exposed to infliximab, 1 to adalimumab, and 1 to an unspecified TNFi. No further information about these cases was available.

Rotavirus vaccine was administered to 46 infants after in utero exposure to adalimumab, certolizumab, infliximab, tocilizumab, or ustekinumab. Only one study reported adverse events – 6 cases of fever and 1 case of diarrhoea. These adverse events occurred following exposure to infliximab in 6 cases and adalimumab in 1 case, and were considered mild events occurring at a rate similar to that expected in the general population. It was not possible to ascertain the last date of biologic exposure in these cases.

Of the remaining infants, 12 received MMR at 6-9 months and 3 at <6 months of age. No adverse events were reported. It was not possible to ascertain the exact bDMARD or timing of last in-utero exposure in these cases.

Discussion:

We found no concerning adverse events from rotavirus vaccination or a small number of early MMR vaccinations in infants exposed to various bDMARDs. The BCG vaccine however remains a concern, with most evidence of harm in infants exposed in-utero to TNFis with high rates of transplacental transfer and in whom the vaccine was administered early (ie: ≤3 months). Most studies were

Study	Biologic	Indication for biologic	Timing & number of drug exposure in 3rd trimester	Timing and number of infant vaccinations	Adverse events	Grade of evidence
Bortlik et al, 2014[8]	IFX	IBD	Last exposure (mean) 23 weeks gestation	BCG: 15; all <1 month	3 large local reactions, 1 axillary lymphadenopathy; all resolved without anti-tuberculous therapy	Low
Cheent et al, 2010[4]	IFX	IBD	Last exposure in 3rd trimester	BCG: 1; 3 months	Infant death secondary to disseminated BCG	Very low
Lee KE et al, 2019[9]	ADA, IFX	IBD	Last exposure (mean) 30 weeks gestation	BCG: 12; 4 received at 1 month, 5 at 6 months, 2 at 7 months, and 1 at 8 months RV: 4; <4 months	Nil recorded	Low
Luu M et al, 2019[10]	ADA, CTZ, GOL, IFX	IBD	61.5% of population as a whole exposed in 3rd trimester; 25 infants received BCG <6 months exposed to TNFi throughout pregnancy	BCG: 88; mean 4.3 months MMR: 15 early receivers; 12 at 6-9 months, 3 at <6 months	Nil recorded	Low
Saito J et al, 2018[11]	TOC IV, ETA	RA	Case 1: TOC to 5 weeks, ETA: until 34 weeks gestation* Case 2: TOC to 2 weeks gestation	BCG: 2; 6 months RV: 1; <4 months	Nil recorded	Very low
Beaulieu DB et al, 2018[12]	ADA, CTZ, IFX, UST	IBD	Unable to ascertain*	RV: 40; 2, 4, and 6 months	6 fever (1 ADA, 5 IFX), 1 diarrhoea (IFX); all mild events at similar rate to general population	Very low
Tada Y et al, 2019[13]	TOC SC	RA	Last exposure in 3rd trimester	BCG: 1; 7 months	Nil recorded	Very low
Kobaner GB et al, 2020[14]	ADA, ETA, IFX, UST	Ps	2 infants exposed in 3rd trimester (1 to ADA, 1 to IFX)	BCG: 6; 2 months in 5/6 infants	Nil recorded	Very low
Prieto-Peña D et al, 2021[15]	CTZ	Uveitis	Last exposure in 3rd trimester	RV: 1; 2, 4, and 6 months	Nil recorded	Very low
Park SH et al, 2020[16]	ADA, IFX	IBD	55 infants exposed in 3rd trimester	BCG: 90; median 6 months	2 swelling of injection site & axillary lymphadenopathy (IFX last given at 27- and 28-weeks' gestation with BCG at 2 weeks of age); 1 swelling of injection site (IFX last given at 31 weeks gestation with BCG at 6 months of age); all resolved without anti-tuberculous therapy	Low
MHRA reports	ADA, IFX, unspecified TNFi	Not specified	Not specified	BCG: 4	4 deaths secondary to disseminated BCG; 2 exposed to IFX, 1 to ADA and 1 to an unspecified TNFi	N/a

Table 1 Summary of outcomes following live vaccination of infants exposed to biological drugs in-utero

Key: ADA = adalimumab, BCG = bacille calmette-guérin CTZ = certolizumab, ETA = etanercept, GOL = golimumab, IBD = inflammatory bowel disease, IFX = infliximab, IV = intravenous, MHRA = Medicines and Healthcare products Regulatory Agency, MMR = measles, mumps and rubella (cases with administration before 9 months of age included), N/a = not applicable, Ps = psoriasis, RA = rheumatoid arthritis, RTX = rituximab, RV = rotavirus vaccine, SC = subcutaneous, TNFi = Tumor

Necrosis Factor α inhibitor, TOC = tocilizumab, UST = ustekinumab; * = additional information sourced from author

reporting outcomes in women with underlying inflammatory bowel disease, so the majority of exposures were to adalimumab and infliximab, with little data available for other bDMARDs and none for tsDMARDs.

Many bDMARDs have an IgG structure, and thus undergo negligible passive diffusion across the placenta until 13-16 weeks gestation. After this time, active transport via pinocytosis is mediated by the neonatal Fc receptor (FcRn) expressed on the syncitiotrophoblast[17]. bDMARDs vary in the efficacy of transplacental transfer, dependent on their exact molecular structure. Complete IgG1 molecules such as infliximab, adalimumab and golimumab are known to have high rates of passage in the 2nd and 3rd trimester leading to high drug levels in cord and newborn blood samples. Fusion proteins (i.e. etanercept) or those lacking the Fc segment (i.e. certolizumab) are transferred less efficiently with very low or negligible levels detected in the newborn[18]. Immature hepato-splenic clearance systems also mean that bDMARDs may persist in infant blood beyond the half-life expected in adults, with infliximab detectable up to 12 months of age[19].

Rotavirus infection causes gastroenteritis with fever, diarrhoea and abdominal cramps, occasionally leading to hospitalisation and rarely, death secondary to dehydration [3]. Introduction of Rotarix® to the UK vaccination schedule in 2013 lead to an 80% reduction in reported cases within 3 years [20]. Common vaccine side-effects include diarrhoea, irritability and fever, as reported in 6/46 infants in our review.

Side-effects are also frequently seen following BCG vaccination, even in immunocompetent infants. Induration and papule formation is an expected reaction seen in the majority of BCG recipients and is sometimes associated with small volume regional lymphadenopathy (<1cm), or more rarely with large volume and/or suppurative lymphadenitis [21,22]. Healing may take weeks or months. As such, the adverse reactions identified in 7/215 infants in our review are not alone necessarily indicative of a bDMARD related immunosuppressed state. However, in addition to one death identified in the systematic review, a further four cases of fatal disseminated BCG infection following in-utero exposure to TNFi were identified from the MHRA. Alongside the primary role of TNFα in the immunological response to mycobacterial infection, there is a clear rationale to continuing to avoid early administration of BCG to bDMARD exposed infants. This approach is particularly important for infants exposed to a TNFis with high rate of transplacental transfer such as infliximab and adalimumab in the 2nd/3rd trimester.

Limitations of our study include the small numbers of cases and the heterogeneity of the included studies. Many papers lacked clear data about the timing of last biologic exposure in-utero, and occasionally, on the exact biologic agent administered. Data from the MHRA in particular is limited to medication (or medication class) and the presumed adverse event – they do not independently verify the cause of death or include details about timing of gestational exposure or vaccine administration.

Whilst current guidelines adopt a restrictive approach to vaccination in bDMARD exposed infants, infants vary in their susceptibility to infection (e.g. prematurity, local tuberculosis rates) and bDMARDs in their individual risk profile (e.g. dependent on molecular structure, dosing strategy and mechanism of action). Therefore, a more personalised approach considering the available data for each bDMARD in relation to each live vaccine, individual infant risks, and population level incidence of the disease being vaccinated against may be more appropriate to avoid withholding all live vaccines from vulnerable infants. Testing the infant's biologic drug level prior to administration of a vaccine to confirm clearance or low titres is also an option, but few laboratories offer this testing for bDMARDs apart from for infliximab and adalimumab. Ongoing caution however, is recommended in the early administration (eg: ≤3 months) of the BCG vaccine to infants exposed in-utero to TNFis with high rates of transplacental transfer in the $2^{nd}/3^{rd}$ trimester.

Acknowledgements: Nil

Competing interests: Competing interests statements: None declared for BG, NC, EP; IG unrestricted research grant funding from UCB pharma, speaker fees from UCB pharma (paid into local research charity) and lead on British Society for Rheumatology Working Group on prescribing anti-rheumatic drugs in pregnancy

Data availability statement: The data underlying this article are available in the article and in its online supplementary material.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

PPI statement: Engagement with the UCL Patient Partners in Rheumatology Research network confirmed the relevance and importance of this research topic to patients and they will be involved in dissemination of results to other organisations.

Ethics: This study does not involve human participants.

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