DOI: 10.1111/apt.15559

Editorial: how safe is it to administer the BCG vaccination to babies exposed to anti-TNFα medications antenatally? Authors' reply

In their editorial accompanying our study,[1,2] Sonia Bouri and Ailsa Hart correctly underlined that our data were collected prior to the European and Toronto recommendations enforcement, which may in their opinion explain the low level (27%) of adherence to the recommendations to postpone live vaccines until after 6 months of age. However, non-adherence to guidelines still needs to be considered. Indeed, French guidelines on the use of anti-tumor necrosis factor α (anti-TNFα) agents use during pregnancy, endorsed by the French National Authority of Health, had already been issued in 2013, the starting year for our data collection.[3] This assumption is further supported by the results of a French cohort of 143 pregnant women with IBD enrolled between 2016 and 2017, all receiving anti-TNFα. Among the 33 babies who received bacillus calmette guerin (BCG) vaccination, 19 of them (55.7%) did so before 6 months of age.[4] Even in this prospective cohort, anti-TNFα blood levels were not monitored after birth, as it had not become standard practice. This persistent low rate of adherence to recommendations despite the existence of current guidelines stresses the need for a better dissemination strategy of guidelines, targeting all physicians including general practicioners.

The report of a fatal disseminated BCG infection post-vaccination[5] warranted the initial precautionary approach in 2015, based on theoretical immunosuppression in this population. However, this position is brought into question by the Rezai study,[6] in which 40% (6/15) of children admitted for disseminated mycobacterial disease were immunocompetent. A recent study in children born to mothers with IBD and exposed to anti-TNFα *in utero* showed adequate immune serologic responses.[7]

The suggestion of postponing live vaccine even up to 1 year of age is based on a single case of a detectable very-low anti-TNFα plasma level (0.03 mg/mL) of unknown immunological significance in a baby with *in utero* exposure.[8] This evidence may not be strong enough to warrant exposing children to avoidable infections, especially tuberculosis, when they are at high susceptibility.

Several authors have favoured an individualised medicine approach for pregnant women with IBD[9] with 'case-by-case' management on whether to administer live vaccines to their children.[10] Similarly, our results combined with the changing and worrying landscape of tuberculosis epidemiology suggest weighing the individual risk-benefit ratio of early vaccination against BCG before 6 months of age. We and others would favour such an approach until another strategy (possibly in the form of monitoring of anti-TNFα clearance in children) proves to be of greater benefit. Alternatively, subsequent confirmation of our conclusions based on longer follow-up and increased number of pregnancies monitored may provide reassurance. The EVASION cohort, which will be enriched with subsequent years data, should enhance the statistical power of existing results.

ACKNOWLEDGEMENT

The authors' declarations of personal and financial interests are unchanged from those in the original article.[2]

LINKED CONTENT

This article is linked to Luu et al and Bouri and Hart papers. To view these articles, visit https://doi.org/10.1111/apt.15504 and https://doi.org/10.1111/apt.15535.

Maxime Luu[1,2]
Eric Benzenine[3]
Alan Barkun[4]
Muriel Doret[5]
Christophe Michiels[6]
Thibault Degand[6]
Catherine Quantin[3,7]
Marc Bardou[1,2]

[1]*Plurithematic Unit, INSERM, CIC1432, Dijon, France*
[2]*Plurithematic Unit, Clinical Investigation Center, Dijon-Bourgogne University Hospital, Dijon, France*
[3]*Biostatistics and Bioinformatics Department, Dijon Bourgogne University Hospital, Dijon, France*
[4]*The McGill University Health Centre, Montreal General Hospital, McGill University, Montreal, Canada*
[5]*Service de Gynécologie Obstétrique, Hospices Civils de Lyon, Hôpital Femme-Mère-Enfant, Bron, France*
[6]*Division of Gastroenterology, Dijon Bourgogne University Hospital, Dijon, France*
[7]*INSERM, Biostatistics, Biomathematics, Pharmacoepidemiology and Infectious Diseases (B2PHI), UVSQ, Institut Pasteur, Université Paris-Saclay, Paris, France*
Email: maxime.luu@chu-dijon.fr

ORCID

Maxime Luu https://orcid.org/0000-0002-9024-293X
Alan Barkun https://orcid.org/0000-0002-1798-5526

REFERENCES

1. Bouri S, Hart AL. Editorial: how safe is it to administer the BCG vaccination to babies exposed to anti-TNFα medications antenatally? *Aliment Pharmacol Ther*. 2019;50:1247.
2. Luu M, Benzenine E, Barkun A, et al. Safety of first year vaccines in children born to mothers with inflammatory bowel disease and exposed in utero to anti-TNFα: a French nationwide population-based cohort. *Aliment Pharmacol Ther*. 2019;50:1189-1196.
3. Goeb V, Ardizzone M, Arnaud L, et al. Recommendations for using TNF-alpha antagonists and French Clinical Practice Guidelines endorsed by the French National Authority for Health. *Joint Bone Spine*. 2013;80:574-581.
4. Bendaoud S, Nahon S, Gornet J -M, et al. Live-vaccines and lactation in newborn exposed in utero to anti-TNF: A multi-centre French experience in inflammatory bowel disease. *J Crohns Colitis*. 2018;12(Suppl 1):S527.
5. Cheent K, Nolan J, Shariq S, Kiho L, Pal A, Arnold J. 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):603-605.
6. Rezai MS, Khotaei G, Mamishi S, Kheirkhah M, Parvaneh N. Disseminated Bacillus Calmette-Guerin infection after BCG vaccination. *J Trop Pediatr*. 2008;54(6):413-416.
7. de Lima A, Kanis SL, Escher JC, et al. Hepatitis B vaccination effective in children exposed to anti-tumour necrosis factor alpha in utero. *J Crohns Colitis*. 2018;12:948-953.
8. Julsgaard M, Christensen LA, Gibson PR, et al. Concentrations of adalimumab and infliximab in mothers and newborns, and effects on infection. *Gastroenterology*. 2016;151:110-119.
9. van der Woude CJ, Kanis SL. IBD: Exposure to anti-TNF agents in utero: controlling health risks. *Nat Rev Gastroenterol Hepatol*. 2016;13(7):387-388.
10. Kathpalia P, Kane S, Mahadevan U. Detectable drug levels in infants exposed to biologics: so what? *Gastroenterology*. 2016;151(1):25-26.

DOI: 10.1111/apt.15534

Editorial: effect of exercise on physical frailty in patients with chronic liver disease

The impact of physical frailty on outcomes in patients with chronic liver disease has been increasingly recognised in recent years. In patients with decompensated cirrhosis waiting for transplant, the degree of frailty and sarcopenia clearly worsen survival.[1] In fact, survival prediction is enhanced with the addition of the frailty index or sarcopenia to the MELD Na score.[1] There is a need to critically evaluate interventions that could safely improve physical function and survival in this complex patient population.

Williams *et al* recently provided a welcome addition to the literature in this area.[2] They comprehensively reviewed the available literature on the effect of exercise on physical frailty in patients with chronic liver disease and developed recommendations through synthesis of the literature. Interventions in compensated cirrhosis, decompensated cirrhosis and liver transplant recipients were reviewed separately. There was heterogeneity in the frequency, intensity and type of exercise programmes among the studies analysed. Despite this heterogeneity, this review provided the clinically helpful take-home point that moderate-to-high intensity exercise involving aerobic and/or resistance training results in improvements in frailty and quality of life.

Overall, the studies demonstrated improved aerobic capacity and muscle mass in the exercise intervention groups.[3,4] Improved VO_2 peaks were shown in supervised aerobic sessions,[5,6] although these did not reach the peaks associated with quantifiable improvements in survival seen in cardiovascular disease.[7] Barriers to reaching these peaks may include the severe fatigue, encephalopathy, fluid overload and profound sarcopenia of many cirrhotic patients as their illness progresses. Additional factors such as psycho-behavioural motivation and nutrition go hand-in-hand with the ability to incorporate exercise. However, even cost-effective, easily accessible forms of aerobic exercise such as walking have been shown to improve performance on the 6-minute walk test.[8,9] Therefore, exercise interventions such as walking could be recommended by physicians to patients with chronic liver disease, particularly in healthcare settings where costly exercise equipment might be cost-prohibitive. The authors recommended combining aerobic and resistance exercise to optimise aerobic capacity and muscle mass, and an exercise programme that is a minimum of 12 weeks in duration to achieve demonstrable results.

Certain limitations of the studies available for review must be acknowledged. Patient age and aetiology and severity of chronic liver disease are likely to have an impact on the ability of a patient to achieve optimal aerobic capacity. For example, a 67-year-old cirrhotic patient with non-alcoholic fatty liver disease (and accompanying comorbidities such as diabetes, obesity and coronary artery disease) is likely to have a different exercise tolerance than a 30-year-old cirrhotic patient with primary sclerosing cholangitis and no other comorbidities.