



Questions on Immunization and Vaccination and Short Answers

Bağışıklama ve Aşı ile İlgili Sorular ve Kısa Cevaplar

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We wanted to address frequently asked questions about immunization related to biologic response modifying agents, which have been used more frequently in recent years, in this question-and-answer section;

Question 1: Can patients using biologic response modulators be vaccinated?

Two main factors should be evaluated when planning vaccination in people who using biologic response modifiers;

- The first is the necessity of vaccination of the clinical picture that requires the use of biologic response modifiers, the possible negative impact on vaccine response, and possible contraindications and complications that the vaccine may cause,

- The second is the need for vaccination that may be caused by the biological agent planned to be used and the contraindication to vaccination and the onset time of this contraindication,

It is recommended that the age and disease status of individuals with a new diagnosis of immune-mediated disease requiring biological response modifying treatment should be evaluated and appropriate vaccination should be completed before starting immunosuppressive treatment if there is no contraindication (1,2).

For optimum immune response, it is emphasized that inactivated vaccines should be completed two weeks before the start of immunosuppressive treatment, if possible; and since no clear time period has been determined for live attenuated vaccines, it should be administered considering the viremia period following vaccination (2).

Question 2: Can babies whose mothers used biologic response modulating agents during pregnancy be vaccinated?

In the passage of biologic agents to the infant, the time period of passive diffusion through the placenta can be neglected until the 13-16th week of pregnancy. However, after these weeks, pinocytosis-mediated active transport via Fc receptors on syncytiotrophoblasts begins and complex IgG1 molecules (infliximab, adalimumab and golimumab...) are highly transmitted to the infant. Fusion proteins such as etanercept or molecules without Fc segments such as sertolizumab pass at a very low or negligible level (4,5).

It has been reported in many studies that infants whose mothers use biological response modulators during pregnancy and who are exposed to these agents through the placenta have detectable drug concentrations in the months after birth, and that the measured values may cause immu-

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nosuppression in the first six months, eight months and even in the 12th month of the baby's life (6). The reason for this is that drug half-lives in infants are longer than in mothers (3.7 times for infliximab and two times for adalimumab) (7).

In the recently published European Chron's disease and colitis pregnancy guideline, it has been emphasized that live attenuated vaccines should be postponed until after the 12th month or until there is no detectable drug in the blood in infants whose mothers use biological response modifying agents (8).

Data flow is increasing with the studies conducted, and there are also recommendations from different authorities that vaccination can be safe earlier. Many different organizations such as European and American guidelines, the British Society of Rheumatology and the French Teratogenic Agent Center have reported that live vaccines can be administered after the sixth month (9-13). The Toronto consensus for inflammatory bowel diseases in pregnancy supported low-quality evidence and strong recommendation against live vaccination in the first six months unless serum drug levels are undetectable. Again, in this source, it is stated that vaccination can be performed by checking serum TNF-alpha levels in children who have recently traveled to a risky area, lived in a risky area, or will be exposed to tuberculosis (11).

In the opinions given for the vaccination of infants exposed to immunosuppressive agents in utero in the third trimester, it was supported that inactivated vaccines should be administered in accordance with immunization calendars, and measles-mumps-rubella (MMR) and varicella vaccines should be administered in accordance with local calendars since they are recommended at the age of one year in immunization calendars (2).

It has been reported that there is no obstacle in immunization of breastfed infants whose mothers are receiving immunosuppressive treatment with inactivated or live attenuated vaccines (2,14).

Question 3: Does an adequate response develop when infants whose mothers use biologic response modifying agents during pregnancy are vaccinated?

In this special patient group, the feasibility of vaccines as well as their level of protection has been a matter of curiosity. Bortlik et al. evaluated serologic responses to tetanus, pneumococcal, diphtheria, rubella, measles and mumps vaccines in 60% of 25 infants who were exposed to biological agents in intrauterine life and found that detectable antibodies developed in all children and that antibodies developed against H influenzae type b (Hib) were below the protective threshold in only six children (15).

In a study conducted by Dawn et al., infants of mothers who used biological agents and infants of mothers who did

not use biological agents were compared in terms of tetanus and Hib vaccine antibody responses, and no significant difference was found. In the same study, babies exposed to biologic agents were grouped according to blood biologic agent levels and compared within themselves and again no significant difference was found (16). Although no difference was found, it was emphasized that antibody responses were below the values reported up to that day.

Similarly, Wieringa et al. revealed lower protective levels in pneumococcal antibody responses in addition to Hib antibody responses (17). In this study, TNF-alpha levels in blood samples obtained at birth were compared with pneumococcal serotypes and a significant correlation was found between TNF-alpha levels and the response measured against serotype 19F. In the same years, Duricova et al. reported that they could not detect antibodies at a protective level in children vaccinated against mumps and Hib (18). In a meta-analysis by Barenbrug et al., it was reported that adequate immune responses were measured for pneumococcus, diphtheria, rubella, measles, and hepatitis B (19).

In 2023, Gispert and Chaparro wrote a review on antibody responses developed with hepatitis B, Hib, tetanus, diphtheria, and pneumococcal vaccines and concluded that adequate protective antibodies developed (6). It was stated that the MMR vaccine efficacy, which was thought to have inadequate response in previous years, was up to 100% and the efficacies of rotavirus and BCG vaccines could not be evaluated. A clear link between blood levels and vaccine antibody response has not been shown and Liu et al. reported that vaccine antibody responses may be variable even if TNF-alpha is not detected in the blood (20). It was concluded that the immune systems of infants exposed to biological agents also play an important role in order to clearly understand the measured antibody levels.

Question 4: Can MMR and varicella vaccine be administered to infants whose mothers used biologic response modifying agents during pregnancy?

There is no harm in administering the MMR and varicella vaccines, which are recommended to be administered at the 12th month in national vaccination calendars, in a timely manner.

In case of an outbreak or travel to risky areas, immunoglobulin can be administered to babies younger than six months, and MMR vaccine or immunoglobulin can be administered to babies between 6-12 months, considering the risk situation and the balance of benefit and harm to be provided. (3)

Luu et al. evaluated 670 infants exposed to anti TNF-alpha treatment during pregnancy and reported that 552 infants were vaccinated with MMR; 12 of these infants were younger than nine months and three were younger than six months and no serious infection due to MMR was found (9).

Again, in a recently published review, five studies evaluating adverse effects after MMR vaccination were evaluated and it was reported that no adverse effect was found except for the minor adverse effects found by Julsgaard et al (6,21).

Question 5: Can BCG vaccine be administered to infants whose mothers used biologic response modifiers during pregnancy?

Since it is not recommended -contraindicated- to administer live vaccine to infants whose mothers are using biologic response modifiers, it is recommended not to administer the BCG vaccine which is administered in the 2nd month in our vaccination schedule. There are different opinions about the optimal time to administer BCG vaccine, which is not recommended in the first six months by different guidelines. The reason for the different opinions was a baby who was exposed to a biological agent in utero and died due to disseminated tuberculosis after BCG vaccine administered in the postnatal 3rd month, which was added to the literature for the first time in 2010 (22). In 2014, 15 infants who were exposed to infliximab in utero and who received BCG vaccine in the first one week of life were followed up, a large local reaction was reported in three and the presence of axillary lymphadenopathy with a large local reaction was reported in one. Spontaneous resolution was observed without anti-tuberculosis treatment in these babies in whom no serious complication developed (15). Duricova et al. also followed up 15 infants with in utero anti TNF-alpha exposure who were also administered BCG vaccine in the first week of life and reported extensive local skin reaction in four infants and axillary lymphadenopathy in one of them (18). However, in a study conducted by Luu et al. in the same years, it was also revealed that 13% of 670 infants with anti TNF-alpha exposure were vaccinated with BCG vaccine (38% of vaccinated infants experienced exposure during the entire gestational period), 73% of vaccinated infants were vaccinated before six months of age and no complications developed in any infant (9).

In a 2020 study by Park and colleagues, 35 infants exposed to anti TNF-alpha treatment for two trimesters and 55 infants exposed for three trimesters were examined. In the first group, 22 infants were vaccinated within the first month of life, one infant had axillary lymphadenopathy, and no reaction was observed in infants vaccinated after one month. In the second group, nine infants were vaccinated within the first month of life and axillary lymphadenopathy was detected in one infant. Local reaction was observed in one of 39 babies in the second group who were vaccinated between one and six months of age, and no adverse effect was reported in babies vaccinated older than six months of age (23). Based on these results, they concluded that there should not be any reservation even if biological agent blood level test cannot be performed for the

patient group in whom vaccination between 6-12 months is necessary.

While positive data were obtained in terms of reliability, a systematic review conducted by Goulden et al. in 2022 called reliability into question. In 276 infants with biological agent exposure who were vaccinated with BCG vaccine, adverse effects were detected in seven infants, two of whom had local reactions with axillary lymphadenopathy, four had local reactions and one had axillary lymphadenopathy. In addition to the first case lost in this study, it was also presented to the literature that there were four more mortal cases reported until 2022 (24).

Question 6: Can rotavirus vaccine be administered to infants whose mothers used biologic response modulating agents during pregnancy?

Data on the safety of rotavirus vaccines in infants exposed to biologic agent treatments during pregnancy are scarce.

In general, it is preferred not to administer rotavirus vaccine when biologic response modifying agents are used during pregnancy. However, although it is also stated that sertolizumab, which does not pass through the placenta due to its pegylated Fab fragment structure, may be considered an exception, there is no clear recommendation for the use of this agent (3). In general, country guidelines still state that vaccine administration is more reliable after it is proven that there is no detectable drug in the blood (13).

In a study organized by Dawn et al., rotavirus vaccine was administered to 40 of 153 infants of mothers exposed to biological agents and fever was observed in six patients and diarrhea was observed in one patient (16). No relationship was found between adverse effects and drug blood levels. When the observed effects were compared with the side effects recorded by Vesikari and his group in the general population after rotavirus vaccination, no difference was found (25).

A study by Chiarella-Redfern et al. revealed that contrary to the guidelines, babies exposed to biological agents could be vaccinated with rotavirus vaccine, but there was no significant difference between hospital admissions due to gastroenteritis between vaccinated babies exposed to biological agents and babies who were not exposed to biological agents and who were not vaccinated with rotavirus vaccine, raising questions about the effectiveness of the vaccine (1).

In a recent review, eight studies on rotavirus were examined, and it was observed that adverse reactions were also addressed in three of these studies (6). No serious adverse effect was found in all three studies, and in the study by Beaulieu et al., it was reported that mild reactions were observed in 17% and this rate did not differ from the general population (16).

Question 7: Can OPA vaccine be administered to infants whose mothers are on biologic response modifying agents after birth?

It is not recommended to administer oral polio vaccine to infants whose mothers are using biological response modifying agents after birth because they are in contact with immunosuppressive individuals.

It is recommended to use inactivated poliovirus vaccine in the vaccination process of infants living in the same environment with patients in this risk group (26).

Question 8: What are the vaccination recommendations for those whose mothers used sertolizumab during pregnancy?

It is stated that sertolizumab, which does not carry an Fc region, can be used safely throughout pregnancy with its limited placental transmission feature.

In a study by Mahadevan et al., it was also shown that there was no sertolizumab in infant or cord blood (27). In another study by Mahadevan et al., it was emphasized that blood levels should not be detectable before rotavirus vaccination (13).

In a study in which 14 pregnant women who used sertolizumab during pregnancy were followed up and 15 healthy babies were born, the babies were followed up for six months and it was reported that the inactive vaccines administered were completely safe. Among live vaccines, rotavirus vaccine was administered to only one baby and no adverse effect was observed (28).

Although sertolizumab is thought to be more reliable than other TNF-alpha inhibitors such as infliximab, adalimumab, etc., it is a fact that there is no clear data on the optimum timing of vaccination and more studies are needed.

References

- Chiarella-Redfern H, Lee S, Jubran B, Sharifi N, Panaccione R, Constantinescu C, et al. Suboptimal vaccination administration in mothers with inflammatory bowel disease and their biologic-exposed infants. *Inflamm Bowel Dis* 2022;28(1):79-86. <https://doi.org/10.1093/ibd/izab033>
- Papp KA, Haraoui B, Kumar D, Marshall JK, Bissonnette R, Bitton A, et al. Vaccination guidelines for patients with immune-mediated disorders on immunosuppressive therapies. *J Cutan Med Surg* 2019;23(1):50-74. <https://doi.org/10.1177/1203475418811335>
- American Academy of Pediatrics. Immunization in Special Clinical Circumstances. In: *Red Book: 2021 Report of the Committee on Infectious Diseases*, 32th, Kimberlin DW (Ed), American Academy of Pediatrics, Itasca, IL 2021. p.82.
- Mariette X, Förger F, Abraham B, Flynn AD, Moltó A, Flipo RM, et al. Lack of placental transfer of certolizumab pegol during pregnancy: Results from CRIB, a prospective, postmarketing, pharmacokinetic study. *Ann Rheum Dis* 2018;77(2):228-33. <https://doi.org/10.1136/annrheumdis-2017-212196>
- Wilcox CR, Holder B, Jones CE. Factors affecting the FcRn-mediated transplacental transfer of antibodies and implications for vaccination in pregnancy. *Front Immunol* 2017;8:1294. <https://doi.org/10.3389/fimmu.2017.01294>
- Gisbert JP, Chaparro M. Vaccines in children exposed to biological agents in utero and/or during breastfeeding: Are they effective and safe? *J Crohns Colitis* 2023;17(6):995-1009. <https://doi.org/10.1093/ecco-jcc/jjad005>
- Julsgaard M, Christensen LA, Gibson PR, Gearry RB, Fallingborg J, Hvas CL, et al. Concentrations of adalimumab and infliximab in mothers and newborns, and effects on infection. *Gastroenterology* 2016;151(1):110-9. <https://doi.org/10.1053/j.gastro.2016.04.002>
- Torres J, Chaparro M, Julsgaard M, Katsanos K, Zelinkova Z, Agrawal M, et al. European Crohn's and Colitis Guidelines on Sexuality, Fertility, Pregnancy, and Lactation. *J Crohns Colitis* 2023;17(1):1-27. <https://doi.org/10.1093/ecco-jcc/jjac115>
- Luu M, Benzenine E, Barkun A, Doret M, Michiels C, Degand T, et al. Safety of first year vaccination in children born to mothers with inflammatory bowel disease and exposed in utero to anti-TNFα agents: A French nationwide population-based cohort. *Aliment Pharmacol Ther* 2019;50(11-12):1181-8. <https://doi.org/10.1111/apt.15504>
- van der Woude CJ, Ardizzone S, Bengtson MB, Fiorino G, Fraser G, Katsanos K, et al. European Crohn's and Colitis Organization. The second European evidenced-based consensus on reproduction and pregnancy in inflammatory bowel disease. *J Crohns Colitis* 2015;9(2):107-24. <https://doi.org/10.1093/ecco-jcc/jju006>
- Nguyen GC, Seow CH, Maxwell C, Huang V, Leung Y, Jones J, et al. IBD in Pregnancy Consensus Group; Canadian Association of Gastroenterology. The Toronto consensus statements for the management of inflammatory bowel disease in pregnancy. *Gastroenterology* 2016;150(3):734-57.e1. <https://doi.org/10.1053/j.gastro.2015.12.003>
- Flint J, Panchal S, Hurrell A, van de Venne M, Gayed M, Schreiber K, et al. BSR and BHPR Standards, Guidelines and Audit Working Group. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: Standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. *Rheumatology (Oxford)*. 2016;55(9):1693-7. <https://doi.org/10.1093/rheumatology/kev404>
- Mahadevan U, Robinson C, Bernasko N, Boland B, Chambers C, Dubinsky M, et al. Inflammatory bowel disease in pregnancy clinical care pathway: A report from the American Gastroenterological Association IBD Parenthood Project Working Group. *Gastroenterology* 2019;156(5):1508-24. <https://doi.org/10.1053/j.gastro.2018.12.022>
- Contraindications and Special Considerations: The Green Book, chapter 6. GOVUK n.d. Available from: <https://www.gov.uk/government/publications/contraindications-and-special-considerations-the-green-book-chapter-6> (Accessed date: 14.09.2023).
- Bortlik M, Duricova D, Machkova N, Kozeluhova J, Kohout P, Hrdlicka L, et al. Impact of anti-tumor necrosis factor alpha antibodies administered to pregnant women with inflammatory bowel disease on long-term outcome of exposed children. *Inflamm Bowel Dis* 2014;20(3):495-501. <https://doi.org/10.1097/01.MIB.0000440984.86659.4f>
- Beaulieu DB, Ananthakrishnan AN, Martin C, Cohen RD, Kane SV, Mahadevan U. Use of biologic therapy by pregnant women with inflammatory bowel disease does not affect infant response to vaccines. *Clin Gastroenterol Hepatol* 2018;16(1):99-105. <https://doi.org/10.1016/j.cgh.2017.08.041>
- Wieringa JW, van Beek RHT, Rövekamp LW, Driessen GJA, van Wering HM. Response to vaccination in infants exposed to antitumor necrosis factor alpha in utero. *Pediatr Infect Dis J* 2021;40(10):912-6. <https://doi.org/10.1097/INF.0000000000003271>

18. Duricova D, Dvorakova E, Hradsky O, Mitrova K, Durilova M, Kozeluho-va J, et al. Safety of anti-TNF-alpha therapy during pregnancy on long-term outcome of exposed children: A controlled, multicenter observation. *Inflamm Bowel Dis* 2019;25(4):789-96. <https://doi.org/10.1093/ibd/izy294>
19. Barenbrug L, Groen MT, Hoentjen F, van Drongelen J, Reek JMPAVD, Joosten I, et al. Pregnancy and neonatal outcomes in women with immune mediated inflammatory diseases exposed to anti-tumor necrosis factor- α during pregnancy: A systemic review and meta-analysis. *J Autoimmun* 2021;122:102676. <https://doi.org/10.1016/j.jaut.2021.102676>
20. Liu Z, Julsgaard M, Zhu X, Martin J, Barclay ML, Cranswick N, et al. CARINA Study Group. Timing of live attenuated vaccination in infants exposed to infliximab or adalimumab in utero: A prospective cohort study in 107 children. *J Crohns Colitis* 2022;16(12):1835-44. <https://doi.org/10.1093/ecco-jcc/jjac093>
21. Julsgaard M, Baumgart DC, Baunwall SMD, Hansen MM, Grosen A, Bibby BM, et al. NOVA Study Group. Vedolizumab clearance in neonates, susceptibility to infections and developmental milestones: A prospective multicentre population-based cohort study. *Aliment Pharmacol Ther* 2021;54(10):1320-9. <https://doi.org/10.1111/apt.16593>
22. 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;4:603-5. <https://doi.org/10.1016/j.crohns.2010.05.001>
23. Park SH, Kim HJ, Lee CK, Song EM, Kang SB, Jang BI, et al. Safety and optimal timing of BCG vaccination in infants born to mothers receiving anti-TNF therapy for inflammatory bowel disease. *J Crohns Colitis* 2020;14(12):1780-4. <https://doi.org/10.1093/ecco-jcc/jjaa099>
24. Goulden B, Chua N, Parker E, Giles I. A systematic review of live vaccine outcomes in infants exposed to biologic disease modifying anti-rheumatic drugs in utero. *Rheumatology (Oxford)* 2022;61(10):3902-6. <https://doi.org/10.1093/rheumatology/keac141>
25. Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, et al. Rotavirus Efficacy and Safety Trial (REST) Study Team. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med* 2006;354(1):23-33. <https://doi.org/10.1056/NEJMoa052664>
26. American Academy of Pediatrics. Poliovirus Infections. In: *Red Book: 2021 Report of the Committee on Infectious Diseases*, 32th, Kimberlin DW (Ed), American Academy of Pediatrics, Itasca, IL 2021. p.601. <https://doi.org/10.1542/9781610025225-part03-ch107>
27. Mahadevan U, Wolf DC, Dubinsky M, Cortot A, Lee SD, Siegel CA, et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2013;11:286-92. quiz e24. <https://doi.org/10.1016/j.cgh.2012.11.011>
28. Prieto-Peña D, Calderón-Goercke M, Adán A, Chamorro-López L, Maíz-Alonso O, De Dios-Jiménez Aberásturi JR, et al. Efficacy and safety of certolizumab pegol in pregnant women with uveitis. Recommendations on the management with immunosuppressive and biologic therapies in uveitis during pregnancy. *Clin Exp Rheumatol* 2021;39(1):105-14. <https://doi.org/10.55563/clinexprheumatol/j9ysbm>