



High accumulation of nivolumab in human breast milk: A case report

Karen de Jong^{a,1}, David Damoiseaux^{a,*,1}, Dick Pluim^a, Hilde Rosing^a, Jos H. Beijnen^{a,b}, Hans van Thienen^c, Thomas P.C. Dorlo^{a,d}, Alwin D.R. Huitema^{a,e,f}, Frédéric Amant^{g,h}

^a Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute, Amsterdam, the Netherlands,

^b Utrecht Institute of Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands,

^c Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands,

^d Department of Pharmacy, Uppsala University, Uppsala, Sweden,

^e Department of Pharmacology, Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands,

^f Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands,

^g Department of Gynecology, The Netherlands Cancer Institute, Amsterdam, the Netherlands

^h Gynecologic Oncology, UZ Leuven, Leuven, Belgium

ARTICLE INFO

Keywords:

Nivolumab
Pharmacokinetics
Melanoma
Breast milk
Breastfeeding
Infant

ABSTRACT

Nivolumab is an immunotherapeutic monoclonal antibody (mAb) that is used for the treatment of several types of cancer. The evidence on its use during lactation is lacking. Here, we report on a 39-year-old woman with metastasized melanoma who was treated with 480 mg nivolumab every four weeks during lactation. Breast milk samples were collected over the course of 34 days, including two cycles of nivolumab. The highest measured concentration of nivolumab during the first cycle was 503 ng/mL at day 13. The cumulative relative infant dose (RID) over the first cycle (28 days) was 9.8 %. The highest overall measured nivolumab concentration was 519 ng/mL at day 33, five days after administration of the second nivolumab cycle. Nivolumab seems to accumulate in breast milk over two consecutive cycles, hence the RIDs of consecutive cycles are expected to be higher. To draw further conclusions regarding safety of breastfeeding during nivolumab therapy, more information about the oral bioavailability of nivolumab in newborns, the nivolumab steady-state concentrations in breast milk and its pharmacodynamic effects are needed.

1. Introduction

Nivolumab is an IgG4 immunotherapeutic monoclonal antibody (mAb) that is used to treat a variety of cancers including melanoma, non-small cell lung cancer, and Hodgkin lymphoma, amongst others. A substantial number of women in the childbearing age are diagnosed with one of these types of cancers [1]. Consequently, patients and physicians can be faced with the dilemma whether or not to combine nivolumab therapy with breastfeeding. The manufacturer recommends to either discontinue nivolumab therapy during breastfeeding or to discontinue breastfeeding [2]. However, no literature is available on nivolumab concentrations in breast milk to support decision-making. Discontinuation of nivolumab therapy could have detrimental effects on the disease course in the mother, and by not breastfeeding, the infant as well as the mother are deprived of the clear health benefits of breastfeeding. Examples are the maternal empowerment caused by

breastfeeding, which contributes to mental health of the mother and for the infant, breastfeeding in the first 6 months after birth is the best protection from infant mortality during the first year after birth.

In the mammary glands, several transporters are present regulating the composition of breast milk. The epithelial cells of these glands contain the neonatal Fc receptor (FcRn). Little is known about the transport of IgGs into breast milk, but the current hypothesis involves FcRn [3]. The extent of IgG transport into breast milk depends on the subclass, with a relatively large accumulation of IgG4 in breast milk [3]. This could be an explanation for the high natalizumab (IgG4) breast milk concentration of 2.83 µg/mL [4]. Furthermore, degeneration of mAb in the gastrointestinal tract of the infant should be considered and was reported to be partial, with approximately 50 % reaching the intestine [5]. In addition, the extent to which mAbs can be absorbed in the gastrointestinal tract of infants is unknown but of high clinical relevancy.

* Correspondence to: Plesmanlaan 121, 1066 CX, Amsterdam, the Netherlands.

E-mail address: d.damoiseaux@nki.nl (D. Damoiseaux).

¹ These authors contributed to the manuscript equally.

There is no consensus regarding guidelines yet amongst oncologists about the combination of anti-cancer mAbs treatment and breastfeeding [6]. With this case study, we contribute to the knowledge and aid with decision-making on the use of nivolumab during breastfeeding.

2. Case

A 39-year-old pregnant woman was diagnosed with melanoma with satellite metastases in November 2020. After several excisions, treatment with nivolumab 480 mg intravenously (IV) every four weeks was initiated in July 2021, six weeks post-partum. Breastfeeding was discontinued after initiation of nivolumab therapy. Breast milk samples were collected during the first and second cycle of nivolumab. Nivolumab was administered on day 1 and day 27 of breast milk sampling. Sampling continued up to day 34.

3. Methods

3.1. ELISA

The ELISA measurements were performed according to the method described by Pluim et al. [7].

3.2. Data analysis

Analysis of the measured concentration was performed in the same way as previously reported [8]. After determination of drug concentrations, the mean concentration of the samples on one day was calculated in case multiple samples were measured on one day. In case of a single sample on one day, this was considered the mean concentration for this day. The mean concentrations per day were then used to calculate the infant daily dose and daily relative infant dose (RID) [9]:

$$\text{Infant daily dose (ng/kg/day)} = \text{concentration in milk} \left(\frac{\text{ng}}{\text{mL}} \right) \times \text{volume milk consumed daily (mL/kg/day)}$$

The infant daily dose is the amount of drug per unit of weight (kilogram) of the infant to which an infant is exposed at a certain day. A standard daily milk volume intake of 150 mL/kg was assumed for full breastfeeding, following longitudinal data on infant milk intake from

infants in the United States [10].

$$\text{RID}(\%) = \frac{\text{infant daily dose (ng/kg/day)}}{\text{maternal daily dose (ng/kg/day)}} \times 100$$

The daily RID is the relative amount of drug to which an infant is exposed on a specific day compared to the maternal dose. The maternal body weight of the mother used in the calculation was 65.8 kg.

At last the cumulative RID, the sum of the available daily RIDs in a cycle, was calculated. After calculations of the RIDs, the sum of the RIDs was calculated, with a n of 28 days after the first dose of nivolumab:

$$\text{Cumulative RID}(\%) = \sum_{i=1}^n \text{RID}_i(\%)$$

The cumulative RID after the second dose of nivolumab could not be calculated because only samples in the first week after administration were available and therefore not resulting in a representable representation of the cumulative RID of this cycle.

4. Results

A total of 72 samples were analyzed. The concentration time data are shown in Fig. 1. Initial nivolumab peak concentrations seem to occur at day 3 (157 ng/mL) when after a short decline in concentrations another increase in concentrations starts at day 7 reaching a more than twice as high concentration as the initial peak at day 13 (503 ng/mL). After administration of the second dose, distribution of nivolumab to the breast milk was higher compared to the first administration. The daily RID was between 0.1 % and 1 % during the first cycle, resulting in a cumulative RID of 9.8 %. The cumulative RID after the second administration is expected to be much higher as the daily RID already exceeds 1 % within 3 days (Fig. 1).

5. Discussion

Nivolumab exhibited unexpected pharmacokinetics in mother milk with two peaks. Concentrations after administration of the second dose of nivolumab were higher compared to the first dose because of drug accumulation. Due to the long half-life of 25 days [2], the concentration

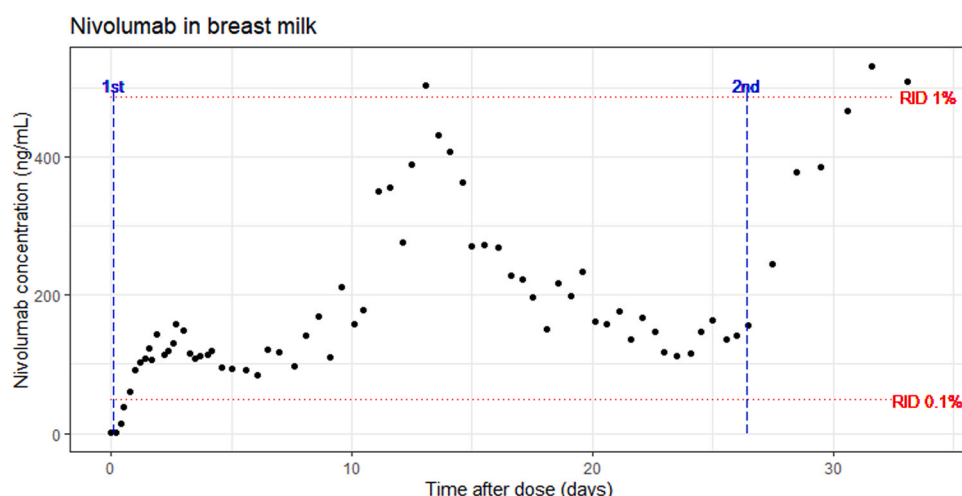


Fig. 1. Nivolumab concentrations in breast milk. Red dashed horizontal lines mark the 0.1 % or 1 % daily relative infant dose (RID) at 48.6 and 486 ng/mL, respectively. The 0.1 % or 1 % daily RID was calculated with the assumption that a child would drink 150 mL/kg/day of the concentration marked by the dashed red line in 1 day. Blue vertical lines mark the time points at which the next cycle was administered with corresponding number. The first two data points were values below limit of quantification (<LLOQ) and were plotted as the LLOQ concentration divided by 2 (1 ng/mL), the first before administration of the first dose of nivolumab and the second shortly after on the same day.

of nivolumab in breast milk could be even higher when steady state is reached in about 19 weeks after initiation of therapy. Previously reported mAb concentrations in breast milk peaked at 1–7 days after infusion, while peak concentrations after 11 and 21 days have also been reported [4,11]. These data suggest a large inter- and possibly intra-patient variability in mAb transport into breast milk.

Usually, a RID of <10 % is considered to be safe for small molecules, although it is unclear whether this applies to therapeutic mAbs as well. It remains important to interpret results in the context of other pharmacological characteristics of the drugs, such as oral bioavailability, safety, and drug metabolism in infants [9]. Large proteins such as mAbs have very distinct pharmacological characteristics compared to small molecules [6]. For instance, the maternal dosing schedules, oral bioavailability and mechanism of action are completely different. Furthermore, the minimal effective concentration of nivolumab in humans has not been clarified yet. The initial approved dose of 3 mg/kg, kinetically comparable to 240 mg fixed dose, every two weeks was chosen relatively arbitrary since no dose- or exposure-response relationships have been established yet. Some even suggest that the current nivolumab dosing exceeds the necessary effective dose because efficacy and maximum PD-1 receptor occupation was already seen at nivolumab doses of 0.1 mg/kg every two weeks in clinical studies [12,13]. This dose is approximately 3 % of the regular dose. The cumulative RID of 9.8 % found in this case study largely exceeds this value, and RIDs after consecutive nivolumab cycles are expected to be even higher. Depending on the oral bioavailability of nivolumab in newborns, it is likely that pharmacological effects can occur.

In a case of infliximab, therapy with 300 mg infliximab IV every four weeks was initiated in a mother three months after childbirth. Breast milk levels four days after the first infusion rose to 119.7 ng/mL, but no maternal serum levels were measured. Five days after the second infusion, maternal infliximab serum concentration was 78,300 ng/mL, and a serum concentration of 1700 ng/mL was found in the infant but no corresponding breast milk levels were obtained. This finding indicates that infliximab, and presumably also other mAbs, can be transferred from mother to infant through breast milk [14]. Nivolumab exposure after a 480 mg dose is similar to the exposure observed in the infliximab case. With the assumption that infliximab and nivolumab have a similar distribution to the breast milk, as observed for infliximab at day 4 of the first cycle (Fig. 1), and a similar bioavailability in infants, the nivolumab serum concentration in infants is likely to be similar to the concentration observed for infliximab. If this were the case, the oral bioavailability of nivolumab in infants would be approximately 18 % (0.13 mg/kg, assuming a volume of distribution of 75 mL/kg) of the received dose through breast milk (cumulative RID, 9.79 % of 7.3 mg/kg maternal dose). This estimation is most likely too conservative as IgG4 mAbs like nivolumab show a selective increased transportation into breast milk in comparison to other IgG subtypes like infliximab (IgG1) [3]. Additional information on infant systemic exposure and clinical safety are of pivotal importance to draw conclusions regarding applicability of nivolumab therapy during breastfeeding. The presented data in this case study show that we should be extra cautious with the use of nivolumab during breastfeeding.

Insights

High accumulation of nivolumab in breast milk with significant potential for pharmacological effects in infants.

CRediT authorship contribution statement

D.D., K.J., H.R., J.B., T.D., A.H., F.A. wrote the manuscript; D.D., K.J. designed the research; D.D., K.J., D.P. performed the research; D.D. analyzed the data; D.D., D.P.

Declaration of Competing Interest

Not applicable.

Acknowledgement

Financial support for this research was granted by Estee Lauder Companies.

References

- [1] M.M. Fidler, S. Gupta, I. Soerjomataram, J. Ferlay, E. Steliarova-Foucher, F. Bray, Cancer incidence and mortality among young adults aged 20-39 years worldwide in 2012: a population-based study, *Lancet Oncol.* 18 (12) (2017) 1579–1589.
- [2] Opdivo: EPAR - Product Information. European Medicines Agency; 2015.
- [3] C. Atyeo, G. Alter, The multifaceted roles of breast milk antibodies, *Cell* 184 (6) (2021), 1486–99.
- [4] T.E. Baker, S.D. Cooper, L. Kessler, T.W. Hale, Transfer of natalizumab into breast milk in a mother with multiple sclerosis, *J. Hum. Lact* 31 (2) (2015) 233–236.
- [5] B.N.P. Sah, J. Lueangsakulthai, B.J. Kim, B.R. Hauser, Y. Woo, A. Olyaei, et al., Partial degradation of recombinant antibody functional activity during infant gastrointestinal digestion: implications for oral antibody supplementation, *Front Nutr.* 7 (2020) 130.
- [6] P.O. Anderson, Monoclonal antibodies during breastfeeding, *Breast Med* 16 (8) (2021) 591–593.
- [7] D. Pluim, W. Ros, M.T.J. van Bussel, D. Brandsma, J.H. Beijnen, J.H.M. Schellens, Enzyme linked immunosorbent assay for the quantification of nivolumab and pembrolizumab in human serum and cerebrospinal fluid, *J. Pharm. Biomed. Anal.* 164 (2019), 128–34.
- [8] D. Damoiseaux, S. Calpe, H. Rosing, J.H. Beijnen, A.D.R. Huitema, C. Lok, et al., Presence of five chemotherapeutic drugs in breast milk as a guide for the safe use of chemotherapy during breastfeeding: results from a case series, *Clin. Pharmacol. Ther.* 112 (2) (2022), 404–10.
- [9] P.O. Anderson, J.B. Sauberman, Modeling drug passage into human milk, *Clin. Pharmacol. Ther.* 100 (1) (2016) 42–52.
- [10] P.O. Anderson, V. Valdés, Variation of milk intake over time: clinical and pharmacokinetic implications, *Breastfeeding Med.* 10 (3) (2015) 142–144.
- [11] K.M. Krysko, S.C. LaHue, A. Anderson, A. Rutatangwa, W. Rowles, R.D. Schubert, et al., Minimal breast milk transfer of rituximab, a monoclonal antibody used in neurological conditions, *Neurol. Neuroimmunol. Neuroinflamm.* 7 (2020) 1.
- [12] S.L. Topalian, F.S. Hodi, J.R. Brahmer, S.N. Gettinger, D.C. Smith, D.F. McDermott, et al., Safety, activity, and immune correlates of anti-PD-1 antibody in cancer, *N. Engl. J. Med* 366 (26) (2012) 2443–2454.
- [13] M.J. Ratain, D.A. Goldstein, Time is money: optimizing the scheduling of nivolumab, *J. Clin. Oncol.* (2018). JCO1800045.
- [14] J. Fritzsche, A. Pilch, D. Mury, C. Schaefer, C. Weber-Schoendorfer, Infliximab and adalimumab use during breastfeeding, *J. Clin. Gastroenterol.* 46 (8) (2012) 718–719.