Effect of Ofatumumab on Pregnancy, Parturition, and Lactation in Cynomolgus Monkeys

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Introduction

- Ofatumumab is a fully human anti-CD20 mAb, with demonstrated superior efficacy versus teriflunomide in the Phase 3 ASCLEPIOS I/II RMS trials[1]
  - Ofatumumab is administered as a monthly 20 mg subcutaneous injection. It is approved for the treatment of RMS in adults in the US[2] and other countries*
- Anti-CD20 therapy exposure during gestation may result in transient B-cell depletion in offspring; anti-CD20 mAbs may cross the placenta and, therefore, have the potential to affect the developing fetus[3]
  - However, there is limited information on the effect of ofatumumab on the developing immune system

Objective

- To determine the effect of ofatumumab on pregnancy, parturition, lactation, and pre/postnatal development in the offspring of pregnant cynomolgus monkeys

Methods: Preclinical study design

- This preclinical, enhanced pre/postnatal development study was conducted in 42 pregnant cynomolgus monkeys (*Macaca fascicularis*) of Asian origin at Covance Laboratories GmbH, Münster, Germany. Maternal animal, mean age: 5–6 years; body weight: 2.8 – 4.9 kg
- Ofatumumab or vehicle control was administered intravenously (infusion volume: 10 mL/kg, for 30 minutes) from gestation day (GD) 20 until parturition in non-fasted monkeys, and were categorized into the groups indicated below

Group	n	Initial dose *(for 5 weeks from GD 20)*	Maintenance dose *(for 8 weeks from GD 62)*
Control	14	Vehicle only	Vehicle only
Low-dose	14	ofatumumab 10 mg/kg weekly	ofatumumab 3 mg/kg biweekly
High-dose	14	ofatumumab 100 mg/kg weekly	ofatumumab 20 mg/kg biweekly

- Administration of ofatumumab was stopped after parturition; maternal monkeys and infants were observed for 6 months prior to necropsy on LD/PND 180±1

*Australia, Canada, Singapore, Switzerland, UAE, Albania, Argentina, India, and Japan

CD20, cluster of differentiation 20; CHMP, Committee for Medicinal Products for Human Use; FDA, Food and Drug Administration; GD, gestation day; LD, lactation day; mAb, monoclonal antibody; PND. postnatal day; RMS, relapsing multiple sclerosis

1. Hauser SL, et al. N Engl J Med 2020;383:546-557; 2. https://www.globenewswire.com/news-release/2020/08/20/2081597/0/en/FDA-approves-Novartis-Kesimpta-ofatumumab-the-first-and-only-self-administered-targeted-B-cell-therapy-for-patients-with-relapsing-multiple-sclerosis.html. Last accessed on Mar 1, 2021; 3. KESIMPTA® (ofatumumab) Prescribing Information. https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf (accessed Mar 1, 2021)

Methods: Assessments

- Toxicokinetic parameters were assessed in maternal monkeys (C_{max} and AUC_{0-168} in serum) and infants (ofatumumab serum concentrations). ADA levels were also assessed
- The Immune function was monitored:
  - Immunophenotyping (including CD20+B cell counts) was determined repeatedly in maternal animals and their infants
  - IgG, IgM and IgA serum levels were assessed in infants on PND 70 and 175
  - The TDAR was assessed in infants by measuring anti-KLH IgG and IgM serum levels after KLH vaccination* on PND 119 and 147
- In infants, prenatal loss, stillbirth, and early and late postnatal mortality, overall development, pathology were assessed

Results: Toxicokinetics and immunogenicity

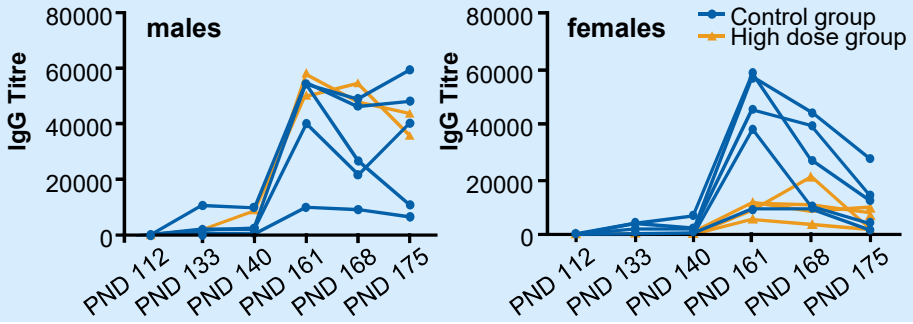
- Maternal animals: C_{max} and AUC_{0-168} values, increased dose proportionally with the increase in dose level from low to high-dose; In infants: ofatumumab was present in the blood of infants on PND 28 at low-dose and up to PND 63/91 at high-dose
- ADA were detected in 5 maternal animals and 7 infants of the low dose group and 5 high dose maternal animals without effects on ofatumumab exposure
- Ofatumumab was undetectable in the blood of 4 additional maternal animals treated at low dose (from GD 48) and their respective infants (as applicable), as a likely consequence of ADA development. These animals also had normal B cell values

Results: Immune function

T cell-dependent antibody response (TDAR)

- For high-dose infants with the lowest B cell levels on PND 91, the specific IgG and IgM response was reduced after the first KLH immunization followed by a robust recall response after the second KLH immunization indicative of a delayed humoral response, B-cell repletion and a highly functional B cell memory. For the other high dose infants, the IgG and IgM responses were similar to the control group response since B cell counts had already reached normal levels for both infants at the time of first KLH immunization
- For low-dose infants, no effects related to ofatumumab treatment were observed on TDAR at the chosen time points

Individual Anti-KLH IgG titres of high-dose and control groups in males and females

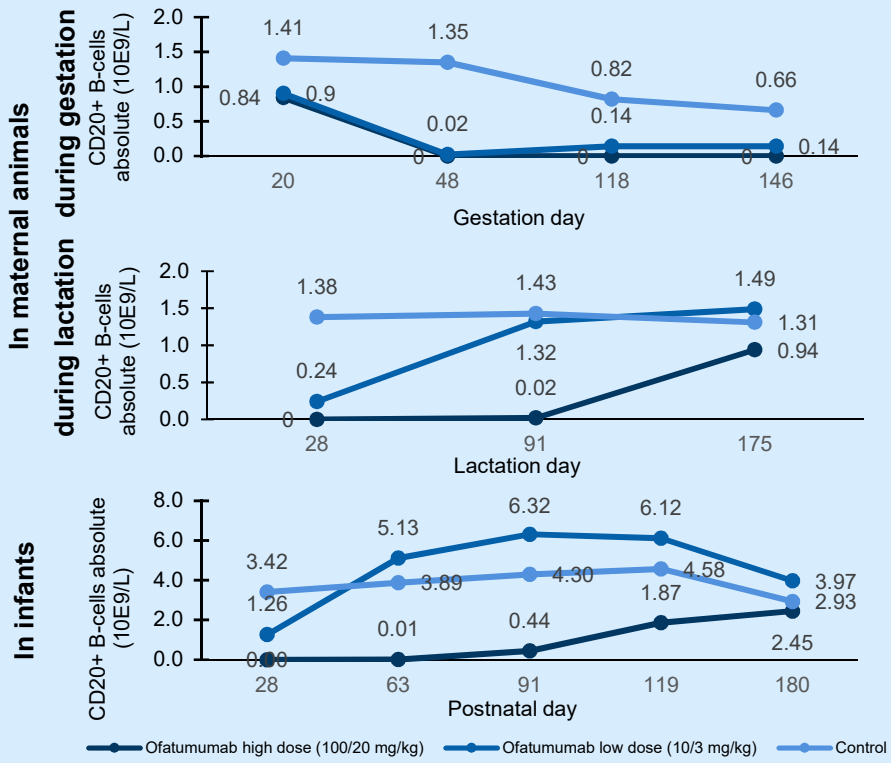


*Sigma or Imject® Mariculture Keyhole Limpet Hemocyanin (1.0 mL)

ADA, anti-drug antibody; AUC, area under curve; CD, cluster of differentiation; GD, gestation day; Ig, immunoglobulin; KLH, Keyhole Limpet Hemocyanin; PND, postnatal day; TDAR, T cell-dependent antibody response

Results: Immune function

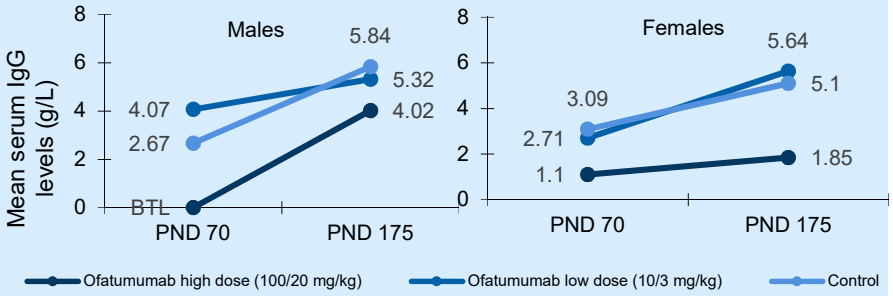
- In maternal animals
  - Near-complete CD20+ B cell depletion observed in both ofatumumab high- and low-dose groups during gestation (treatment period) and up to LD28
  - Ofatumumab high-dose group: CD20+ B cell counts had returned to the physiological range by LD 175
  - Ofatumumab low-dose group: CD20+ B cell counts had nearly completely recovered by LD 91
- In infants:
  - Ofatumumab high-dose group: CD20+ B cell counts were at the detection level on PND 28 and 63 and were restored to physiological ranges between PNDs 119 and 180
  - Ofatumumab low-dose group: CD20+ B cell counts were at the detection level on PND 28 and were restored to physiological ranges from PND 63 onwards
- No ofatumumab-related effects were noted in CD3+ T cells, CD3+ CD4+ T helper cells, CD3+ CD8+ cytotoxic T cells, CD16+ natural killer cells or CD14+ monocytes in either maternal animals or infants



CD, cluster of differentiation; GD, gestation day; LD, lactation day; PND, postnatal day; TDAR, T cell-dependent antibody response

Results: Immune function

IgG levels in infants on PND 70 and 175



Ofatumumab high-dose group:

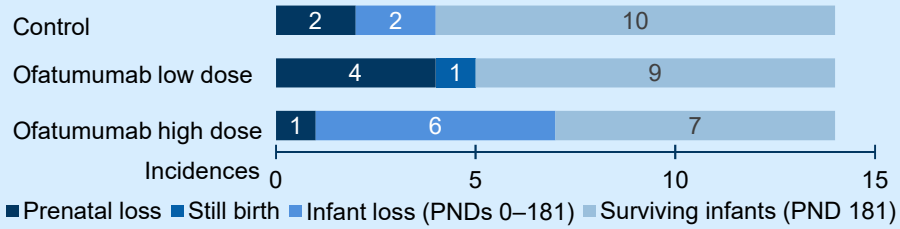
- IgG levels: all infants had lower IgG levels on PND 70
  - On PND 175, IgG levels in male infants had increased and were not significantly different
  - In female infants IgG levels remained lower vs the control group infants (Figure). These females also had lowest B cell levels on PND 91
- IgA and IgM levels were broadly similar to control group infants

Ofatumumab low-dose group:

- No meaningful changes in IgG, IgA or IgM vs control group infants

Results: Pregnancy outcomes, development and NOAEL

Pregnancy outcome and infant loss (figure)



- 3 of 6 high-dose infant deaths in the high dose group were likely a consequence of potential infections (as evidenced by histologic findings) secondary to immunomodulation; Other infant deaths in this group were incidental.
- There were no infant loss in the low dose group
- Infants of the low and high dose groups developed normally
- Histopathological examination at 6 months showed no ofatumumab-related findings in any infants of the low and high dose groups

NOAEL

- NOAEL in infants was defined at 100/20 mg/kg for pre/postnatal development and at 10/3 mg/kg for pharmacological effects corresponding to safety margins of 160-fold and 22-fold, respectively, vs the therapeutic dose of 20 mg in terms of AUC
- NOAEL in maternal animals was considered to be 100/20 mg/kg

AUC, area under curve; BTL, below test limit; Ig, immunoglobulin; NOAEL, no-observed adverse-effect level; PND, postnatal day

Conclusions

- Increases in ofatumumab mean maternal C_{max} and AUC_{0-168} values were approximately dose-proportional. Ofatumumab was detected in the blood of the infants from female monkeys exposed to ofatumumab during gestation, confirming placental transfer of ofatumumab and persistency of fetal exposure postnatally
- Exposure to ofatumumab during gestation caused no maternal toxicity and no adverse effects on the prenatal or postnatal development. All infants developed normally
- Exposure to intravenous ofatumumab at low or high dose to cynomolgus monkeys throughout pregnancy led to the pharmacologically expected depletion of CD20+ B cells in maternal animals and their infants. A reduced humoral immune response was only seen in infants at high dose. Upon treatment cessation, B-cells repleted and consequently, immune response normalized (as observed in high-dose group male vs female infants)
- Difference in postnatal survival between the high dose and control groups was related to the early death of 3 high dose infants which was likely a consequence of potential infections secondary to immunomodulation.
- The non-clinical safety profile of ofatumumab in monkeys is similar to the profile of other anti-CD20 antibodies like rituximab, ocrelizumab, or obinutuzumab, but with expected high safety margins related to the low clinical therapeutic dose of ofatumumab and no long-lasting effects
- Clinical doses as per US FDA approved label is 20 mg monthly, which translates to <0.3 mg/kg for a 70 kg adult, leading to more than 20-fold lower exposures than the animals in the “low dose” group dosed at 10/3 mg/kg; this dose margin supports the safety profile of ofatumumab at recommended dose in humans

Disclosures

Muriel Bellot, Morten Bagger, Courtney Horvath, Esther Sutter, Anthony DeLise, Dominique Brees, José M Carballido, Ratnakar Pingili and Krishnan Ramanathan are employees of Novartis.
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