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Short communication

Measles virus neutralizing antibodies in immunoglobulin lots produced from plasma collected in Europe or the United States

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ABSTRACT

Vaccination against measles has reduced disease, although measles virus antibody (MVAb) levels are lower after vaccination than natural infection. Immunoglobulin (IG) preparations thus contain decreasing MVAb titers. US IG lot release requires a minimum titer of MVAb, yet equivalent information is not available for other geographies. Using a measles virus neutralization assay, IG fractionated from US or EU plasma is shown to contain similar levels of MVAb always above US regulatory requirements, supportive of equivalent protection against MV infection. Thus, the dosage for post-exposure prophylaxis in the EU could be aligned with the US FDA's treatment recommendations.

1. Introduction

Vaccination-induced measles virus antibody (MVAb) titers are lower than after natural infection [1]. Wide use of the vaccine has resulted in a significant decrease in measles cases as well as in a progressive decline of MVAb titers in human plasma for fractionation [2] and thus in individual lots of immunoglobulin (IG) [3]. The minimum MVAb specification for IG lot release in the US, as defined by Food and Drug Administration (FDA), has been increasingly difficult to meet, and in November 2018 was lowered to avoid product shortages [4]. In the same announcement, amended treatment recommendations for the passive protection of people with immune deficiencies (PID), both prophylactically as well as after potential exposure, were defined, to ensure adequate protection. Beyond PID, however, passive protection also remains the only available intervention to safeguard at-risk populations not eligible for vaccination, i.e. pregnant women or newborns. Several US states and various European countries are subject to ongoing measles outbreaks [5], with notable recent increases e.g. in Austria, France, Poland, and Italy, and more than 10,000 cases and 33 deaths reported in Europe for the last 12 months [6]. This highlights the importance of protective MVAb titers in IG, but other than for lots released to the US market, determination of MVAb titers in IG preparations is not required, and this information is thus not generally available. Given the significant clinical relevance and recently voiced concerns about regional differences between IG products [7,8], an in depth analysis of the topic was felt necessary.

2. Methods

MVAb titers were determined in 1739 IG lots (Gammgard Liquid / KIOVIG [Baxter Healthcare Corporation, Westlake Village, CA, USA]), fractionated between 2013 and 2018 by the same manufacturing process [9] from plasma collected in the US or in Austria, Germany and the Czech Republic (collectively designated EU), which constitute the leading European countries in terms of plasma collection. Plasma was obtained either by plasmapheresis (source plasma), or from whole blood donations (recovered). Titers were determined as neutralization titer NT_{50} [1:X], i.e. the reciprocal dilution resulting in 50% MV neutralization, by a fully validated

Abbreviations: ATCC, American Type Culture Collection; BW, body weight; FDA, Food and Drug Administration; IG, immunoglobulin; MVAb, measles virus antibody; NT, neutralization titer; PID, primary immune deficiency; SEM, standard error of the mean; WHO, World Health Organization.

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neutralization assay on Vero cells (ATCC CCL-81) in duplicate, essentially as described [2]. Data was processed using R software (www.rstudio.com) and visualization was performed with GraphPad Prism v7.03 software. Between-group comparisons were conducted with GraphPad Prism using an unpaired *t*-test, while longitudinal statistical analysis was performed with MiniTab v17 software using a second order polynomial model.

3. Results

Overall, EU plasma derived IG lots had higher MV neutralizing antibody titers (mean NT_{50}[1:X] ± standard error of the mean (SEM); 1521 ± 33) than US plasma derived IG lots (1373 ± 13; $p < 0.0001$; Fig. 1). MVAb titers for IG lots fractionated from recovered plasma (2000 ± 29) were significantly higher ($p < 0.0001$) than those from source plasma (1245 ± 10). This difference was evident in both geographies, when lots fractionated from US recovered (1966 ± 31) and US source plasma (1222 ± 10) as well as from EU recovered (2194 ± 72) and EU source plasma (1366 ± 28) were compared (Fig. 2).

For IG lots from US source plasma, which constitutes the quantitatively main starting material for IG production and thus the most robust source of data, a significant ($p < 0.0001$) decay of MVAb for the data analyzed was evident, while an equally significant ($p < 0.0001$) quadratic term confirmed that this decay is flattening with time (Fig. 3).

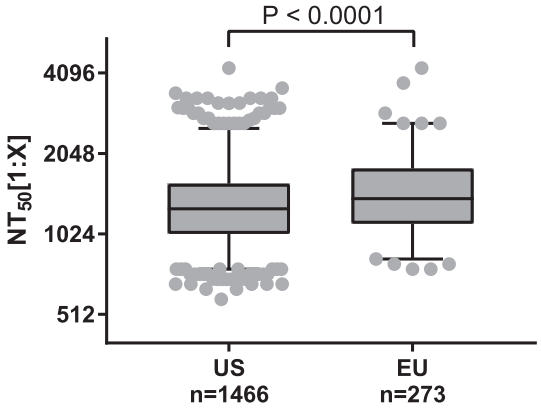

Fig. 1. Measles virus neutralizing antibody titers determined as NT_{50} [1:X], i.e. the reciprocal dilution resulting in 50% virus neutralization of IG lots plotted according to geographic origin (US or EU). Plotted on a $\log_2$ scale, whiskers of boxplots depict 2.5 and 97.5 percentiles. Differences in titers were assessed by unpaired *t*-test.

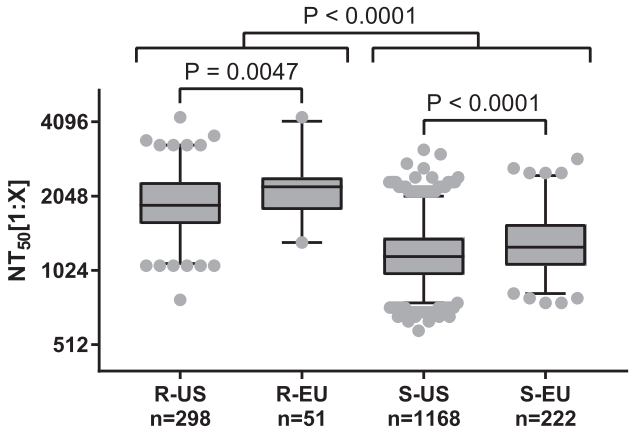

Fig. 2. Measles virus neutralizing antibody titers determined as NT_{50} [1:X], i.e. the reciprocal dilution resulting in 50% virus neutralization of IG lots plotted according to geographic origin and plasma used to fractionate the respective IG lots, i.e. recovered plasma collected in the US (R-US) or the EU (R-EU), or source plasma collected in the US (S-US) or the EU (S-EU). Plotted on a $\log_2$ scale, whiskers of boxplots depict 2.5 and 97.5 percentiles. Differences in titers were assessed by unpaired *t*-test.

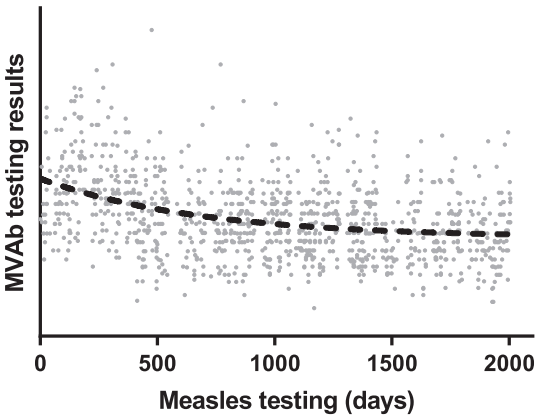

Fig. 3. Longitudinal analysis of measles virus neutralizing antibody levels in IG lots derived from source plasma collected in the US between 2013 and 2018. Values for individual IG lots are depicted as grey dots; dashed black line depicts interpolated curve of 3-parameter exponential regression model.

4. Discussion

Blood donors are generally of higher average age than source plasma donors. For example, in the USA, around 50% of all blood donations are contributed by donors over 45 years of age [10], while approximately 55% of the US source plasma donor pool is below the age of 35 [11]. In Germany, the country that contributes the highest volume of plasma for fractionation in Europe, 19% of repeat whole blood donors were 55+ years of age, while only 4.7% of plasmapheresis donors fell into this age cohort [12]. It can therefore be expected that a larger proportion of blood donors were born before introduction of the measles vaccine in 1963, who are thus more likely to have experienced MV infection, which results in higher antibody titers [1]. As the IG lots tested here are produced by identical manufacturing process irrespective of the plasma origin [11] this difference in donor demography is reflected in higher MVAb titers in IG lots fractionated from recovered as compared to source plasma (Fig. 2). As the measles vaccine was implemented around 10 years later in Europe than in the US, the proportion of previously MV infected donors is expected to be even greater in the EU countries. In addition, the WHO region Europe still reports an approximately 15-fold higher incidence of MV infections as compared to the WHO region Americas, i.e. 27 vs. 1.7 cases/million population [13], a consequence of inconsistent compliance with vaccination recommendations across the different European countries. Together, these factors could explain the higher MVAb titers seen in IG lots fractionated from EU plasma (Fig. 1). However, while different with high statistical significance, the mean values of MVAb titers of the four subgroups of IG determined by plasma collection modality (source vs. recovered), as well as collection geography (US vs. EU), were within a factor of only two, i.e. the IG dilution increments used for the MVAb assay. Thus, whether plasma is collected in the US or EU, and whether the starting material is either source or recovered plasma, IG derived thereof may be considered as functionally equivalent with respect to protection against measles infection. The serum level of MVAb that corresponds with clinical protection has been reported as >120 mIU/mL [4]. Also, while testing for a minimum threshold of MVAb is only required for release of IG to the US, all EU plasma lots

fulfilled the lot release criterion as per FDA regulation even before the recent limit adjustment from previously 0.48 × CBER Standard lot 176 to currently 0.36 × CBER Standard lot 176 (estimated titer of CBER Standard lot 176, a 16.5% solution, is 42 IU/mL) [4].

Two clinical studies have recently investigated the MVAb trough (intravenous IG) or steady state (subcutaneous IG) levels in treated PID [14,15], and found these above protective levels, even when extrapolated to the now lowered FDA release specification [4]. Beyond PID treatment, IG is also indicated for post-exposure prophylaxis in individuals not eligible for vaccination, such as infants and unvaccinated pregnant women exposed to measles. The current study, which presents the test results for >1000 IG lots, reliably demonstrates that IG lots available in the EU are functionally similar, if not somewhat superior, to IG lots available in the US, with respect to MV neutralizing antibodies. The data reported for 9 IG lots available on the German market 2015–2016 is fully consistent with this observation [8]. Post-exposure prophylaxis in the EU should thus be aligned with US recommendations of 400 mg/kg body weight (BW) for PID [4], i.e. including a 2-fold safety margin. The German Standing Committee on Vaccination (STIKO) also recommends 400 mg/kg BW in at-risk populations; a lower dose (200 mg/kg BW), i.e without the safety margin, is recommended by the French National Competent Authority ANSM [16]. Of note, the current dosage recommendation for the UK is even lower [17].

With the MV vaccine in use for >50 years by now, and marginal circulation of MV in the geographies of plasma collection, a steady state reflective of an exclusively vaccinated plasma donor population should be expected at some point. Indeed, such a steady-state was noted in a recent study of MV neutralizing titers in US plasma [2] and was confirmed in the present study for MVAb titers in IG lots (Fig. 3).

Collectively, this study demonstrates that the levels of MV neutralizing antibodies in IG preparations vary somewhat, depending on plasma type (recovered > source), as well as donor residence (EU > US). While statistically significant, the relatively minor variation as compared to assay precision supports similar protective properties for all IG preparations analyzed. Further, data from the testing of >1000 lots of IG over the course of several years seems to indicate that the currently protective MVAb titers, as recently confirmed by US and EU regulatory bodies, seem to converge to a still protective steady-state, reflective of an only vaccinated donor population.

5. Potential conflicts of interest

A.S. and R.I. are employees of Baxter AG, Vienna, Austria, now part of the Takeda group of companies. M.R.F., M.K., P.O.R. and T. R.K. are employees of Baxter AG, Vienna, Austria, now part of the Takeda group of companies, and Takeda stock owners.

Author contributions

M.R.F. and T.R.K. conceptualized the study. M.K., P.O.R., A.S. and R.I. curated and analyzed the data. M.R.F., M.K. and T.R.K. wrote the manuscript. All authors reviewed the final version of the manuscript.

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