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Rubella antibodies in Australian immunoglobulin products

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Abstract

Rubella antibodies are not routinely measured in immunoglobulin products and there is a lack of information on the titre in Australian products. To facilitate future studies of the effectiveness of passive immunisation for preventing rubella and congenital rubella syndrome, this study measured the concentration of rubella-specific antibodies in Australian intramuscular (IM) and intravenous (IV) human immunoglobulin products suitable for post-exposure prophylaxis using a chemiluminescent immunoassay. The GMT ± GSD for the IM product was 19 ± 1.2 IU/mg (2980 ± 1.2 IU/mL). The GMT ± GSD for the IV product was 12 ± 1.5 IU/mg (729 ± 1.5 IU/mL). At present, Australian guidelines recommend offering non-immune pregnant women exposed to rubella 20 mL of intramuscular immunoglobulin within 72 hours of exposure. This equates to 42,160 IU of rubella antibodies if the lowest titre obtained for the Australian IM product is considered. The same dose would be delivered by 176 mL of the Australian IV product at the lowest measured rubella-specific antibody titre.

Keywords: rubella, immunoglobulin, Australia, blood products, titres

Congenital rubella syndrome, manifesting as heart and eye abnormalities and sensorineural deafness is devastating for families and causes significant burden to health systems (1-4). Prevention of congenital rubella syndrome is best achieved by pre-pregnancy vaccination. For pregnant women who are non-immune, vaccination is contra-indicated (5), so if they are exposed to rubella, passive immunisation is the only alternative to either a watch and wait approach and/or termination of pregnancy. Passive immunisation as post-exposure prophylaxis for rubella for non-immune pregnant women is a part of the disease control guidelines in a number of countries, but is recommended only in certain circumstances (5-9).

Recommendations about passive immunisation for post-exposure prophylaxis are inconsistent across different national guidelines, and this most likely stems from the paucity of evidence of effectiveness (10). A systematic review noted the lack of recent evidence on this intervention, but found studies from the 1950s - 1970s seemed to indicate effectiveness for preventing rubella in non-pregnant subjects when given up to five days post-exposure (10). The review concluded that further evaluation of the intervention should be undertaken, and highlighted the need for the concentration of rubella-specific antibodies in immunoglobulin products to be available so that definition of an effective dose could be determined.

Rubella antibodies are not routinely measured in immunoglobulin products and there is a lack of information on the titre in Australian products. This study aimed to measure the concentration of rubella-specific antibodies in Australian

intramuscular and intravenous human immunoglobulin products suitable for post-exposure prophylaxis, to facilitate future studies of the effectiveness of this intervention.

Results

The GMT ± GSD for the IM product was 19 ± 1.2 IU/mg (2980 ± 1.2 IU/mL). The GMT ± GSD for the IV product was 12 ± 1.5 IU/mg (729 ± 1.5 IU/mL) (Figure 1).

There was a statistically significant difference between the GMT of Australian IM immunoglobulin and Australian IV immunoglobulin ($p<0.001$).

Discussion

The aim of this study was to establish the rubella titre in two Australian immunoglobulin products. Rubella titres in Australian IM and IV immunoglobulin products were found to range from 4 to 26 IU/mg. Geometric mean titres were significantly different for the intramuscular and intravenous products ($p<0.001$). The difference is likely due to the manufacturing process (Bertolini, unpublished data) as both products are derived from the same plasma pool.

Enzyme Immunoassay (EIA) calibrated against the WHO international standard, as reported in this and a number of other studies, is well accepted as the test of choice for quantitating rubella antibodies (11). Variability of results has been noted when the same sample of serum has been tested with different commercial EIA kits (11, 12). No published studies comparing rubella antibody

titres in immunoglobulin products across different EIA kits were identified. The magnitude of variation reported upon testing a single serum sample on multiple assays was small, but clinically significant at the lower titres found in serum (11). A similar magnitude of variation (up to approximately 100 IU/mL) when applied to rubella titres measured in immunoglobulin products would not impact greatly on the conclusions drawn from this study as 100 IU/mL is within the GSD of the results.

Few other studies have quantitated rubella antibodies in immunoglobulin products. Krause et al (13) found between 4.5 and 6.2 EIA units/mL of rubella antibodies in five different intravenous immunoglobulin products from Italy, Israel, Switzerland and the United States of America. In the absence of a common unit of measurement, it is not possible to compare these results to the current study. Wu et al (14) tested four different intravenous products from Taiwan and the United States of America with different protein concentrations. The product from Taiwan had a rubella titre of 260.2 IU/mL (4.3 IU/mg). The products from the United States of America had rubella titres ranging from 351.6 - 786.3 IU/mL (7.0-7.9 IU/mg) (IgG concentrations of the products tested were obtained by personal communication with DY Wang). Matejtschuk et al (15) analysed two intravenous products derived from plasma from the United States of America, one intravenous product derived from United Kingdom plasma and three products for which the source of plasma was either the United States of America or Europe, but for which the specific origin was unknown. The United Kingdom product had a rubella titre of 1,055 IU/mL or 21.1 IU/mg. The products from the United States of America had rubella titres of 670 and 630

IU/mL or 13.4 and 12.6 IU/mg respectively. In the three products of unknown specific origin, rubella titres were 1,319, 828 and 303 IU/mL or 26.4, 16.6 and 6.1 IU/mg respectively (IgG concentration of the products tested were obtained by personal communication with J More). The results of this study fall within the range of results reported by these latter two studies.

At present, Australian guidelines recommend offering non-immune pregnant women exposed to rubella 20 mL of intramuscular immunoglobulin within 72 hours of exposure (5). This equates to 42,160 IU of rubella antibodies if the lowest titre obtained for the Australian IM product is considered. The same dose would be delivered by 176 mL of the Australian IV product at the lowest measured rubella-specific antibody titre.

Only two studies were identified that measured rubella antibodies serially in the serum of non-immune recipients of immunoglobulins (16, 17). du Pan et al (17) infused three healthy non-immune volunteers with either 40 or 60 mL of a solution of immunoglobulins. The haemagglutination inhibition (HI) titre of the product was 1:2048 in one instance and 1:1024 in the other two instances. The protein concentration of neither the product nor the solution used for infusion was reported. These authors noted serum rubella HI titres peaked at five minutes after infusion and were still detectable two weeks post-infusion. One volunteer (infused with 60 mLs of solution containing immunoglobulins with 1:2048 rubella antibody titre) maintained an 'immune' titre of HI 1:8 at two weeks.

Field et al (16) reported titres at or in excess of the 'immune' level (HI 1:8) for five previously non-immune recipients of 3,000 mg of immunoglobulins for at least two weeks after injection. This dose of immunoglobulins is equivalent to the Australian recommendation (20 mLs of immunoglobulins with protein content of 16 mg/mL). However, it is not clear whether the dose of rubella antibodies recommended under Australian guidelines is equivalent to that used in Field et al's study. That study does report that the product used had a measured rubella HI titre of between 1:1600 and 1:12,800 (16), but, as with du Pan et al (17), there is no information on assay standardisation. Without this knowledge it is not possible to convert the doses of rubella antibodies used in these studies into international units (18) and further compare them to current Australian recommendations.

As rubella vaccine is widely and freely available in Australia, it would be unethical to repeat similar studies here. Future observational or pharmacokinetic modeling studies, with the assistance of the data provided by this study, may help to further investigate the effectiveness of passive immunisation, including the optimal dose of immunoglobulins, for preventing rubella in non-immune pregnant women post-exposure.

Methods

Samples of 14 batches of intramuscular (IM) and 18 batches of intravenous (IV) immunoglobulins, manufactured between 2011 and 2013, were obtained from CSL Behring (Australia) Pty Ltd. The IM product was manufactured by the Cohn-Oncley ethanol precipitation procedure, while the IV product was manufactured

using a chromatographic-based process. The formulated products differ with respect to protein concentration, pH and excipient [IM (16% w/v; pH 6.6; glycine); IV (6% w/v; pH 4.25; maltose)].

Rubella testing was performed using a chemiluminescent immunoassay (CLIA) (Access Rubella IgG reagent (Beckman Coulter Catalogue no 34430) using the Access Immunoassay System). Testing was performed in duplicate at 1:50 and 1:100 on the IM product samples and at 1:10 and 1:20 on the IV product samples. The titre of the sample was the average of the results obtained at the two dilutions. Inter-assay precision was 8.2%.

The geometric mean titres (GMT) and geometric standard deviations (GSD) were calculated for each product. The titres of the products were compared using the Mann-Whitney U test. A nonparametric test was chosen because of the small sample sizes.

Ethical approval was not required for this study.

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Competing interests statements

Megan Young is a PhD student examining the effectiveness and efficiency of normal human immunoglobulin for the public health management of communicable diseases. She is also a public health physician practising in Queensland.

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Allan Cripps is the supervisor of Megan Young's PhD.

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Figure 1. Rubella antibody titres in Australian intramuscular and intravenous immunoglobulin product samples by year of manufacture