DYNAMIC CHANGES IN THE CONCENTRATION OF ANTI-SARS-COV-2 ANTIBODIES WITHIN 12 MONTHS AFTER RECOVERY FROM COVID-19

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Generation and maintenance of immunity to SARS-CoV-2 is essential for overcoming the pandemic of the novel coronavirus infection COVID-19. The study was aimed to assess the dynamic changes in the levels of IgG antibodies against the SARS-CoV-2 receptor-binding domain (RBD) with the use of the enzyme-linked immunosorbent assay (ELISA) kits, calibrated using the International Standard for anti-SARS-CoV-2 immunoglobulin (IS-SARS-CoV-2). The concentrations of anti-RBD-IgG were measured in the cohort of individuals, who had recovered from COVID-19, with an interval of a month for 6 months, and at a time point of 12 months, using the ELISA kits, calibrated with the use of IS-SARS-CoV-2; the results were expressed in binding antibody units (BAU) per 1 mL. A total of 97 blood serum samples, obtained from 20 individuals with SARS-CoV-2 infection, confirmed by PCR, were collected. The geometric mean titer (GMT) of anti-RBD-IgG was 433 BAU/mL (range 36-25,900 BAU/mL) within a month after the infection. The concentration of anti-RBD-IgG gradually decreased with time and reached the GMT value of 68 BAU/mL by the 12th month; anti-RBD-IgG persisted in 13 individuals (93%) out of 14, examined 12 months after the infection. The standardized quantitative serological data play a vital part in monitoring the immune response and make in easier to compare the studies, providing the basis for seeking the common serological correlate of the protective immunity to SARS-CoV-2.

Keywords: SARS-CoV-2, anti-RBD IgG, dynamic changes, concentration, BAU/mL

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Compliance with ethical standards: the study was approved by the Ethics Committee of the Pirogov Russian National Research Medical University (protocol № 197 dated May 21, 2020).

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ДИНАМИКА КОНЦЕНТРАЦИИ АНТИТЕЛ К SARS-COV-2 В ТЕЧЕНИЕ 12 МЕСЯЦЕВ ПОСЛЕ ПЕРЕНЕСЕННОЙ ИНФЕКЦИИ COVID-19

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Формирование и поддержание иммунитета против SARS-CoV-2 является важным условием преодоления пандемии новой коронавирусной инфекции COVID-19. Целью работы было охарактеризовать динамику уровня антител IgG к рецептор-связывающему домену (RBD) SARS-CoV-2 с использованием набора для иммуноферментного анализа (ИФА), откалиброванного при помощи Международного стандарта анти-SARS-CoV-2-иммуноглобулинов (IS-SARS-CoV-2). Концентрацию анти-RBD-IgG измеряли в когорте лиц после выздоровления от COVID-19 с интервалом в месяц в течение 6 месяцев и в точке 12 месяцев с использованием наборов ИФА, откалиброванных IS-SARS-CoV-2; результаты представляли в единицах связывания антител (BAU) на 1 мл. Всего исследовали 97 образцов сыворотки крови от 20 человек с ПЦР-подтвержденной инфекцией SARS-CoV-2. К первому месяцу после заражения средний геометрический титр (GMT) анти-RBD-IgG составил 433 BAU/мл (диапазон 36–25900 BAU/мл). Со временем концентрация IgG против RBD постепенно снижалась, достигая GMT в 68 BAU/мл к 12 месяцу; анти-RBD-IgG сохранялись у 13 из 14 (93%) лиц, обследованных через 12 месяцев после инифицирования. Стандартизированные количественные серологические данные играют важную роль в мониторинге иммунного ответа и облегчают сравнение между исследованиями, создавая основу для поиска общего серологического коррелята иммунной защиты против SARS-CoV-2.

Ключевые слова: SARS-CoV-2, анти-RBD IgG, динамика, концентрация, BAU/мл

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The natural infection and vaccination against COVID-19 result in the production of antibodies against viral antigens, playing a vital part in the immune response monitoring [1]. Although it is expected that the naturally acquired immunity against SARS-CoV-2 would last long [2-3], serological equivalent of antiviral host defense has not yet been discovered. The lack of a standardized approach to laboratory testing is one of the obstacles to defining such correlates, which probably explains the conflicting literature data on the serological assessment of SARS-CoV-2 infection. The WHO have recently introduced the International Standard for anti-SARS-CoV-2 immunoglobulin (IS-SARS-CoV-2), which makes it possible to unify the results of measuring the levels of anti-SARS-CoV-2 antibodies using the IS-SARS-CoV-2 units, namely the binding antibody units (BAU) [1]. The study was aimed to measure the concentration of IgG against the SARS-CoV-2 receptor-binding domain

(RBD) at different times over the 12-month period in a cohort of healthcare professionals, who have recovered from the SARS-CoV-2 infection, using the enzyme-linked immunosorbent assay (ELISA) kits, calibrated using the IS-SARS-CoV-2.

METHODS

The study, carried out from May 2020 to June 2021, involved the staff members of the Russian Children's Clinical Hospital, Pirogov Russian National Research Medical University. Inclusion criteria: positive PCR test result for COVID-19. There were no exclusion criteria.

In April and May 2020, after returning to work, individuals with positive PCR test results for COVID-19 gave the blood serum samples with an interval of a month for the anti-RBD-IgG measurement. The samples were collected on a monthly basis for 6 months, and the last sample was obtained 12 months after the positive PCR test result; a total of 4–7 samples was obtained from each subject. The samples collected were stored at a temperature of –80 °C.

In July 2021, all the samples were assayed in one batch using the ELISA kit for the anti-RBD-IgG quantification (XEMA; Russia) [4], calibrated using the IS-SARS-CoV-2. The analytical measuring range was 15–240 BAU/mL; samples with the anti-RBD-IgG concentration exceeding 240 BAU/mL were further diluted 10–100 times and measured repeatedly in a separate batch. The samples were considered positive when the level of anti-RBD-IgG was 15 BAU/mL.

Statistical processing was performed using the IBM SPSS Statistics 27.0 software package (IBM Corp.; USA).

RESULTS

A total of 97 serum samples were obtained from 20 individuals during the study, including 14 women (70%) with the SARS-CoV-2 infection, confirmed by PCR. The median age was 50 years (Q_1–Q_3, 40–57 years). All the subjects had mild to moderate COVID-19, there were no severe cases of the disease.

In three individuals, blood serum samples were obtained a month before the SARS-CoV-2 infection; no anti-RBD-IgG were found in these samples. A month after the positive PCR test result for SARS-CoV-2, anti-RBD-IgG were found in all subjects in a concentration exceeding the threshold value of 15 BAU/mL, with the geometric mean titer (GMT) of 433 BAU/mL (95% CI 123–1,527 BAU/mL; range 36–25,900 BAU/mL) (see Figure). At the time point 2 of the month the median GMT was similar, 456 BAU/mL (95% CI 154–1,353 BAU/mL). Later the concentration of anti-RBD-IgG gradually decreased and reached the median GMT value of 68 BAU/mL (95% CI 35–131 BAU/mL) by the 12th month. All samples were anti-RBD-IgG-positive during the period between the first and the sixth months. Among 14 individuals assessed 12 months after the SARS-CoV-2 infection, 13 individuals (93%) were still seropositive for anti-RBD-IgG with the GMT values exceeding 15 BAU/mL. The median concentration of anti-RBD-IgG was 6.7 times lower (95% CI 4.4–10.3 times) after 12 months compared with the highest median GMT value, defined during the second month after the SARS-CoV-2 infection.

DISCUSSION

To date, the data of only a few studies, involving the standardized values of the amount of antibodies against SARS-CoV-2 after the natural infection and/or vaccination, have been reported

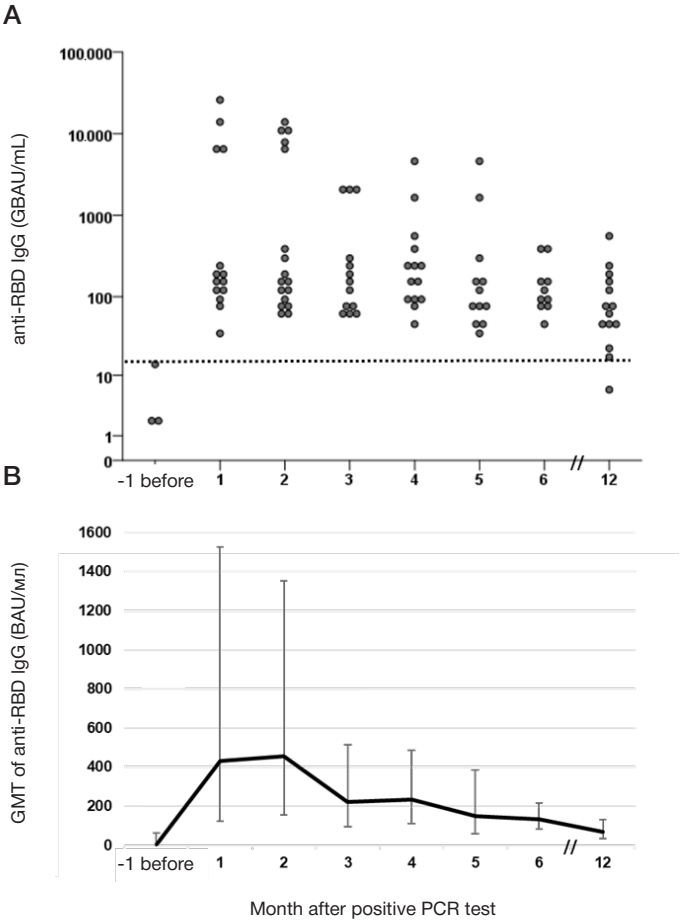

Fig. Concentration of anti-RBD IgG as a function of time after the positive PCR test result for SARS-CoV-2. (**A**) individual values for 97 samples and (**B**) geometric mean titers (GMT) of anti-RBD IgG with the 95% CI, expressed in BAU/mL; *dotted line* in (**A**) at the level of 15 BAU/mL specifies the positivity threshold

[5–7]. Thus, the live viral neutralization assay showed that anti-RBD-IgG in a concentration of ≥100 BAU/mL ensured the complete neutralization of three SARS-CoV-2 variants of concern a year after infection, which reduced the risk of reinfection with these virus strains [5]. Another report mentioned that on day 14 after vaccination, the anti-RBD-IgG GMT in individuals, vaccinated with mRNA vaccine, was 7,756 BAU/mL [6]. Thus, quantitative results provide the basis for seeking the common serological correlate of the protective immunity to SARS-CoV-2. Moreover, these data are important for monitoring the natural immunity and facilitate the comparison of immune responses to various vaccines [1]. Significant differences and systematic error in the numerical results, expressed in BAU/mL, associated with the use of different test systems [7], encourage further efforts to unify serological tests for detection of antibodies against SARS-CoV-2.

CONCLUSIONS

The study analyzes dynamic changes in the antibody response to SARS-CoV-2 infection during the natural immunity production. The use of IS-SARS-CoV-2 for calibration of the ELISA test system made in possible to demonstrate a change in the concentration of anti-RBD IgG over a wide range of 36–25, 900 BAU/mL with the widest disparity within two months after the infection. The levels of anti-RBD-IgG gradually decreased with time, however, positive values persisted throughout 12 months of follow-up in the majority of subjects.

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